Journal of The Association of Physicians of India

VOL NO. 71 | ISSUE NO. 12 | DECEMBER 2023 | ISSN : 0004 - 5772

Editor-in-Chief: Prof. Dr. Mangesh Tiwaskar

JAPI

www.japi.org app: myJAPI Price: ₹ 800

Published on 1st of every month

JAPI
JOURNAL OF THE ASSOCIATION OF PHYSICIANS OF INDIA
Editor-in-Chief: **Prof. Dr. Mangesh Tiwaskar**

Contents

JAPI JOURNAL OF THE ASSOCIATION OF PHYSICIANS OF INDIA
Editor-in-Chief: **Prof. Dr. Mangesh H Tiwaskar**

Editorial Board (2023-2024)

Subscription Information
Journal of The Association of Physicians of India is published monthly. The annual subscription is ₹12,000 (India) and US $500 (other countries). The Journal is dispatched within India by surface mail and to other countries by sea mail.

Business Correspondence
Enquiries concerning subscription, advertisement, etc. should be addressed to **Prof. Dr. Mangesh Tiwaskar**, Editor-in-Chief, JAPI, No. 006 & 007, Turf Estate, Dr. E. Moses Road, Opp. Shakti Mill Compound, Mahalaxmi (West), Mumbai-400 011.
Tel.: (022) 6666 3224
***e-mail*: onlinejapi@gmail.com/ mangesh.japi@gmail.com/ api.hdo@gmail.com**

Published and Edited by
Prof. Dr. Mangesh Tiwaskar, on behalf of **The Association of Physicians of India**, Journal of The Association of Physicians of India, Turf Estate, Unit No. 006 & 007, Opp. Shakti Mill Compound, Off Dr. E. Moses Road, Near Mahalaxmi Railway Station (West), Mumbai-400 011.
Editor-in-Chief: **Prof. Dr. Mangesh Tiwaskar**.

***Advertorial Enquiry*:**
Prof. Dr. Mangesh Tiwaskar,
Editor-in-Chief, JAPI,
No. 006 & 007, Turf Estate,
Dr. E. Moses Road, Opp. Shakti Mill Compound, Mahalaxmi (West),
Mumbai-400 011.
Tel.: (022) 6666 3224
***e-mail*: onlinejapi@gmail.com/ mangesh.japi@gmail.com**

Jaypee Brothers Medical Publishers (P) Ltd.
New Delhi

JAPI App: myJAPI
www.japi.org

Association of Physicians of India

GOVERNING BODY (2023-2024)

President Elect
Milind Nadkar (Mumbai) (2024)

President
Girish Mathur (Kota) (2024)

Past President
Shyam Sundar (Varanasi) (2024)

Vice Presidents

AP Misra (New Delhi) (2024)
V Palaniappen (Dindigul, TN) (2025)
NP Singh (New Delhi) (2026)

Hon. General Secretary
Agam C Vora (Mumbai) (2025)

Jt. Secretary (HQ)
Ashit M Bhagwati (Mumbai) (2025)

Hon. Treasurer
Amit Saraf (Mumbai) (2026)

Members

Munish Prabhakar (Gurgaon)	(2024)	**Anupam Prakash** (New Delhi)	(2025)	**Naval Chandra** (Hyderabad)	(2026)
S Sreenivasa Kamath (Kochi)	(2024)	**Sangram S Biradar** (Gulbarga)	(2025)	**SS Dariya** (Jaipur)	(2026)
Narayan Deogaonkar (Nashik)	(2024)	**Pramod Kumar Sinha** (Gaya)	(2025)	**DG Jain** (New Delhi)	(2026)
Sekhar Chakraborty (Siliguri)	(2024)	**Puneet Saxena** (Jaipur)	(2025)	**Udas Ghosh** (Kolkata)	(2026)
DP Singh (Bhagalpur)	(2024)	**PS Karmakar** (Kolkata)	(2025)	**R Chandni** (Kozhikode)	(2026)
Amit Verma (Dehradun)	(2024)	**Pradeep Bhaumik** (Agartala)	(2025)	**BK Singh** (Aurangabad) Bihar	(2026)

Zonal Members

North Zone	**Atul Bhasin** (New Delhi)	(2026)	South Zone	**N Balamurugan** (Salem)	(2026)
North West Zone	**Ashok K Taneja** (Gurugram)	(2026)	Mid East Zone	**Amit Kumar Das** (Muzaffarpur)	(2026)
Central Zone	**GD Ramchandani** (Kota)	(2026)	East Zone	**Hari Shankar Pathak** (Naihati)	(2026)
West Zone	**Anil Kumar Kulshrestha** (Ahmedabad)	(2026)	North East Zone	**Dwijen Das** (Tezpur)	(2026)
Mid South Zone	**Ravikeerthy M** (Bangalore)	(2026)			

Invited Member

Editor-in-Chief, API Text Book
Shashank R Joshi (Mumbai)

Editor-in-Chief, JAPI
Mangesh Tiwaskar (Mumbai)

Chairman, API House Committee
KK Pareek (Kota)

Ex-Officio Member

Dean, ICP
Jyotirmoy Pal (Talpulkar)

Director, PRF
Gurpreet Singh Wander (Ludhiana)

Co-opted Members

Jt. Secretary (President's place)
Ashutosh Chaturvedi (Jaipur)

Armed Forces, Medical Services
Maj. Gen. Sandeep Thareja (New Delhi)

Organising Secretary, APICON 2023 (Ahmedabad)
Banshi Saboo (Ahmedabad)

Organising Secretary, APICON 2024 (Delhi)
Rajesh Upadhyay (New Delhi)

Indian College of Physicians

FACULTY COUNCIL (2023-2024)

Chairman
Girish Mathur (Kota) (2024)

Dean
Jyotirmoy Pal (Talpukar) (2024)

Dean Elect
RK Singal (New Delhi) (2024)

Vice Deans
Y Satyanarayana Raju (Hyderabad) (2024)
BB Rewari (New Delhi) (2025)
Jayanta Kumar Panda (Cuttack) (2026)

Hon. Gen. Secretary
Agam C Vora (Mumbai) (2025)

Past Dean
Alaka Deshpande (Mumbai) (2024)

Jt. Secretary (H.Q.)
Ashit M Bhagwati (Mumbai) (2025)

Jt. Secretary (Dean's place)
Nandini Chatterjee (Kolkata) (2024)

Hon. Treasurer
Amit Saraf (Mumbai) (2026)

Elected Members

MPS Chawla (New Delhi)	(2024)	**Ghanshyam Pangtey** (New Delhi)	(2025)	**Prakash Keswani** (Jaipur)	(2026)
Soumitra Ghosh (Kolkata)	(2024)	**Hem Shankar Sharma** (Bhagalpur)	(2025)	**S Chandrasekar** (Chennai)	(2026)
Sanjeev Maheshwari (Ajmer)	(2024)	**Ashish Kumar Saha** (Kolkata)	(2025)	**NK Soni** (Greater Noida)	(2026)
R Rajasekar (Kumbakonam)	(2024)	**SV Kulkarni** (Raigad)	(2025)	**Devi Ram** (Purnea)	(2026)

Ex-Officio Members

President Elect	*Editor-in-Chief, JAPI*	*Director - PRF*	*Editor-in-Chief, API Text Book*
Milind Nadkar (Mumbai)	**Mangesh Tiwaskar** (Mumbai)	**GS Wander** (Ludhiana)	**Shashank R Joshi** (Mumbai)

Physicians Research Foundation

BOARD OF DIRECTORS (2023-2024)

Chairman
Girish Mathur (Kota) (2024)

Director
GS Wander (Ludhiana) (2025)

Past Director
YP Munjal (Gurugram) (2024)

Hon. General Secretary
Agam C Vora (Mumbai) (2025)

Jt. Secretary (Director's Place)
Rajender Bansal (Ludhiana)

Hon. Treasurer
Amit Saraf (Mumbai) (2026)

Members

MM Mehndiratta (New Delhi)	(2024)	**Sandeep Garg** (New Delhi)	(2025)	**Prabhat Pandey** (Durg)	(2026)
Satyabrata Ganguly (Kolkata)	(2024)	**Sudhir Mehta** (Jaipur)	(2025)	**Liyakhat Ali Gouri** (Bikaner)	(2026)

Invited Members

Editor-in-Chief, JAPI	*Dean, ICP*	*Editor-in-chief, API Text Book*
Mangesh Tiwaskar (Mumbai)	**Jyotirmoy Pal** (Talpukar)	**Shashank R Joshi** (Mumbai)

EDITORIAL

Fracture Liaison Services in India: Challenges and Opportunities

Aasim Maldar[1], Manoj Chadha[2*]

Introduction

Osteoporosis, often referred to as the "silent thief of bones," is defined by the National Institutes of Health as the "skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk for fracture."[1] Fragility fractures, which result from minor or unnoticed trauma, are more than just physical injuries; they have far-reaching consequences that not only lead to severe pain and reduced mobility but also affect aspects like quality of life, healthcare costs, and overall societal well-being. Literature shows that in postmenopausal women after hip fractures, the expected survival decreases from 12 to 20%.[2] A majority, exceeding 50% of the postmenopausal women and approximately one-third of men aged 60 years and above, are expected to encounter at least one major fragility fracture during the course of their remaining lifespans.[3] Experiencing a fragility fracture not only increases the lifetime risk of another fracture twofold but also introduces a dynamic risk profile that evolves over time.[4] In fact, this risk can surge to as much as five times higher within the immediate 18 months following the initial fracture.[5] Medications aimed at addressing osteoporosis have proven to be both safe and efficient, offering the potential to decrease the likelihood of subsequent vertebral fractures by as much as 70%, hip fractures by up to 50%, and nonhip and nonvertebral fractures by approximately 20–30%.[6] However, less than one-fifth of the patients with fragility fractures undergo appropriate evaluation and treatment for the root cause of their fracture, that is, osteoporosis.[7] In 2013, the International Osteoporosis Foundation (IOF) launched the "Capture the Fracture" campaign as a strategic response to enhance osteoporosis care.[8] This campaign was meticulously designed to amplify the awareness surrounding secondary fracture prevention, recognizing the critical significance of addressiwng recurrent fractures. A pivotal facet of this initiative is the advocacy for the Fracture Liaison Service (FLS), a multidisciplinary program tailored to the systematic identification and comprehensive treatment of patients afflicted by fractures. Currently, the Capture the Fracture network includes 861 FLS in 55 countries worldwide.

Osteoporosis, the Indian Scenario

As the demographic landscape of India evolves, it brings to the forefront a new range of healthcare challenges, and osteoporosis and related fragility fractures are emerging as significant concerns. Often asymptomatic until a fracture occurs, osteoporosis poses a dual challenge in India. The country's diverse demographics, marked by an expanding elderly population and a surge in chronic diseases, have converged to create a scenario where osteoporosis, though prevalent, remains largely unnoticed. The challenge of osteoporosis in India is compounded by factors such as inadequate awareness, cultural perceptions surrounding bone health, and limited access to specialized care.

The current population of India is estimated at >143 crores, with >17% of the population aged >50 years.[9] There is a paucity of robust data regarding the prevalence of osteoporosis and fragility fractures from India, and studies from different centers have reported osteoporosis prevalence ranging from 10 to 55% in women, and 3–20% in men, by various methods and in various age groups.[10–13] Indian studies over the past decade have reported an annual hip-fracture incidence rate of 163 and 121 per 100,000 per year in women and men, respectively, above the age of 55 years and with 15–20% of older urban adults aged over 50 years showing evidence of at least one vertebral fracture.[14,15]

Empirical surveys have shown that only 10–15% of the Indian population is aware of osteoporosis.[16] The deficiency in addressing osteoporosis extends beyond the general population, and 80% of patients suffering from osteoporosis in India do not receive accurate diagnosis and requisite treatment from healthcare practitioners. Even in instances where treatment is initiated, the adherence rate remains a modest 64%.[17] Since 2018, under the aegis of the Indian Society of Bone and Mineral Research (ISBMR), FLS has been initiated at three centers in India—Post Graduate Institute of Medical Education and Research Chandigarh, PD Hinduja Hospital and Medical Research Center Mumbai, and Maulana Azad Medical College New Delhi.[18]

Understanding FLS

In 2015, the Royal Osteoporosis Society (ROS) in the United Kingdom unveiled a set of Best Practice Guidelines, including recommendations for secondary fracture prevention, meticulously formulated by a multidisciplinary consortium, which garnered endorsement from pertinent national professional bodies as well as the IOF.[19]

Fracture Liaison Service (FLS) is a specialized multidisciplinary program designed to identify, assess, and manage patients who have suffered fragility fractures. The primary objective of FLS is to break the cycle of fractures by implementing comprehensive care strategies that address both acute fracture treatment and long-term fracture prevention. FLS encompasses a spectrum of activities, including fracture identification, bone health assessment, and personalized intervention plans.

Key Components of FLS

Fracture Identification

Early identification of patients who have sustained fragility fractures is a fundamental step. Hospitals and clinics with FLS programs implement systematic methods to ensure that patients are not only treated for their fractures but are also assessed for underlying osteoporosis.

Bone Health Assessment

Through bone mineral density (BMD) tests (by Dual Energy X-ray Absorptiometry, BMD-DXA), fracture risk scores, and clinical evaluations, FLS determines the individual's fracture risk and identifies contributing factors such as lifestyle, medications, and medical conditions.

[1,2]Consultant Endocrinologist, PD Hinduja Hospital and Medical Research Centre, Mumbai, Maharashtra, India; *Corresponding Author

How to cite this article: Maldar A, Chadha M. Fracture Liaison Services in India: Challenges and Opportunities. J Assoc Physicians India 2023;71(12):11–13.

Individualized Treatment Plans

Fracture Liaison Service (FLS) develops personalized treatment plans that may involve medication, nutritional guidance, physical therapy, and fall prevention strategies. These plans are tailored to each patient's unique needs and risk factors.

Patient Education and Empowerment

Fracture Liaison Service (FLS) emphasizes patient education to enhance awareness about osteoporosis, fracture risk reduction, and the importance of adherence to treatment plans.

Follow-up and Monitoring

Continuity of care is crucial. FLS programs include follow-up appointments and regular monitoring to assess treatment efficacy, address concerns, and modify plans as needed.

An array of diverse FLS models exist, varying in the level of services extended within the program. In a systematic review conducted in 2013,[20] interventions were categorized into distinct models of care based on the intensity of the intervention (Table 1). However, despite this diversity, a common thread unites them all: the primary objective of identifying patients at high risk and connecting them with the FLS coordinator. Subsequently, depending upon the specific model, the coordinator undertakes one or a combination of the following tasks: investigation, patient education, treatment administration, and follow-up care.

Implementing FLS in India: Challenges and Opportunities

While the concept of FLS holds immense promise for India, its successful implementation comes with its own set of challenges and opportunities.

Table 1: Fracture liaison service (FLS) (secondary fracture prevention) models

Type of model	*Services included*
A	Identification; assessment (including investigations); education (patient and primary caregiver); initiation of treatment
B	Identification; assessment (including investigations); education (patient and primary caregiver); treatment recommendation to the referring physician
C	Identification; education (patient and primary caregiver); communication with the referring/ primary physician
D	Identification; education (patient and primary caregiver)

- Awareness and education: Limited awareness about osteoporosis and its implications is a major hurdle. Public health campaigns and educational initiatives aimed at healthcare professionals and the general public are crucial to fostering understanding and promoting early intervention.
- Multidisciplinary collaboration: FLS requires collaboration among orthopedic surgeons, physicians, endocrinologists, rheumatologists, gynecologists, radiologists, physical therapists, and other healthcare providers. Establishing effective communication channels and referral pathways is essential.
- Infrastructure and resources: Adequate infrastructure, including bone density testing facilities and access to relevant medications, is vital for the success of FLS. Ensuring the availability and affordability of these resources is a key consideration.
- Culturally tailored approach: India's diverse cultural and social landscape requires FLS to be culturally sensitive and adaptable. Localizing educational materials and strategies can enhance engagement and acceptance.
- Telemedicine and technology: With India's vast geographical expanse, leveraging telemedicine and digital platforms can extend the reach of FLS to underserved areas, enabling remote consultations and follow-ups.

Operational Steps of FLS Implementation at Our Institute

The FLS at our institute operates through a well-defined sequence of steps.

Patient Identification

Identification criteria: Patients meeting fragility fracture criteria, including both females and males over 50 years with fractures resulting from falls from standing height or less, are identified by the primary caregiver.

Coordinated referral with multidisciplinary support: Coordinating the referral process is a pivotal aspect of our FLS, fortified by the active engagement of various medical specialties, including general medicine, orthopedics, radiology, and rheumatology.

Detection of asymptomatic vertebral fractures: Vertebral fractures detected incidentally during routine medical imaging are also brought to the notice of the FLS coordinator by the Radiology and Preventive Health-check departments.

Patient Risk Assessment

Patient education: Patients referred to the FLS program are educated by the FLS coordinator about the implications of fragility fractures and the FLS program itself.

In-depth Evaluation

- Bone health evaluation: BMD measurement and Fracture Risk Assessment Tool (FRAX) calculation are conducted in all the consenting patients.
- Secondary causes assessment: Clinical evaluation to identify underlying secondary causes of osteoporosis and relevant investigations, if necessary, are also carried out.
- Fall risk analysis: Assessment of lifestyle factors contributing to the risk of falls is noted.
- Medication review: A comprehensive assessment of patients' medications with potential osteoporotic effects is also done.

Treatment Provision

- Individualized treatment plans: Based on the risk assessment outcomes, personalized treatment plans are formulated for each patient. The same are discussed with the primary physician and then finalized.
- Fall prevention strategies: Patients identified at risk of falls are provided with specialized education and interventions for fall prevention.

Adherence Monitoring and Follow-up

- Adherence check: The FLS coordinator ensures monitoring of treatment adherence at 6 and 12 months through follow-up appointments or telephonic conversations.
- Continual engagement: Annual telephonic contacts are maintained to sustain patient engagement, evaluate treatment progress, and inquire about potential adverse effects.

Database Management

- Institutional database: Patient information is systematically cataloged within the institution.
- Regional and national sharing: Plans are in place to share this data with regional and national databases.
- Evaluation of outcomes: The reduction in refracture risk (expressed as a hazard ratio) is a key parameter to be evaluated.

Impact and Future Directions

The implementation of FLS has demonstrated significant improvements in patient

outcomes. Studies have shown reductions in subsequent fractures, hospitalizations, healthcare costs, as well as subsequent mortality.[21,22] As FLS programs continue to evolve, technological advancements such as telemedicine and wearable devices could further enhance patient engagement and monitoring.

Challenges and Considerations

Despite the promising impact of FLS, challenges persist. Limited awareness among both healthcare professionals and patients, fragmented healthcare systems, and financial barriers can hinder the widespread adoption of FLS. Additionally, maintaining patient adherence to treatment plans and lifestyle modifications remains a challenge.

Conclusion: Empowering Fracture Prevention

By addressing the gaps in care that often lead to recurrent fractures, FLS programs hold the potential to improve the quality of life for individuals at risk. The ongoing evolution of FLS models, coupled with efforts to raise awareness and facilitate interdisciplinary collaboration, has the capacity to reshape the landscape of osteoporosis management and fracture prevention on a national scale.

References

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. JAMA 2001;285(6):785–795.
2. Bliuc D, Nguyen ND, Milch VE, et al. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA 2009;301(5):513–521.
3. Nguyen ND, Ahlborg HG, Center JR, et al. Residual lifetime risk of fractures in women and men. J Bone Miner Res 2007;22(6):781–788.
4. Klotzbuecher CM, Ross PD, Landsman PB, et al. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res 2000;15(4):721–739.
5. van Geel TA, van Helden S, Geusens PP, et al. Clinical subsequent fractures cluster in time after first fractures. Ann Rheum Dis 2009;68(1):99–102.
6. Leslie WD, Giangregorio LM, Yogendran M, et al. A population-based analysis of the post-fracture care gap 1996-2008: the situation is not improving. Osteoporos Int 2012;23(5):1623–1629.
7. Roux C, Briot K. The crisis of inadequate treatment in osteoporosis. Lancet Rheumatol 2020;2(2):e110–e119.
8. Akesson K, Marsh D, Mitchell PJ, et al. Capture the Fracture: a best practice framework and global campaign to break the fragility fracture cycle. Osteoporos Int 2013;24(8):2135–2152.
9. Updated on August 29, 2023, with the latest August 2023-2024 estimates from the United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects: The 2022 Revision.
10. Cherian KE, Kapoor N, Meeta M, et al. Screening tools for osteoporosis in India: where do we place them in current clinical care? J Midlife Health 2021;12(4):257–262.
11. Silvanus V, Ghosal K, Behera A, et al. Screening for osteopenia and osteoporosis in an urban community in India. Nepal Med Coll J 2012;14(3):247–250.
12. Agrawal NK, Sharma B. Prevalence of osteoporosis in otherwise healthy Indian males aged 50 years and above. Arch Osteoporos 2013;8:116.
13. Marwaha RK, Tandon N, Garg MK, et al. Bone health in healthy Indian population aged 50 years and above. Osteoporos Int 2011;22(11):2829–2836.
14. Dhanwal DK, Siwach R, Dixit V, et al. Incidence of hip fracture in Rohtak district, North India. Arch Osteoporos 2013;8(0):135.
15. Marwaha RK, Tandon N, Gupta Y, et al. The prevalence of and risk factors for radiographic vertebral fractures in older Indian women and men: Delhi Vertebral Osteoporosis Study (DeVOS). Arch Osteoporos 2012;7:201–207.
16. Nallasivan S. Current treatment of osteoporosis. Indian J Rheumatol 2019;14(1):57–60.
17. Jhaveri S, Upashani T, Bhadauria J, et al. Current clinical practice scenario of osteoporosis management in India. J Clin Diagn Res 2015;9(10):RC04–RC08.
18. Chadha M, Shingare A, Prasanth A, et al. Fracture liaison service: prevention by coordination. Indian J Endocrinol Metab 2018;22(6):719–721.
19. Javaid MK, Kyer C, Mitchell PJ, et al. Effective secondary fracture prevention: implementation of a global benchmarking of clinical quality using the IOF Capture the Fracture® Best Practice Framework tool. Osteoporos Int 2015;26(11):2573–2578.
20. Ganda K, Puech M, Chen JS, et al. Models of care for the secondary prevention of osteoporotic fractures: a systematic review and meta-analysis. Osteoporos Int 2013;24(2):393–406.
21. Wu CH, Tu ST, Chang YF, et al. Fracture liaison services improve outcomes of patients with osteoporosis-related fractures: a systematic literature review and meta-analysis. Bone 2018;111:92–100.
22. Li N, Hiligsmann M, Boonen A, et al. The impact of fracture liaison services on subsequent fractures and mortality: a systematic literature review and meta-analysis. Osteoporos Int 2021;32(8):1517–1530.

ORIGINAL ARTICLE

Effect of Vaccination on COVID-19 Severity and Outcome: A Comparative Study in a Tertiary Care Hospital

Yad Ram Yadav[1], Sanjiv Maheshwari[2*], Aakash Garg[3], Ala Ram[4], Shakti Singh[5], Sonakshi Mangal[6], Kopal Maheshwari[7], Vishakha Notani[8], Shivalika Sharma[9], Vaishnavi Bansal[10]

Received: 07 February 2023; *Revised:* 24 August 2023; *Accepted:* 12 September 2023

Abstract

Introduction: Vaccination is an important aspect of preventing/decreasing the severity of any viral disease including severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). This disease being very new in the experience of mankind has very little data on the effect of vaccination on the severity of this disease. We conducted this study with the primary objective to assess the severity and clinical outcome of COVID-19 infections among nonvaccinated and vaccinated individuals.

Materials and methods: This was a hospital-based retrospective cohort study including all individuals developing microbiologically confirmed COVID-19 over 5 months from February to 31st July 2021. A questionnaire was used to acquire demographic details, history of vaccination with dates, severity of COVID-19 infection, comorbidities, and outcome. Patients found positive microbiologically for SARS-CoV-2 before any dose of its vaccine were considered nonvaccinated, while patients developing SARS-CoV-2 infection even after a single dose or both doses of vaccine were considered "vaccinated." The outcome and mortality among the vaccinated and nonvaccinated patients were evaluated and compared.

Results: The study included 2,879 patients, but complete data were obtained only from 1,500 patients. A total of 1,500 patients were analyzed, out of which 880 are male and 620 are female. The severity of the disease was categorized into mild, moderate, and severe in the age-group of <60 years and >60 years with urban (1051, 70.07%) and rural (449, 29.93%) populations. A total number of recovered patients (n = 245), died patients (n = 215) in the age-group of >60 years while the total recovered patients (n = 823) and dead patients (n = 217) in the age-group <60 years with p = 0.001. Total vaccinated patients in the age-group >60 years (n = 204) and not vaccinated (n = 256) while in the age-group of <60 years total vaccinated n = 229 and not vaccinated n = 811. The outcome of disease in the age-group of >60 years in nonvaccinated 50% recovered and 50% died during the course of illness while in the vaccinated 57.3% recoverd and 42% died p-value 0.14, while in the age-group of <60 years recovery in nonvaccinated 77.6% and death in nonvaccinated was 27.32% while in vaccinated patients 82.28% were recovered and 15% died with significant p-value 0.04. Disease outcome was not found significantly associated with a number of doses with p-values of 0.84 and 0.507 in the age-group of >60 years and <60 years, respectively. A total number of 56 patients received Covaxin and 377 patients received Covishield and disease outcome was not found significantly associated with the type of vaccine.

Conclusion: Vaccination against COVID-19 was significantly effective in terms of hospitalization and disease severity. Vaccinated persons were less among patients with COVID-19 hospitalization and with severe disease progressing to death. These findings indicate vaccination is helpful in reducing the development of severe COVID-19 infection as compared to nonvaccinated status.

Journal of the Association of Physicians of India (2023): 10.59556/japi.71.0403

Introduction

Mankind has witnessed a severe impact on every aspect of human life and health, including physical, psychological, behavioral, and social well-being by COVID-19 infection.[1] As there was no specific treatment to cure this disease, infection prevention practices like the use of masks, frequent hand hygiene, etc., and mass vaccination remain the mainstay in controlling the disease.[2] India pioneered the largest COVID-19 vaccination program in the world on 16th January 2021. Covishield (Serum Institute, Pune, India) and Covaxin (Bharat Biotech, Hyderabad, India) were the two major vaccines available in this country; both were given as intramuscular injections at 12 weeks apart.[3] Vaccination was initially started for healthcare workers, followed by frontline workers and the elderly population (60 years plus). Later, vaccination expanded to the middle-aged population with comorbidities (45–60 years), followed by all middle-aged population, and eventually to young adults (18–45 years). The phenomenon of vaccine hesitancy is very old and universal including in the world's most developed countries.[4] Our tertiary care center was designated as one of the sites for COVID-19 vaccination where both Covishield and Covaxin were administered. Studies have revealed the protective efficacy of these vaccines in reducing hospitalization duration and severity and in averting mortality. However, only limited studies have evaluated the protective efficacy of vaccines in preventing COVID-19 in real life.

Very few studies are there assessing the dose effect of vaccines (number of doses and time since the last dose of vaccine) and their ability to prevent acquiring the disease, and/or protection from hospitalization, intensive care unit (ICU) admissions, and/or death. This study was conducted to analyze the association between vaccination status, with the severity of illness among reverse transcription polymerase chain reaction (RT-PCR) positive patients. This study was conducted with the primary objective to assess the severity and clinical outcome of COVID-19 infections among nonvaccinated/partially vaccinated and vaccinated patients. The secondary objective of this study was to assess the clinical outcome of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection among nonvaccinated/partially vaccinated and vaccinated patients.

Materials and Methods

The study conducted by us was a hospital-based retrospective case-control type carried out in a tertiary care teaching hospital in Ajmer, Rajasthan, India, providing management to COVID-19 patients. All patients who developed COVID-19 confirmed by RT-PCR from February 2021 to 31st July 2021, were included. Patients found positive previously for COVID-19 prior to the study period and with missing vaccine status were excluded. Confirmatory RT-PCR tests were performed and interpreted as per the Indian Council of Medical Research (ICMR) guidelines. The status of vaccination

[1]Assistant Professor; [2]Senior Professor and Head; [3–5]Resident, Department of Medicine; [6–10]MBBS Student, JLN Medical College, Ajmer, Rajasthan, India; *Corresponding Author

How to cite this article: Yadav YR, Maheshwari S, Garg A, *et al.* Effect of Vaccination on COVID-19 Severity and Outcome: A Comparative Study in a Tertiary Care Hospital. J Assoc Physicians India 2023;71(12):14–16.

for COVID-19 was recorded along with their demographic, clinical profile, and outcome. Patients found positive for SARS-CoV-2 before any dose of the COVID-19 vaccine were considered "nonvaccinated" while patients developing SARS-CoV-2 even after a single or both doses of vaccine were considered partially vaccinated and completely vaccinated, respectively. This was done because the vaccine we rolled out on 16th January 2021, as per national guidelines, the two doses of vaccination were given 28 days apart and the second wave of the COVID-19 pandemic started upsurging as early as March 2021 by which time most of the patients have received only one dose. The starting point of the study was a telephonic collection of data from COVID-19-infected patients who were microbiologically confirmed COVID-19. Those patients who denied consent or could not be contacted were also excluded. Data was telephonically recorded from the kin of the patient in case of death due to COVID-19, or else it was obtained retrospectively from the patients. Records of the admitted patients were also reviewed wherever available.

The response was on a voluntary basis, and if the participant agreed, data was collected using an interviewer-administered, and pretested questionnaire. It includes sociodemographic data of patients, history of vaccination, comorbidities, management (home or hospital-ICU/isolation ward as per the Ministry of Health and Family Welfare guidelines),[7] severity of disease (mild/moderate/severe) based on the minimum saturation of oxygen recorded, and computed tomography (CT) severity score. All patients selected according to the inclusion and exclusion criteria were evaluated for the severity of COVID-19 into mild/moderate/severe categories. Patients who reported oxygen saturation above 93% oxygen (O_2) were classified as mild, those who reported 90–93% O_2 were classified as moderate, and those who reported <90% O_2 were classified as severe.[7] Lung involvement in COVID-19 disease is being estimated radiologically as CT severity score index which is a scoring system used to assess the involvement of lung area approximately. Each of the five lung lobes has been visually scored and given a score from 1 to 5. The final score is the summation of individual lobar scores and is out of 25. The source of the data regarding vaccination is the ICMR/specimen referral form for COVID-19 testing, which mandates the recording of vaccination status as one of the components. For admitted patients, the medical records were also reviewed for clinical profile and outcome along with telephonic confirmation. The outcome and mortality among the vaccinated/ partially vaccinated and nonvaccinated groups were calculated and compared.

Statistical Analysis

Data were analyzed using VassarStats. Categorical variables such as vaccination status, severity, etc. were presented as proportions. Continuous variables were presented as mean (standard deviation). The Chi-squared test and Fisher exact test were used for bivariate analysis. A p-value < 0.05 was considered significant for statistical computations.

Ethics Approval

Required approval was taken from the Institutional Review Board and Ethics Committee.

Results

Data were collected from 2,879 patients, but complete data were obtained only from 1,500 patients. A total of 1,500 patients were analyzed, out of which 880 were male and 620 were female. The severity of the disease was categorized into mild, moderate, and severe in the age-group of <60 years and >60 years with urban (1051, 70.07%) and rural (449, 29.93%) populations.

In Table 1, disease severity, that is, mild, moderate, and severe was compared with the outcome (recovered and died). Patients in both above and below 60 groups showed a significant association between severity and outcome.

Table 2 shows an association between disease severity and vaccination status for both ages above and below 60 age-groups. No association was found between disease severity and vaccination status in the above-60 age-group, but in the below-60 group, disease severity was found to be associated with vaccination status.

Table 3 association between disease outcome and vaccination status. No association was found between disease outcome and vaccination status in the above-60 age-group, but in the below-60 group, disease outcome was found to be associated with vaccination status.

Table 4 shows an association between disease outcome and number of doses. Disease outcome was not found associated with a number of doses.

Table 5 shows an association between disease outcome and the type of vaccine (Covaxin vs Covishield). Disease outcome was not found to be associated with the type of vaccine.

Table 1: Distribution of patients according to disease severity

N = 1,500	*Age > 60 (N = 460)*			*Age < 60 (N = 1,040)*		
Disease severity	*Recovered N = 245*	*Died N = 215*	*p-value*	*Recovered N = 823*	*Died N = 217*	*p-value*
Mild	40 (16.33%)	8 (3.72%)	<0.0001*	284 (34.51%)	7 (3.23%)	<0.0001*
Moderate	89 (36.33%)	19 (8.84%)		253 (30.74%)	23 (10.60%)	
Severe	116 (47.35%)	188 (87.44%)		286 (34.75%)	187 (86.18%)	

*, Chi-squared test; $, Fisher exact test

Table 2: Association between disease severity and vaccination status

	Age > 60 N = 460			*Age < 60 N = 1,040*		
Disease severity	*Not vaccinated N = 256*	*Vaccinated N = 204*	*p-value*	*Not vaccinated N = 811*	*Vaccinated N = 229*	*p-value*
Mild	28 (9.80%)	20 (9.80%)		221 (27.25%)	70 (30.57%)	<0.001
Moderate	55 (21.48%)	53 (25.98%)	0.5194*	204 (25.15%)	72 (31.44%)	
Severe	173 (67.58%)	131 (64.22%)		386 (47.60%)	87 (37.99%)	

*, Chi-squared test; $, Fisher exact test

Table 3: Association between disease outcome and vaccination status

N = 1,500	*Age > 60 (N = 460)*			*Age < 60 (N = 1,040)*		
Outcome	*Nonvaccinated N = 256*	*Vaccinated N = 204*	*p-value*	*Nonvaccinated N = 811*	*Vaccinated N = 229*	*p-value*
Recovery	128 (50.0%)	117 (57.35%)	0.14	630 (77.68%)	193 (84.28%)	0.04*
Death	128 (50.0%)	87 (42.65%)		181 (22.32%)	36 (15.72%)	

*, Chi-squared test; $, Fisher exact test

Table 4: Association between disease outcome and number of doses

N = 1,500	*Age > 60 N = 204*			*Age < 60 N = 229*		
Outcome	*Single dose N = 162*	*Double dose N = 42*	*p-value*	*Single dose N = 178*	*Doubledose N = 51*	*p-value*
Recover y	94 (58.02%)	23 (54.76%)	0.84	148 (83.15%)	45 (88.24%)	0.5071*
Death	68 (41.98%)	19 (45.24%)		30 (16.85%)	6 (11.76%)	

*, Chi-squared test; $, Fisher exact test

Table 5: Association of disease outcome with type of vaccine

	Age > 60 N = 204			*Age < 60 N = 229*		
	Covaxin N = 25	*Covishield N = 179*	*p–value*	*Covaxin N = 31*	*Covishield N = 198*	*p-value*
Recovery	12 (48.0%)	105 (58.66%)	0.43*	25 (80.65%)	168 (84.85%)	0.3
Death	13 (41.34%)	74 (41.34%)		6 (19.35%)	30 (15.15%)	

*, Chi-squared test; $, Fisher exact test

Discussion

In this study, we assessed the association between COVID-19 vaccination status and the severity (and mortality) of the disease. No association was found between disease severity and vaccination status in the above-60 age-group, but in the below-60 group, disease severity was found to be associated with vaccination status. Tenford et al. also found that vaccination status was associated with the severity of the disease.[5] Vaccinated patients were found with less severe disease. There was a significantly low number of people in the <60 years age-group who developed severe disease after getting vaccinated compared to nonvaccinated patients. This is also in concordance with studies done in Bihar and Rajasthan.[6,7]

In the current study, vaccination status was found associated with outcomes in the below <60 years age-group.

Vaccinated patients had favorable outcomes. This was consistent with other studies from India[6,7] and the United States of America.[5] Clinical trials are already there demonstrating high vaccine efficacy rates (95 and 94.1% for BNT162b2 and mRNA1273, respectively) in the American population.[5]

There is not much published data to date even after such mass vaccination campaigns favoring the beneficial role of the Indian vaccines in the real-world scenario for preventing the disease or reducing its severity. This study clearly reveals that both the vaccines used for mass vaccination in India are significantly effective in preventing COVID-19 and/or reducing disease severity (hospitalization and death).

We realize that this study required responses obtained from the patients by telephonic interviews, therefore, is liable to recall bias. This study also does not report the COVID-19 virus strain data of individual patients.

Conclusion

Vaccination against COVID-19 was significantly effective in terms of reducing hospitalization and disease severity. Vaccinated persons were less among patients with COVID-19 hospitalization and with severe disease progressing to death. These findings indicate vaccination is helpful in reducing the development of severe COVID-19 infection as compared to nonvaccinated status.

References

1. Hossain MM, Tasnim S, Sultana A, et al. Epidemiology of mental health problems in COVID-19: a review. F1000Res 2020;9:636.
2. Fiolet T, Kherabi Y, MacDonald CJ, et al. Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern: a narrative review. Clin Microbiol Infect 2022;28(2):202–221.
3. Embi PJ, Levy ME, Naleway AL, et al. Effectiveness of 2-Dose vaccination with mRNA COVID-19 vaccines against COVID-19-associated hospitalizations among immunocompromised adults - nine states, January-September 2021. Morb Mortal Wkly Rep 2021;70(44):1553–1559.
4. Yasmin F, Najeeb H, Moeed A, et al. COVID-19 vaccine hesitancy in the United States: a systematic review. Front Public Health 2021;9:770985.
5. Tenforde MW, Self WH, Adams K, et al. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. JAMA 2021;326(20):2043–2054.
6. Singh C, Naik BN, Pandey S, et al. Effectiveness of COVID-19 vaccine in preventing infection and disease severity: a case-control study from an Eastern state of India. Epidemiol Infect 2021;149:e224.
7. Thathai A, Gahlot R, Gahlot NK, et al. Study of COVID-19 infection, its severity and outcome in COVID-19 vaccinated people at tertiary health care center, North West Rajasthan. J Assoc Physicians India 2021;69(9):11–12.

8th INTERNATIONAL DIABETES SUMMIT – 2024 | PUNE

15th – 17th MARCH 2024 | JW Marriott, Pune

Chellaram Diabetes Institute

With faculty from

University of Leicester, UK | Mayo Clinic, USA | Imperial College, UK | Karolinska Institutet, Sweden
Stellenbosch University, South Africa | National University of Singapore, Singapore
Keele University, UK | University of Dundee, UK

And Well-Known National Faculty!

Applying for MMC credit points

HIGHLIGHTS – 7th INTERNATIONAL DIABETES SUMMIT – 2023

- **70** National and 10 Best in class International Speakers from the USA, UK, and Europe.
- **2200** delegate registrations from all over India and abroad.
- Oral abstract presentations by 83 young researchers.
- The Chellaram Foundation Diabetes Research Awards were presented. A total prize of Rs. 6,00,000/- was awarded to the winners for outstanding research in basic and clinical sciences each.
- The 3-day mega event comprised a number of interesting sessions on advances in diagnosing diabetic foot and retinal diseases, diabetes in the young focusing on diet, lifestyle, and type 1 diabetes session with on-table display and a visual toolkit of diet.
- The Maharashtra Medical Council awarded 10 Credit Points to the Summit 2023.

REGISTRATION FORM

First Name: _____ Surname _____ Gender M/F _____

MMC/ Other Council No. _____ Hospital / Institution _____

Qualification _____ Speciality _____

Address For Communication _____

City _____ Pincode _____ State/Country _____

Mobile No/Contact No (with Area Code) _____ Email _____

PAYMENT DETAILS

REGISTRATION FEE (FEE/ PERSON in INR and USD) + 18% GST

Category	Upto 1st Jan 2024	Upto 14th March 2024	Spot
National Delegate	INR 13,000	INR 14,000	INR 15,000
PG Student*	INR 8,000	INR 9,000	INR 10,000
HCPs #	INR 13,000	INR 14,000	INR 15,000
Accompanying Person	INR 13,000	INR 14,000	INR 15,000
International Delegate	USD 400	USD 500	USD 600

*Includes PHFI / CDI course participants #Health Care Providers Non MBBS / Para Medics / Researchers
Note: Final decision on registration will be taken by Organizing Committee.

THE CHELLARAM FOUNDATION DIABETES RESEARCH AWARD - 2024

Win Medals & Prizes upto Rs. 6,00,000 with 1st prize of Rs. 2,00,000 each for Outstanding Research in Basic and Clinical Science

Last date for abstract submission 20th February 2024

The Secretariat Address:
8th International Diabetes Summit 2024
Chellaram Diabetes Institute
1st Floor, Lalani Quantum, Opp. Calsoft, Pune Bangalore NH4 Bavdhan (Budruk), Pune - 411021
Contact: Ms. Shraddha U. Mahajan
020-66839771 | +91 77450 15553
E-mail: ids@cdi.org.in

For Registration Contact
Vama Events Pvt. Ltd.
Kohinoor Square Phase I, B Wing, Office No. 1004, N. C. Kelkar Road, Shivaji Park, Dadar West, Mumbai - 400028
Tel.: + 022 35131930/31/32/33, 022 46052832
Email: conferences@vamaevents.com

Chellaram Diabetes Institute
International Diabetes Federation

in association with

Venue
JW MARRIOTT.
Senapati Bapat Road, Pune - 411053

For Online registration
www.cdidiabetessummit.org | www.cdi.org.in

ORIGINAL ARTICLE

The Role of Absolute Eosinophil Count as a Diagnostic and Prognostic Marker for Sepsis and Its Relation with Sequential Organ Failure Assessment/Quick Sequential Organ Failure Assessment Score

Deepti Sharma[1], Sony Joseph[2*], Narendra Fageria[3], Sreedev Aravind[4], Gordhanlal Nagar[5]

Received: 24 February 2022; *Revised:* 07 July 2022; *Accepted:* 21 July 2022

Abstract

Aims and background: Sepsis is a dysregulated host response to an infection that causes organ failure that poses a serious risk to life. Although culture results are not always available right away and the majority of patients continue to test culture negative, microbial culture is still the gold standard for diagnosing sepsis. Therefore, the objective of the current study was to assess absolute eosinophil count as a new marker for diagnosing sepsis and also to assess the prognosis of the patient in relation to Sequential Organ Failure Assessment (SOFA)/quick Sequential Organ Failure Assessment (qSOFA) score.

Resources and procedures: In this cross-sectional study, 100 patients with sepsis were enrolled. The other 100 patients without any evidence of sepsis were taken as controls. Absolute eosinophil count (AEC), SOFA/qSOFA scores of all the patients were measured on the 1st, 3rd, and 7th day and data was analyzed statistically.

Results: The mean AEC on admission day in sepsis patients was 49.5. The mean AEC among survivors was >50 and nonsurvivors was <50. AEC and SOFA/qSOFA scores exhibit a statistically significant and inverse correlation on the 1st, 3rd, and 7th day of illness.

Conclusion: Absolute eosinophil count (AEC) is a simple and cost-effective marker that may be helpful in diagnosis as well as in predicting the prognosis of sepsis as evidenced by its linear inverse correlation with SOFA/qSOFA score.

Journal of the Association of Physicians of India (2023): 10.59556/japi.71.0367

Introduction

Sepsis is described as life-threatening organ dysfunction induced by an abnormal host response to infection.[1] Following the publication of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), the definition of sepsis was modified in 2016.[1]

"Sepsis-3" clinical criteria for sepsis diagnosis include: (1) a suspected/documented infection and (2) acute organ dysfunction, defined as an increase by two or more points from baseline (if known) on the Sequential (or sepsis-related) Organ Failure Assessment (SOFA) score.[1,2] The SOFA score is a 24-point scale that assesses organ dysfunction across six organ systems (renal, cardiovascular, pulmonary, hepatic, neurologic, and hematologic), with 0–4 points awarded to each organ system.[1,3,4]

In Sepsis-3 clinical criteria, a new criterion, quick Sequential Organ Failure Assessment (qSOFA), was also established with range 0–3. If the following criteria are met, they will each receive one point—systolic hypotension (≤ 100 mm Hg), tachypnea (>22) or altered mental status. A qSOFA score of ≥2 points has a predictive value for sepsis similar to that of more complicated measures of organ dysfunction.[1]

Microbial culture is still the gold standard for diagnosing sepsis, although findings are not always available correctly. Furthermore, a considerable proportion of sepsis patients are culture-negative. As a result, the diagnosis of this group of sepsis patients is mainly on clinical criteria and subjective clinical opinion.

The substantial fall in the number of circulating eosinophils in acute infection was first described by Zappert in 1893[5] and was used as a valuable diagnostic tool during the first quarter of the previous century.

Eosinophil production is regulated by interleukin-3 (IL-3), IL-5, and GM-CSF, which are not considerably activated in sepsis, resulting in relative eosinopenia. Another theory is that the early eosinophilic response in acute inflammation is caused by the fast peripheral sequestration of circulating eosinophils.[6]

Absolute eosinophil count (AEC) is a low-cost, easily accessible test in both rural and urban institutions. In addition to its predictive significance, eosinopenia may be a useful tool in counseling physicians as a swift and affordable indicator of sepsis on admission.

As a result, the current study sought to ascertain the role of absolute eosinophil count as a diagnostic and prognostic marker for sepsis, as well as its relationship with SOFA/qSOFA.

Methodology

A cross-sectional study was conducted in the Government Medical College and attached groups of hospitals in Kota from August 2020 to September 2021, with consent from the Internal Ethical Committee. Before joining the trial, all patients provided informed written consent.

The study comprised 100 adult patients of both sexes who were diagnosed with sepsis using the Sepsis-3 criteria and were hospitalized in the emergency, general, and intensive care units.

The study comprised patients over the age of 18 who were admitted to MBS Hospital Kota with sepsis. Patients excluded from the study were aged <18 years, patients with hematological malignancy, patients diagnosed with tropical diseases such as malaria, dengue, Leptospira, and *Rickettsiae*, systemic acute or chronic inflammatory or autoimmune or connective tissue diseases or myocardial infarction, patients receiving

[1]Senior Professor; [2–5]Junior Resident, Department of general medicine, Government Medical College, Kota, Rajasthan, India; *Corresponding Author

How to cite this article: Sharma D, Joseph S, Fageria N, *et al.* The Role of Absolute Eosinophil Count as a Diagnostic and Prognostic Marker for Sepsis and Its Relation with Sequential Organ Failure Assessment/Quick Sequential Organ Failure Assessment Score. J Assoc Physicians India 2023;71(12):18–23.

Table 1: AEC and SOFA scores of ICU patients on days 1, 3, and 7

AEC D1	*AEC D3*	*AEC D7*	*SOFA D1*	*SOFA D3*	*SOFA D3*
40	42	55	8	6	5
55	53	56	0	0	0
33	30	15	14	17	19
40	39	30	10	14	17
50	55	67	4	1	0
75	77	76	3	2	1
25	48	78	9	6	3
31	52	79	8	5	2
45	60	63	2	1	0
48	65	67	2	1	0
10	10	15	12	16	20
90	95	94	1	0	0
15	10	10	10	15	18
49	51	65	2	0	0
48	80	82	1	0	0
15	13	9	19	21	24
70	75	80	0	0	0
30	30	29	10	12	17
19	15	16	15	20	21
70	90	92	0	0	0
13	13	10	12	18	24
75	75	79	2	0	0
69	70	75	3	1	0
74	80	80	0	0	0
65	70	71	1	1	0
30	20	10	11	15	20
48	28	10	15	18	21
49	65	70	3	0	0
18	11	11	19	21	24
92	95	100	1	0	0
35	60	78	12	5	1
20	15	11	19	21	24
70	90	92	0	0	0
28	18	12	11	15	20
100	98	100	0	0	0
40	35	32	11	16	19
45	55	60	7	3	3
70	75	78	1	0	0
25	18	17	19	21	24
38	30	27	20	21	24
49	49	48	10	10	10
66	71	73	1	1	0
19	12	12	19	21	24
51	55	54	0	0	0
20	15	11	19	21	24
88	87	85	1	0	0
33	20	20	6	12	18
34	59	79	12	5	1
20	13	12	19	21	24
30	16	12	19	21	24

corticosteroids, patient refusing to give informed consent.

Absolute eosinophil count (AEC) and SOFA/qSOFA score was assessed in all patients at the time of admission, 3rd day, and 7th day of admission then data were analyzed statistically (Tables 1 and 2). Statistical Software for Social Sciences was used to conduct the statistical analysis. Data on categorical factors of patients, such as age, gender, and so on, were expressed as frequencies and percentages. After validating the normality of the data with the Kolmogorov–Smirnov test, the data is displayed as mean standard deviation. The Chi-squared test was used to compare categorical variables between the clinical outcomes. Statistical significance was defined as a *p*-value of < 0.05.

Observations and Results

The maximum number of cases in our study belonged to the age group 45–55 years (25%). The mean age of the cases was 51.72 ± 18.75 years. Maximum number of controls in our study belonged to the age group >65 (23%). The mean age of the control was 48.42 ± 16 years (Table 3 and Fig. 1).

In our study population, 54% of cases were males and 46% were females, while 53% of controls were males and 47% were females.

In our study, the mortality rate was 31 and 69% of patients survived.

In our control group, the mortality rate was 7 and 93% of patients survived.

Around 50% of our study group were intensive care unit (ICU) patients, 30% were from emergency medicine wards and 20% were from general wards (Fig. 2).

In our study group, 70% of sepsis cases were due to pneumonia, 21% were due to urinary tract infection, 5% were due to cellulitis, 2% was due to liver abscess, 1% was due to meningitis, and the remaining 1% was due to surgical site infection (Fig. 3).

It is found that in 67 out of 100 patients with sepsis (67%), absolute eosinophil count was <50, and 33 out of 100 sepsis patients (33%) absolute eosinophil count was >50.4 out of 100 controls (4%), absolute eosinophil count was <50, and 96 out of 100 controls (96%) absolute eosinophil count was >50 (Table 3 and Fig. 1).

The mean AEC on admission day in sepsis patients was 49.58 ± 20.62. The mean AEC on admission day among controls was 89.95 ± 20.62 (Table 4).

In our study, it was found that among survivors 56.52% of patients had 1st day AEC <50, while 43.47% of patients had it >50. Among 90% of expired had 1st day AEC <50, while only 10% of expired had it >50 (Table 5 and Fig. 4).

Our study found that among survivors 7.24% of patients had 3rd day AEC <50, while 92.75% of survivors had it >50. Among 97% of expired had 3rd day AEC <50, while only 3% of expired it had >50 (Table 6 and Fig. 5).

In our study, it was found that among survivors 2.8% of survivors had 7th day AEC <50, while 97.1% of survivors had it >50. Among expired 97% had 7th day AEC <50, while only 3% of expired had it >50 (Table 7 and Fig. 6).

The mean AEC on admission day among survivors was 56.44 ± 18.55, whereas the mean AEC among nonsurvivors was 34.29 ± 16.56.

The mean AEC on day 3 among survivors was 71.02 ± 15.20, whereas the mean AEC among nonsurvivors was 28.32 ± 16.69.

The mean AEC on day 7 among survivors was 75.57 ± 13.29, whereas the mean AEC among nonsurvivors was 23.77 ± 16.15.

When day 1 AEC is plotted on the X-axis and day 1 SOFA score is plotted on the Y-axis, a statistically significant and strong inverse

Table 2: AEC and qSOFA scores of non-ICU patients on days 1, 3, and 7

AEC D1	*AEC D3*	*AEC D7*	*qSOFA D1*	*qSOFA D3*	*qSOFA D7*
49	89	89	1	1	1
48	79	85	2	1	1
45	79	80	0	0	0
80	85	86	1	0	0
50	55	70	3	2	0
80	88	90	0	0	0
55	45	40	1	3	3
46	81	81	0	0	0
50	69	82	2	1	0
45	44	30	3	3	3
80	80	80	0	0	0
42	60	62	1	0	0
30	78	85	1	0	0
48	70	75	2	1	0
38	70	75	1	0	0
49	66	66	0	0	0
48	40	39	2	3	3
47	71	75	0	0	0
80	80	80	0	0	0
50	40	24	3	3	3
45	88	88	0	0	0
100	100	101	0	0	0
85	85	87	1	0	0
47	37	30	2	2	3
48	78	80	0	0	0
40	70	73	0	0	0
35	35	35	0	0	0
46	80	79	0	0	0
67	68	68	1	0	0
49	67	66	0	0	0
40	50	61	1	0	0
70	72	73	0	1	1
43	56	74	2	1	0
38	36	35	2	3	3
48	81	80	0	0	0
49	55	60	1	0	0
79	80	80	0	0	0
39	56	55	1	2	0
40	61	65	1	0	0
46	70	71	1	0	0
51	37	32	0	3	3
65	66	66	0	0	0
39	77	78	2	1	0
87	85	84	3	3	3
47	91	90	0	0	0
35	35	35	2	0	0
49	45	44	2	3	3
68	70	71	1	0	0
35	80	89	2	3	1
90	100	101	3	2	1

Table 3: Distribution of study group according to age

Age group	*Case*	*Control*	*p-value*
18–25	8	9	
25–35	15	15	
35–45	19	20	
45–55	25	22	
55–65	9	11	
>65	24	23	
Total	100	100	**0.9999**

Table 4: Admission day AEC in the study population

Day-1 AEC	*Case*	*Control*	*p-value*
<50	67	4	**0.0001**
>50	33	96	**0.0001**

correlation is obtained with a correlation coefficient of −0.79 (Fig. 7).

When day 3 AEC is plotted on the X-axis and day 3 SOFA score is plotted on the Y-axis, a statistically significant and very strong inverse correlation is obtained with a correlation coefficient of −0.9 (Fig. 8).

When day 7 AEC is plotted on the X-axis and day 7 SOFA score is plotted on the Y-axis, a statistically significant and very strong inverse correlation is obtained with a correlation coefficient of −0.94 (Fig. 9).

Similarly, we assessed the relation between AEC and qSOFA scores on the 1st, 3rd, and 7th day and obtained a statistically significant and inverse correlation with correlation coefficients −0.37, −0.44, and −0.60, respectively.

Discussion

The mean age of the cases in our study was 51.72 ± 18.75 years, with the greatest number of cases falling between the ages of 45 and 55.

Similarly, the average age of the study group in Tinoco-Sánchez et al.'s paper "usefulness of eosinopenia as a prognostic marker of severity in sepsis" was 51 years.[7]

In contrast, in a study conducted in India by Joy et al., the mean age of the population was 61 ± 18.15 years,[8] this is because most of the patients were above the age of 60 in their study.

In our study percentage of males was 54% and females was 46%.

Similarly in the study "eosinophil count and neutrophil–lymphocyte count ratio as prognostic markers in patients with bacteremia" conducted by Terradas et al.[9] percentage of males was 56% and females was 44%.[10]

In our study mortality was 31% and the survival rate was 69%. In our study, maximum mortality was seen in patients with age more than 65 (71%). The elderly group was the most affected. The average age of the survivors was 46.50 ± 15.87, while the average age group of patients who died was 63.32 ± 19.96.

In our investigation, the death rate appears to be high. This could be owing to the lack of a dedicated infectious disease unit, limited healthcare resources, or the delayed presentation of critically ill patients.

In our study, we discovered that absolute eosinophil count was <50 in 67% of patients with sepsis and >50 in 33% of patients with sepsis.

Around 4% of controls had absolute eosinophil count <50 and 96% of controls (96%) had absolute eosinophil count >50.

In our study mean, AEC on admission day in sepsis patients was 49.58 ± 20.62. The mean AEC on admission day among controls was 89.95 ± 20.62.

The mean AEC on admission day among survivors was 56.44 ± 18.55, whereas the mean AEC among nonsurvivors was 34.29 ± 16.56. The mean AEC on day 3 among survivors was 71.02 ± 15.20, whereas the mean AEC among

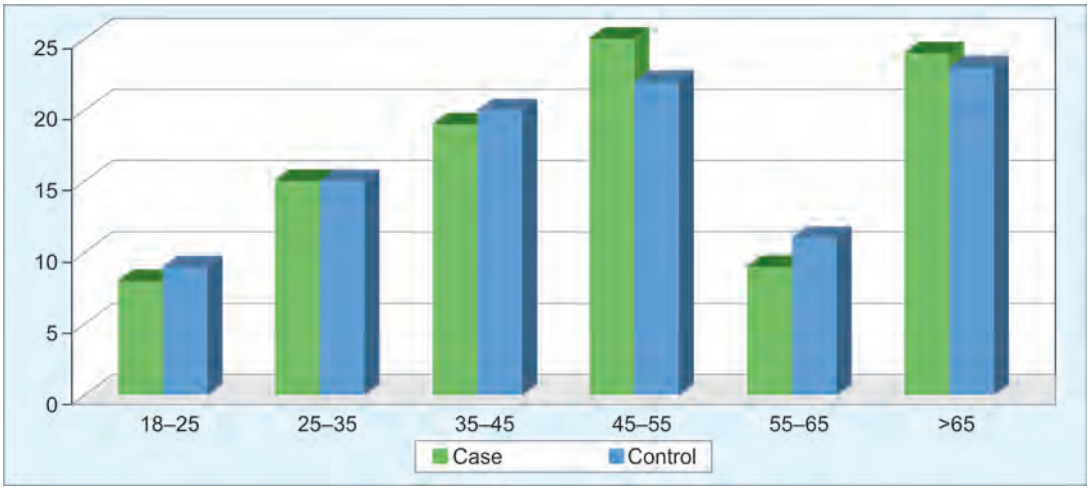


Fig. 1: Distribution of study group according to the age

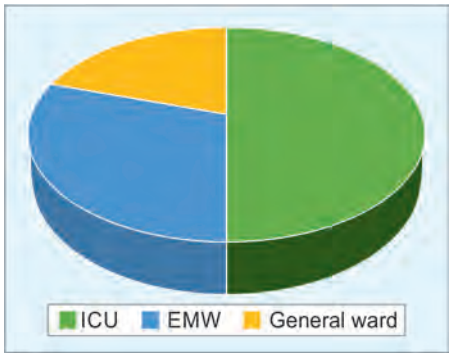


Fig. 2: Breakup of patients in EMW, ICU, and general ward

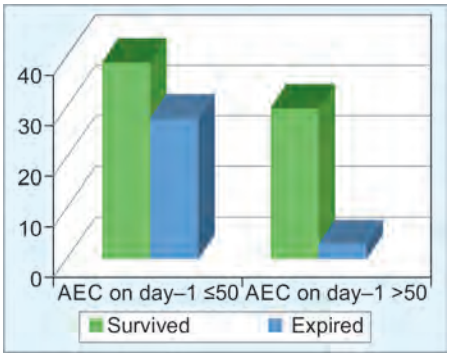


Fig. 4: Association between AEC on day 1 and mortality

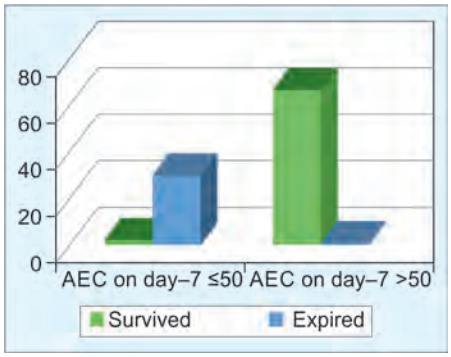


Fig. 6: Association between AEC on day 7 and mortality

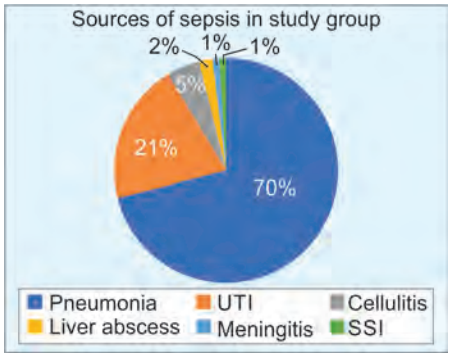


Fig. 3: Sources of sepsis in the study group

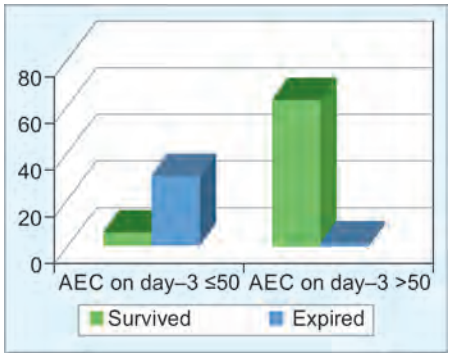


Fig. 5: Association between AEC on day 3 and mortality

Table 5: Association between AEC on day 1 and mortality

AEC D1	*Survived*	*Expired*	*Total*	*% survived*	*% expired*	*Check*	*p-value*
≤50	39	28	67	56.52	90	11.05	**0.0009**
>50	30	3	33	43.47	10		
Total	69	31	100	100	100		

nonsurvivors was 28.32 ± 16.69. The mean AEC on day 7 among survivors was 75.57 ± 13.29, whereas the mean AEC among nonsurvivors was 23.77 ± 16.15.

This shows that AEC has a strong correlation with mortality in sepsis patients, as the disease process worsens AEC decreases and the severity of the patient increases.

Similarly, in a study conducted by Wibrow et al., eosinopenia, or an undetectable eosinophil count of <10/mm^3, was more common in cases than controls (46.5 vs 21.5%, respectively). Eosinopenia has a high specificity (79%) for predicting bloodstream infection in adults, but a moderate sensitivity (47%).[11]

In Joy et al. study mean value of AEC on day 1 was 160 cells/mm^3, a slightly higher side when compared to our study.

Ahmed et al. conducted a study in which the mean eosinophil count was 250 ± 170 cells/mm^3 from the EONS group and for the nonconfirmed EONS group, it was 670 ± 470 cells/mm^3[12] slightly on the higher side as compared to our study.

Abidi et al.[13] and Shaaban et al. found comparable results, but the mean value of eosinophil count was lower in all groups compared to our study. In their tests, they found very low eosinophil levels, even zero/mm^3.

In contrast to our study, studies of Smithson et al.[14] and Setterberg et al.[15] there was no link discovered between eosinopenia and infection. The most

Table 6: Association between AEC on day 3 and mortality

AEC D3	*Survived*	*Expired*	*Total*	*% survived*	*% expired*	*Check*	*p-value*
≤50	5	30	35	7.24	97	75.36	**0.0001**
>50	64	1	65	92.75	3		
Total	69	31	100	100	100		

Table 7: Association between AEC on day 7 and mortality

AEC D7	*Survived*	*Expired*	*Total*	*% survived*	*% expired*	*Check*	*p-value*
≤50	2	30	32	2.8	97	86.62	**0.0001**
>50	67	1	68	97.10	3		
Total	69	31	100	100	100		

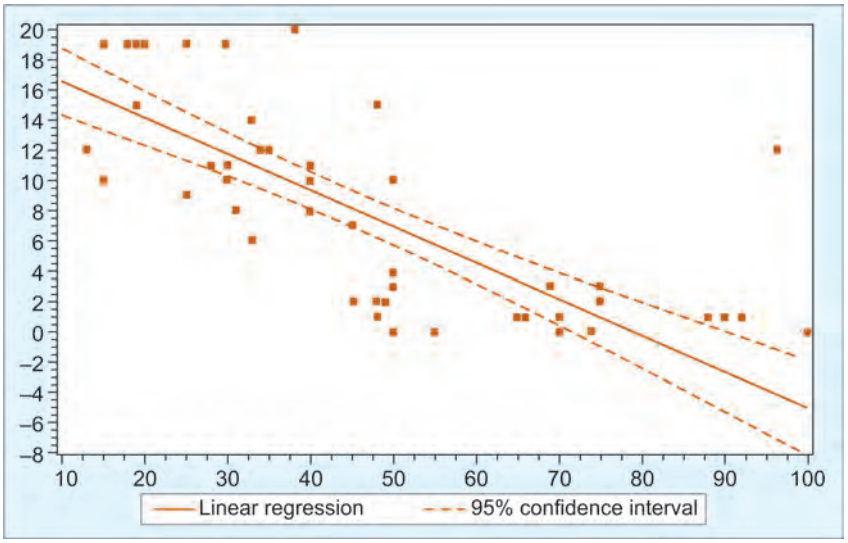


Fig. 7: Correlation between AEC day 1st and SOFA score day 1

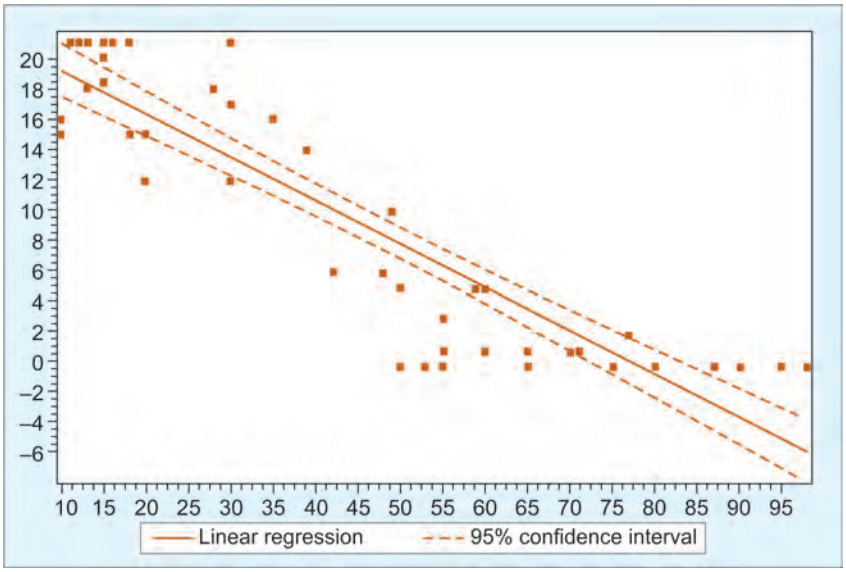


Fig. 8: Correlation between AEC day 3rd and SOFA day 3

likely explanation for this was that the retrospective nature of their study resulted in methodological limitations, such as some data not being available for all patients and they did not describe how the infection was defined and confirmed, which could lead to the exclusion of sepsis patients.

Eosinopenia in sepsis occurs due to immune dysregulation in sepsis leading to reduced activation of eosinophils[16] and due to reduced production of IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor causing a relative eosinopenia. Secondly due to the rapid sequestration of eosinophils into the inflammatory site.[6] In addition, it occurs also due to glucocorticoids and epinephrine released during inflammatory stress.[17]

Our study assessed the correlation between AEC and SOFA scores in sepsis patients on day 1st, 3rd, and 7th and found that AEC and SOFA score exhibits a statistically significant and inverse correlation with correlation coefficients −0.79, −0.9, and −0.94, respectively.

Wilson et al.'s work "Low Absolute Eosinophil Count Predicts In-Hospital Mortality in Cirrhosis with Systemic Inflammatory Response Syndrome" supports our findings.

They assessed the correlation of AEC with mortality and found the following (hazard ratio: 0.993, 95% confidence interval (CI), correlation coefficient 0.987, $p = 0.016$). The correlation coefficient of their study matches that of the AEC and SOFA scores on the 3rd day. Our study differs from their study in terms of cut-off AEC they took <198.5 whereas we took 50. Also, they took cirrhotic patients with SIRS as cases whereas we took sepsis patients.[18]

Another study done by Laimoud and Alanazi found that an initial SOFA score ≥13 measured upon ICU admission had 85% sensitivity and 73.9% specificity for predicting hospital mortality. (AUROC curve = 0.862, 95% CI: 0.791–0.932;) with (81% positive predictive calue, 79.1% negative predictive value, *p*-value < 0.0001).[19] This study matches with our study in terms of day 1 AEC and SOFA score, as day 1 AEC decreases SOFA score increases and it can predict mortality.

Similarly, we assessed the relation between AEC and qSOFA scores on the 1st, 3rd, and 7th day and obtained a statistically significant and inverse correlation with correlation coefficients −0.37, −0.44, and −0.60, respectively.

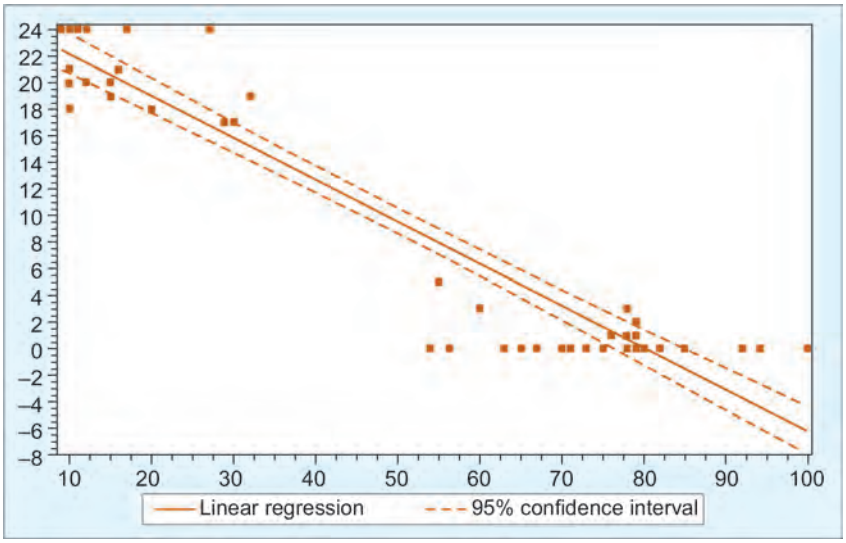


Fig. 9: Correlation between AEC day 7th and SOFA day 7

Conclusion

Absolute eosinophil count is a quick, simple, cost-effective, and easily obtainable marker that may be helpful in diagnosis as well as in predicting the prognosis of sepsis as evidenced by its linear inverse correlation with SOFA/qSOFA score. Though more studies are needed to validate our result, our study supports the routine calculation of AEC in sepsis patients.

References

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315(8): 801–810.
2. Harrison's Principles of Internal Medicine. 20th ed. New York: McGraw-Hill. Chapter 297, pp. 2044–2052.
3. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22(7):707–710.
4. Minne L, Abu-Hanna A, de Jonge E. Evaluation of SOFA-based models for predicting mortality in the ICU: a systematic review. Crit Care 2008;12(6):R161.
5. Zappert J. Ueber das Vorkommen der Eosinophilen Zellen in menschlichen Blute. Z Klin Med 1893;23: 227–308.
6. Bass DA, Gonwa TA, Szejda P, et al. Eosinopenia of acute infection: production of eosinopenia by chemotactic factors of acute inflammation. J Clin Invest 1980;65(6):1265–1271.
7. Tinoco-Sánchez M, Suárez-Cuenca JA, Rubio-Guerra AF. Usefulness of eosinopenia as prognostic marker of severity in sepsis. Med Int Mex 2017;33(5):572–579.
8. Joy AS, Murali AB, Joshi MA, et al. Absolute eosinophil count as a diagnostic and prognostic marker compared to C- reactive protein and procalcitonin in patients with sepsis. CEGH 2020;8(2):632–636.
9. Terradas R, Grau S, Blanch J, et al. Eosinophil count and neutrophil-lymphocyte count ratio as prognostic markers in patients with bacteremia: a retrospective cohort study. PLoS One. 2012;7(8):e42860.
10. Zhou T, Zheng N, Li X, et al. Prognostic value of neutrophil-lymphocyte count ratio (NLCR) among adult ICU patients in comparison to APACHE II score and conventional inflammatory markers: a multi center retrospective cohort study. BMC Emerg Med 2021;21(1):24.
11. Wibrow BA, Ho KM, Flexman JP, et al. Eosinopenia as a diagnostic marker of bloodstream infection in hospitalised paediatric and adult patients: a case-control study. Anaesth Intensive Care 2011;39(2): 224–230.
12. Abdelmoktader A, Hussein S, Ali D, et al. Diagnostic value of eosinopenia and neutrophil to lymphocyte ratio in early onset neonatal sepsis. Fayoum Univ Med J 2020;7(1): 161–171.
13. Abidi K, Khoudri I, Belayachi J et al. Eosinopenia is a reliable marker of sepsis on admission to medical intensive care units. Crit Care 12, R59 (2008).
14. Smithson A, Perelló R, Nicolas JM. Is eosinopenia a reliable marker of sepsis? Crit Care 2009;13(3):409.
15. Setterberg MJ, Newman W, Potti A, et al. Utility of eosinophil count as predictor of bacteremia. Clin Infect Dis 2004;38(3):460–461.
16. Al Duhailib Z, Farooqi M, Piticaru J, et al. The role of eosinophils in sepsis and acute respiratory distress syndrome: a scoping review. Can J Anaesth 2021;68(5):715–726.
17. Savitskiy A, Rudnov V, Bagin V. Eosinopenia as a marker of sepsis and mortality in critically ill patients. Crit Care 2015;19(Suppl 1):P47.
18. Wilson V, Kantan Velayudhan K, Rao H, et al. Low absolute eosinophil count predicts in-hospital mortality in cirrhosis with systemic inflammatory response syndrome. Cureus 2021;13(1):e12643.
19. Laimoud M, Alanazi M. The validity of SOFA score to predict mortality in adult patients with cardiogenic shock on venoarterial extracorporeal membrane oxygenation. Crit Care Res Pract 2020;2020:3129864.

ORIGINAL ARTICLE

Clinical Profile and Outcome of Critically-ill Hospitalized COVID-19 Patients Aged 18–50 Years: A Limited Resource Setting Perspective

Minal Shastri[1], Raj Vekaria[2], Darshankumar Manubhai Raval[3], Shashwat Mallik[4*], Shahin Khan[5]

Received: 21 April 2022; *Revised:* 21 July 2023; *Accepted:* 22 July 2023

Abstract

Objectives: The coronavirus disease of 2019 (COVID-19) pandemic started by affecting the older age groups with comorbidities but gradually advanced to severely affect even young adults. This study attempts to clinically evaluate critically ill young and middle-aged adults hospitalized with COVID-19 and study the association of risk factors and the markers of inflammation and coagulation with their outcome.

Materials and methods: A prospective observational study on 146 patients was conducted in a tertiary care hospital in Western India. History taking, clinical examination, laboratory investigations, and chest X-rays were done for all patients, and investigations were repeated after 3 days. Treatment, including ventilation, was given according to standard guidelines.

Results: Difficulty in breathing was the most common chief complaint, and the majority of patients had a normal body temperature on admission. Involvement of >2 lung zones on chest X-ray, a high neutrophil to lymphocyte (N/L) ratio, the presence of complications, raised D-dimer and serum ferritin, and invasive ventilation were all associated with higher mortality. While the presence of a single comorbidity did not affect the outcome, a combination of multiple comorbidities increased the mortality.

Conclusion: The presence of multiple comorbidities and complications along with radiological abnormalities and raised D-dimer and serum ferritin are associated with critically ill COVID-19 patients and may indicate a higher risk of mortality. Administration of remdesivir has no significant influence on the outcome, but tocilizumab decreases the mortality. The inflammatory markers scoring system has utility in the prognosis of patients, especially in limited-resource settings.

Journal of the Association of Physicians of India (2023): 10.59556/japi.71.0354

Introduction

After first being reported from Wuhan city in China, the continued spread and resulting deaths due to the novel coronavirus disease of 2019 (COVID-19) led the World Health Organization (WHO) to declare a pandemic on 12th March 2020.[1] While the infection can occur at any age during the pandemic's initial phase, it mostly affected the older age group due to higher incidences of comorbid conditions such as obesity, diabetes mellitus (DM), hypertension (HTN), and cardiovascular diseases in them.[2] But >20% of total cases are now contributed by people below 30 years of age. The common presenting symptoms of patients can range from fever, dry cough, chest pain, dyspnea, fatigue, and generalized weakness.[3] Complications such as acute respiratory distress syndrome (ARDS), shock, and multi-organ failure can also develop.[4,5]

The inflammatory process can induce an unusual immune response by decreasing the lymphocyte count while increasing neutrophil production, which results in an increased neutrophil to lymphocyte (N/L) ratio in patients with severe clinical presentation as compared to mildly sick patients.[6,7] A high level of proinflammatory cytokines and D-dimer is also associated with increased tissue damage.[8,9] The current treatment modalities for COVID-19 include antivirals like remdesivir, which has controversial opinions about its efficacy. However, an interleukin-6 (IL-6) receptor antagonist, tocilizumab, has shown a slight but promising reduction in mortality. Systemic corticosteroids, though widely used, have predisposed patients to secondary infections.[10]

We found no prospective studies on young adults who were critically ill with COVID-19 infections. This study has thus attempted to clinically evaluate critically ill young and middle-aged adults hospitalized with COVID-19 pneumonia and correlate the presence of risk factors, markers of inflammation, and coagulation with the final outcome.

Materials and Methods

This was a prospective observational study over a duration of 1 year (March 2020-March 2021) carried out in SSG Hospital, Vadodara, after obtaining prior approval from the Institutional Ethics Committee for Biomedical and Health Research (IECBHR/180-2020). Out of the total patients admitted to the COVID-19 intensive care unit (ICU) at our tertiary care hospital during the study period, 146 patients who fulfilled the inclusion criteria were selected for the study. The inclusion criteria were critically ill young and middle-aged adults of 18–50 years hospitalized for COVID-19 with oxygen saturation (SpO_2) <90% on room air on admission, positive by reverse transcriptase polymerase chain reaction or rapid antigen test. Stable patients were excluded.

History taking, clinical examination, and investigations were done for all the patients. All patients were followed daily till death or discharge. They were treated according to standard guidelines. Treatment given to the patients, including anticoagulants, steroids, remdesivir, tocilizumab, treatment of comorbidities, and treatment of complications, were analyzed. Clinical data included presenting complaints like fever, cough, generalized weakness, sore throat, diarrhea, headache, loss of taste, loss of smell, loss of appetite, difficulty in breathing, or chest pain. On admission, the vitals, namely SpO_2, respiratory rate, pulse, temperature, and blood pressure (BP), were measured, and a thorough respiratory examination was done. All investigations were repeated on every 3rd day of follow-up, including complete blood count, blood urea, serum creatinine, liver function tests, ferritin, D-dimer, C-reactive protein (CRP), arterial blood gas analysis, chest X-ray (PA view), and electrocardiography which were compared to their normal values. Different modes of

[1]Professor; [2,3]Resident Doctor; [4,5]Undergraduate, Department of Medicine, Government Medical College, Baroda, Gujarat, India; *Corresponding Author

How to cite this article: Shastri M, Vekaria R, Raval DM, *et al.* Clinical Profile and Outcome of Critically-ill Hospitalized COVID-19 Patients Aged 18–50 Years: A Limited Resource Setting Perspective. J Assoc Physicians India 2023;71(12):24–27.

oxygen therapy given to the patients were assessed with daily follow-ups. The fraction of inspired oxygen (FiO_2) was calculated using the formula FiO_2 = 20% + (4 × oxygen liter flow). Patients with nasal cannulas were placed on 1–6 L, simple oxygen masks were placed on 5–12 L, nonrebreather masks (NRBM) were placed on 8–15 L, and those on bilevel positive airway pressure (BiPAP) and invasive ventilation were placed on 15 L on the oxygen flow meter.[11,12] We have modified the version of the scoring system of Shastri et al.'s study by adding D-dimer and serum glutamic pyruvic transaminase (SGPT) and removing IL-6 to find out the association of the score with the outcome.[10]

Parameter	*Score 0*	*Score 1*
N/L ratio	1–3	>3
CRP	≤5 mg/dL	>5 mg/dL
Serum ferritin	≤300 µg/L	>300 µg/L
Lactate dehydrogenase (LDH)	≤460 units/L	>460 units/L
SGPT	≤50 units/L	>50 units/L
D-dimer	≤500 ng/mL	>500 ng/mL

The data were entered into an Excel sheet and analyzed by Epi Info software. Frequency, percentage, and the chi-square test were used to derive conclusions for qualitative data, while mean, standard deviation, and the independent *t*-test were used to do the same for quantitative data. A *p*-value of <0.05 was considered significant.

Results

Out of the total 146 patients, 10 (6.85%) were between 18 and 25 years, 29 (19.86%) were in the 26–35 years age group, and 107 (73.29%) were in the age group of 36–50 years. A total of 102 (69.86%) patients were male, while 44 (30.14%) were female. The majority of patients (91.09%) presented with the complaint of difficulty in breathing. 41.1% of the patients had no history of fever, while 45.2% had no complaint of cough (Table 1). A total of 48 (32.87%) patients didn't have any comorbidities while 69 (47.26%) had DM, 75 (51.36%) had HTN, 69 (47.26%) had obesity, six (4.11%) had chronic kidney disease, two (1.37%) were pregnant or postpartum, two (1.37%) had asthma, nine (6.16%) had ischemic heart disease, four (2.74%) had hypothyroidism, and 12 (8.22%) had other comorbidities like sickle cell anemia, myasthenia gravis, obesity, tuberculosis or human immunodeficiency virus.

More than half of the patients (56.85%) required invasive ventilation, 61 (41.78%) required nasal O_2, 84 (57.53%) were on NRBM, 118 (80.8%) were on BiPAP while 19 (13.01%) didn't require either BiPAP or invasive ventilation. All the patients were treated with anticoagulants and steroids. A total of 126 (86.30%) were given injections of remdesivir and 21 (14.38%) were given injections of tocilizumab. The majority of patients (98.63%) had a normal body temperature on admission, while two (1.37%) had decreased body temperature. Around 91 (62.33%) presented with a pulse rate >100, 54 had a normal pulse rate, and one patient had a nonrecordable pulse. Three patients presented with a nonrecordable BP, while 15 (10.27%) had a systolic BP >140 mm Hg, and one patient had a diastolic BP <60 mm Hg. A total of 120 (82.19%) patients presented with a respiratory rate ≥24, while 26 (17.81%) presented with a respiratory rate of <24 per minute. The baseline investigations were compared with the follow-up investigations, and the difference was noted (Table 2).

Out of the total 146 patients, there were 90 (61.64%) deaths, and 56 (38.36%) were discharged as per discharge criteria. There was a statistically significant difference in the average duration of hospital stay between discharged patients (18.5 ± 5.27 days) and the patients who died (6.02 ± 4.12 days) with a *p*-value of <0.0001. Out of the 126 patients given remdesivir, 54 were discharged, while 72 died ($p = 0.03$). Out of the 21 patients given tocilizumab, 17 were discharged, while four died ($p < 0.001$). Among patients having ≤2 zones of lung involvement on chest X-rays, 18 (56.25%) were discharged, and 14 (43.75%) died ($p > 0.05$). Among patients having 3–4 zones of lung involvement, 22 (31.88%) were discharged, and 47 (68.12%) died ($p < 0.0001$). Among those having >4 zones of lung involvement, 16 (35.56%) were discharged, and 29 (64.44%) died ($p < 0.05$).

On analyzing the complications, 126 (86.30%) patients had ARDS, 60 (41.10%) had septicemia/septic shock, 26 (17.81%) had electrolyte disturbances, 24 (16.44%) had acute kidney injury (AKI), eight (5.48%) had anemia, seven (4.79%) had heart failure, five (3.42%) had diabetic ketoacidosis, and three (2.05%) had a pulmonary embolism. The outcome of different complications was analyzed (Table 3). Among patients with N/L ratio ≤3.5, 24 were discharged and 24 died ($p = 0.8383$). But among those with an N/L ratio >3.5, 32 were discharged, while 66 died ($p < 0.0001$). Among patients having SpO_2/FiO_2 ratio >300, 33 (49.25%) were discharged, and 34 (50.74%) died. Among those having a SpO_2/FiO_2 ratio <300, 23 (29.11%) were discharged, and 56 (70.88%) died ($p = 0.012$). 81 out of 118 patients (68.6%) on BiPAP died, while all 83 patients (100%) put on invasive ventilation died. The presence of individual comorbidities had no significant association with the final outcome. However, the presence

Table 1: Chief complaints of patients

Sr. No.	*Complaint*	*Frequency (n = 146)*
1	Difficulty in breathing	133 (91.09%)
2	Fever	86 (58.90%)
3	Cough	80 (54.79%)
4	Generalized weakness	44 (30.14%)
5	Aches and pain	22 (15.07%)
6	Loss of appetite	16 (10.96%)
7	Diarrhea	15 (10.27%)
8	Headache	15 (10.27%)
9	Sore throat	8 (5.48%)
10	Loss of taste and smell	8 (5.48%)
11	Chest pain	3 (2.05%)

Table 2: Mean values of laboratory investigations

Sr. No.	*Investigation*	*Baseline*	*Follow-up*	*p-value*
1	Hemoglobin (Hb)	11.99 ± 2.18	11.84 ± 2.30	0.4411
2	N/L ratio	6.17 ± 4.36	7.08 ± 4.85	0.08
3	Platelet count (lakhs/mm^3)	2.33 ± 1.02	2.70 ± 1.29	0.006
4	Urea (mg/dL)	54.50 ± 32.73	60.70 ± 34.43	0.02
5	Creatinine (mg/dL)	1.51 ± 1.74	1.46 ± 1.69	0.57
6	SGPT	52.94 ± 50.68	51.57 ± 37.75	0.78
7	Potassium	4.04 ± 0.67	4.16 ± 0.76	0.14
8	Sodium	137.56 ± 5.31	138.22 ± 6.73	0.33
9	Random blood sugar	195.21 ± 79.52	200.99 ± 81.37	0.47
10	D-dimer	2836.08 ± 3731.92	5211.38 ± 5874.45	0.0001
11	Serum ferritin	557.83 ± 417.87	774.68 ± 1204.38	0.11
12	CRP	93.77 ± 88.89	68.06 ± 77.91	0.02
13	LDH	1150.75 ± 784.43	1189.77 ± 678.60	0.71

Table 3: Complications and final outcome

Sr. No.	*Complications*	*Discharged*	*Death*	*p-value*
1	ARDS	36 (28.57%)	90 (71.43%)	<0.0001
2	Septicemia/septic shock	17 (28.33%)	43 (71.66%)	<0.0001
3	AKI	3 (12.5%)	21 (87.5%)	<0.0001
4	Severe anemia (Hb <7 gm/dL)	3 (37.5%)	5 (62.5%)	0.6171

Table 4: Comorbidities and final outcome

Sr. No.	*Comorbidities*	*Discharged*	*Death*	*p-value*
1	DM (without HTN and obesity)	6 (60%)	4 (40%)	0.1447
2	HTN (without DM and obesity)	5 (41.66%)	7 (58.33%)	0.8055
3	Obesity (without DM and HTN)	1 (25%)	3 (75%)	0.5775
4	DM + HTN	2 (28.57%)	5 (71.42%)	0.5853
5	DM + obesity	2 (22.22%)	7 (77.77%)	0.3041
6	HTN + obesity	7 (53.84%)	6 (46.15%)	0.2288
7	DM + HTN + obesity	10 (23.25%)	33 (76.74%)	0.0153
8	No comorbidities	22 (45.83%)	26 (54.16%)	0.1934

Table 5: Inflammatory markers and final outcome

Sr. No.	*Inflammatory markers*		*Discharged*	*Death*	*p-value*
1	D-dimer	<2,000	40 (51.28%)	38 (48.71%)	0.0005
		>2,000	16 (23.52%)	52 (76.47%)	
2	Serum ferritin	<500	34 (47.88%)	37 (52.11%)	0.0212
		>500	22 (29.33%)	53 (70.66%)	
3	CRP	<24	13 (48.14%)	14 (51.85%)	0.2464
		>24	43 (36.13%)	76 (63.87%)	
4	LDH	<700	9 (39.13%)	14 (60.87%)	0.8354
		>700	44 (37.93%)	72 (62.07%)	

of DM + HTN + obesity led to a significant increase in mortality (Table 4).

Raised values of D-dimer and serum ferritin showed a significant association with mortality, while raised CRP and LDH had no significant influence on the outcome (Table 5). On counting the score of inflammatory markers by using cutoff values stated in the methodology, it was found that five (29.41%) patients died, and 12 (70.58%) were discharged among those who had a score of ≤3. A total of 85 (65.89%) patients died, and 44 (34.10%) were discharged among those who had a score of >3 with a significant *p*-value of 0.0364.

Discussion

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is among the most virulent pathogens causing severe acute respiratory illness in humans, and since the initial case studies from China, considerable differences in demographic and clinical patterns have been observed between countries across the world. Variations over time have also been noted as different genetic variants of the virus predominated during different times.

The demographic distribution of our study population showed that the majority of patients were in the 36–50 years age group with a male preponderance. This is similar to a study by Jamil et al., while Soni et al. had the majority of their patients in the 26–35 years age group, though the male preponderance was still noted.[13,14] The most common chief complaint was difficulty in breathing, whereas 41.1% had no history of fever and 45.2% had no history of cough. These findings are comparable to Jamil et al. but differ from a study by Chen et al. in which 94.1% of patients had a fever, 66.75% of patients had a cough, and only 33.5% had dyspnea.[13,15] In our study, 32.87% of patients did not have any comorbidities, 47.26% had DM, and 51.36% had HTN, which is similar to Jamil et al. But in comparison, in the study by Soni et al., only 14.9% had DM and 16.6% had HTN, while 70.1% had no comorbidities.[13,14] In our study, more than half of the patients (56.85%) required invasive ventilation, which is comparable to a study by Bahloul et al., in which 40% of patients required it.[16] Around 61.64% of patients died, and 38.36% were discharged in this study, and a similar final outcome was seen in the study by Grasselli et al.[17]

A statistically significant difference in the final outcome with injection tocilizumab (80.95% discharged and 19.04% died) was seen as compared to injection remdesivir (42.86% discharged and 57.14% died). A similar result with tocilizumab therapy was obtained by Somers et al.[18] Patients with an N/L ratio >3.5 on admission had higher mortality, which is in concordance with studies by Ciccullo et al. and Liu et al.[9,19] On comparing the SpO_2/FiO_2 ratio on admission with the final outcome, there was a significant difference between death and discharge in both groups, that is, ratio >300 and <300. A study by Vopelius-Feldt has also used the SpO_2/FiO_2 ratio as a predictor of the outcome in COVID-19 patients.[20] In this study, the presence of multiple comorbidities had a significant influence on the outcome, which is similar to the findings of Ge et al. However, Elezkurtaj et al. reported no such association.[21,22] This study showed an association of elevated levels of D-dimer and serum ferritin with poor outcomes in the patients, which is similar to the results of Stoeckle et al., while in contrast to the findings of Stoeckle et al., raised levels of CRP and LDH showed no significant association.[23]

Limitations

Exclusion of stable patients may have led to selection bias and higher mortality. As this study comprised 146 patients, multi-centric studies on larger populations are warranted to extrapolate our results on the general population. Also, as we know, COVID-19 is an evolving disease with different mutations and variants; we recommend further studies to compare critically ill young and middle-aged adults and their outcomes among different variants of the SARS-CoV-2. Vaccines against COVID-19 were not available to the general population at the time of data collection, and hence, the severity of illness and the outcome may have an association with it, so further studies are required.

Conclusion

The study concluded that difficulty in breathing was the most common chief complaint in critically ill patients aged 18–50 years hospitalized with COVID-19 pneumonia. While the presence of any single comorbidity had no influence on the final outcome, a combination of DM + HTN + obesity significantly increased the mortality.

The administration of tocilizumab resulted in positive outcomes. The involvement of >2 lung zones on chest X-rays and complications like ARDS, septic shock/septicemia, and AKI resulted in a higher mortality rate. An increase in the N/L ratio/D-dimer/serum ferritin was associated with higher mortality; however, a combined score of >3 on the inflammatory markers scoring system is associated with a worse outcome. Hence, the inflammatory markers scoring system can be used in limited-resource settings to determine the prognosis of COVID-19 patients and allocate resources to those who require it the most.

Orcid

Darshankumar Manubhai Raval https://orcid.org/0000-0002-8521-5494
Shashwat Mallik https://orcid.org/0000-0002-6557-6794
Shahin Khan https://orcid.org/0000-0002-4581-787X

References

1. General WHOD-. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [Internet]. World Healthn Organisation. 2020 [cited 2022]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020#:~:text=WHO%20has%20been%20assessing%20this,to%20use%20lightly%20or%20carelessly.2
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497–506.
3. CDC. [Internet]. Demographic Trends of COVID-19 cases and deaths in the US reported to CDC. 2020 [cited 2022]. Available from: https://covid.cdc.gov/covid-data-tracker/#demographics
4. Manubhai Raval DK, Mallik S, Khan S. Omicron - is it really a variant of concern? Int J Sci Res 2022;11(1):15–16.
5. Öztürk R, Taşova Y, Ayaz A. COVID-19: pathogenesis, genetic polymorphism, clinical features and laboratory findings. Turk J Med Sci 2020;50(SI-1):638–657.
6. Jin Y, Yang H, Ji W, et al. Virology, epidemiology, pathogenesis, and control of COVID-19. Viruses 2020;12(4):372.
7. Tufan A, Avanoğlu Güler A, Matucci-Cerinic M. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. Turk J Med Sci 2020;50(SI-1):620–632.
8. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054–1062.
9. Liu Y, Du X, Chen J, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect 2020;81(1):e6–e12.
10. Shastri M, Raval DM, Rathod VM, et al. Adjuvant tocilizumab in the treatment of patients with moderate to severe COVID-19 pneumonia: an observational study. J Assoc Physicians India 2022;70(1):11–12.
11. Fuentes S, Chowdhury YS. Fraction of Inspired Oxygen. 2022 Feb 17. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 32809702.
12. Rizwan A. How to calculate FIO_2 from liters [Internet]. biomadam. 2021 [cited 2022Apr17]. Available from: https://www.biomadam.com/how-to-calculate-fio2-from-liters
13. Jamil M, Bhattacharya PK, Barman B, et al. Clinical and demographic profile of COVID-19 patients: a tertiary level hospital-based study from Northeast India. Cureus 2021;13(10):e18881.
14. Soni SL, Kajal K, Yaddanapudi LN, et al. Demographic & clinical profile of patients with COVID-19 at a tertiary care hospital in north India . Indian J Med Res2021;153(1 & 2):115–125.
15. Chen Y, Zhang K, Zhu G, et al. Clinical characteristics and treatment of critically ill patients with COVID-19 in Hebei. Ann Palliat Med 2020;9(4):2118–2130.
16. Bahloul M, Kharrat S, Chtara K, et al. Clinical characteristics and outcomes of critically ill COVID-19 patients in Sfax, Tunisia. Acute Crit Care 2022;37(1):84–93.
17. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected With SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA 2020;323(16):1574–1581.
18. Somers EC, Eschenauer GA, Troost JP, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. Clin Infect Dis 2021;73(2):e445–e454.
19. Ciccullo A, Borghetti A, Zileri Dal Verme L, et al. Neutrophil-to-lymphocyte ratio and clinical outcome in COVID-19: a report from the Italian front line. Int J Antimicrob Agents 2020;56(2):106017.
20. Vopelius-Feldt JV. Estimated Sp02/Fio2 ratio to predict mortality in patients with suspected COVID-19 in the emergency department: a prospective cohort study. MedRxiv 2022.
21. Ge E, Li Y, Wu S, et al. Association of pre-existing comorbidities with mortality and disease severity among 167,500 individuals with COVID-19 in Canada: a population-based cohort study. PLoS One 2021;16(10):e0258154.
22. Elezkurtaj S, Greuel S, Ihlow J, et al. Causes of death and comorbidities in hospitalized patients with COVID-19. Sci Rep 2021;11(1):4263.
23. Stoeckle K, Witting B, Kapadia S, et al. Elevated inflammatory markers are associated with poor outcomes in COVID-19 patients treated with remdesivir. J Med Virol 2022;94(1):384–387.

ORIGINAL ARTICLE

The Scope of Pre- and Probiotics as an Add-on to Proton-pump Inhibitors in Various Clinical Indications

Sanjay Kalra[1*], Ameya Joshi[2], Mangesh Tiwaskar[3], Navneet Agrawal[4], Shehla Shaikh[5], Birender Singh Bhatia[6], Ashok Kumar Jhingan[7], Pawan Rawal[8], Ashok Kumar Das[9], Saidu Kannu Nishad[10], Hemant Manjrekar[11], Spandan Bhadury[12]

Received: 22 September 2023; *Accepted:* 23 October 2023

Abstract

Objective: To understand the national pattern of proton-pump inhibitor (PPI) prescriptions and to disseminate evidence-based recommendations for using probiotics as an adjunct to PPIs across diverse clinical indications.

Methods: Healthcare professionals' (HCPs) inputs and views were collected through a survey (n = 1,007) and four round table meetings (RTMs, n = 4). A standardized questionnaire focusing on the utilization of PPIs in clinical practice was developed, deliberated upon, and assessed by experts specializing in the treatment of diverse acid-related gastrointestinal (GI) conditions across various geographical regions.

Results: Of the total 1,007 contributors, most (43.40%) opined that 10–30% of their patients were prescribed PPI for a long duration. The majority of contributors commonly prescribed PPIs for the prophylaxis of gastroesophageal reflux disease (GERD)—induced gastritis (70.90%), peptic ulcer disease (58.39%), and various GI conditions. The majority of contributors (91%) agreed or strongly agreed that long-term use of PPIs disturbs the GI flora. Antibiotic-associated diarrhea (AAD) (78.05%) was the most preferred indication for using pre- and probiotics. The duration for co-prescription varied, with a substantial portion advocating for 1–4 weeks (49.65%), while others supported durations of 4–8 weeks or beyond. Around 85% of contributors/HCPs agreed or strongly agreed on prescribing pre- and probiotics as prophylaxis to prevent GI disturbances. The study emphasized the growing trend of patient-centered co-prescription of PPIs and pre-/probiotics, with a majority of contributors favoring this approach.

Conclusion: The results underscore the importance of informed prescribing practices, including the co-prescription of probiotics, to mitigate potential side effects associated with long-term PPI use and optimize patient well-being.

Journal of the Association of Physicians of India (2023): 10.59556/japi.71.0409

Introduction

Proton-pump inhibitors (PPIs) are widely prescribed for various gastrointestinal (GI) conditions, including dyspepsia, gastroesophageal reflux disease (GERD), peptic ulcer disease, and *Helicobacter pylori* infection.[1,2] However, the surge in PPI prescribing trends has raised concerns about their irrational use without valid indications. Despite their symptomatic relief, the potential impact of PPIs on gut microbiota has gained recent attention.

Recent research has shown a significant reduction in gut flora abundance and diversity among PPI users compared to nonusers.[3] Given the pivotal role of gut microbiota in metabolic, physiological, and immune processes, PPI-induced alterations in its composition could have far-reaching effects.[4,5] To address this issue, two strategies emerge—promoting judicious PPI usage and exploring adjuvant therapies to mitigate potential risks.

Probiotics have emerged as a promising adjuvant to PPIs, as they restore gut microbiota balance and improve treatment adherence and quality of life.[6] Through competition with harmful bacteria and metabolite production, probiotics support PPI therapy and counteract drug-induced intestinal dysbiosis.[7] However, the literature is lacking that discusses different aspects of the use of probiotics as an adjunctive therapy to PPI to reduce its side effects. Therefore, this consensus was conducted to comprehend the national pattern regarding PPI prescriptions and to disseminate evidence-based recommendations for the utilization of probiotics as an adjunct to PPIs across diverse clinical indications.

Methods

Inputs and views of healthcare professionals (HCPs) were recorded based on survey (n = 1,007) and round table meetings (RTMs, n = 4). A standard questionnaire about the use of PPIs in clinical practice was prepared, discussed, and evaluated by experts who treat patients with various acid-related GI disorders. To avoid result bias, HCPs were enrolled across all four zones.

The survey included a total of 12 questions. The identified HCPs were sent an introductory e-mail containing a link to the survey and requested voluntary participation. The survey was only available in English and took 5 weeks (from July to August 2023) to complete. The survey results were discussed during the four pan-India RTM meetings conducted in August 2023.

Results

A total of 1,007 HCPs participated in the survey, of which the majority were from the south (n = 322) and west (n = 322) zones, followed by east (n = 184) and north (n = 179) zones of India.

Prescription Pattern of PPIs

Of the total 1,007 HCPs, most (43.40%) opined that 10–30% of their patients were prescribed PPI for 3–6 months; 27.31, 23.44, and 5.86% mentioned that <10, 30–50, and 50–70% of their patients received PPIs for 3–6 months

[1]Consultant, Department of Endocrinology, Bharti Hospital, Karnal, Haryana; [2]Consultant, Department of Endocrinology, Bhakti Vedant Hospital & Personal Clinic; [3]Consultant, Department of Medicine, Shilpa Medical Research Centre, Mumbai, Maharashtra; [4]Consultant, Department of Diabetology, Diabetes Obesity and Thyroid Center, Indore, Madhya Pradesh; [5]Consultant, Department of Endocrinology, Saifee Hospital, Mumbai, Maharashtra; [6]Consultant, Department of Medicine, Bhatia Heart & Diabetes Centre, Chandigarh; [7]Consultant, Department of Endocrinology, BLK Hospital, Delhi; [8]Consultant, Department of Gastroenterology, Artemis Hospital, Gurugram, Haryana; [9]Consultant, Department of Gastroenterology, Mahatma Gandhi Medical & Research College, Pondicherry; [10]Consultant, Department of Diabetology, SSNM Hospital, Chennai, Tamil Nadu; [11]Consultant, Department of Medicine, Deenanath Mangeshkar Hospital and Research Center, Pune, Maharashtra; [12]Consultant, Department of Gastroenterology, North Bengal Hospital, Kolkata, West Bengal, India; *Corresponding Author

How to cite this article: Kalra S, Joshi A, Tiwaskar M, *et al.* The Scope of Pre- and Probiotics as an Add-on to Proton-pump Inhibitors in Various Clinical Indications. J Assoc Physicians India 2023;71(12):28–31.

duration (Table 1). Long-term PPI use is most commonly (70.90%) used for the prophylaxis against GERD-induced gastritis, followed by peptic ulcer disease (58.39%), gastroparesis (46.47%), prophylaxis for nonsteroidal anti-inflammatory drug (NSAID)-induced gastritis (45.40%), and in irritable bowel syndrome (IBS) (41.11%). The majority of contributors/HCPs (91%) agreed or strongly agreed that long-term use of PPIs disturbs the GI flora (Fig. 1). Abnormal bowel habits (63.65%) were the most commonly reported symptoms with long-term use of PPI, followed by bloating (49.65%), micronutrient deficiencies (46.28%), flatulence (44.69%), and abdominal pain and discomfort (41.41%).

Prescription Pattern of Pre- and Probiotics

Antibiotic-associated diarrhea (AAD) (78.05%) was the most preferred indication for using pre- and probiotics, followed by acute infectious diarrhea (62.07%), inflammatory bowel disease (IBD)/IBD-like symptoms (51.64%), diabetes mellitus (28.7%), and hepatic encephalopathy (18.67%) (Table 2). Nearly 55% of contributors/HCPs (midterm PPI use: 33.66% and long-term PPI use: 20.95%) consider that co-prescription of PPI with pre- and probiotics is needed for >3 months to prevent GI disturbances, and 35.35% believe it is needed for >1 month (short-term). A significant proportion of contributors/HCPs (62.66% agreed and 27.01% strongly agreed) believed that co-prescribing pre- and probiotics with a PPI can lead to favorable outcomes and ultimately improve overall quality of life (QoL) (Fig. 1). The majority of contributors/HCPs (35.15%) mentioned that pre- and probiotics should be prescribed for more than the duration of PPI, followed by 28% who mentioned that the duration should be equal. Most contributors/HCPs (49.65%) consider that pre- and probiotics will exert clinical improvement when co-prescribed with PPIs from 1 to 4 weeks. However, 34.96% consider the duration between 4 and 8 weeks for co-prescription will exert clinical improvement. The majority of contributors/HCPs (85%) agreed or strongly agreed on prescribing pre- and probiotics as prophylaxis to prevent GI disturbances (Fig. 1).

The most common suggestive current practice is patient-centric co-prescription of PPI and PPBs (71.30%). Around 22.74% believe they should be co-prescribed in all (universal co-prescription); however, only 6% consider that they should not be co-prescribed (Fig. 2). Most contributors/HCPs mentioned using PPI along with PPBs in patient-centric co-prescription (67.92%) is ideal, followed by universal co-prescription (26.81%) (Fig. 2). Based on the survey results, panelists recommended five commandments summarized in Table 3.

Table 1: Prescription pattern of PPIs

Questions	*Opinion options*	*Response*
Proportion of patients with PPI for more than long-term (3–6 months)	<10%	275 (27.31)
	10–30%	437 (43.40)
	30–50%	236 (23.44)
	50–70%	59 (5.86)
Indications that warrant chronic PPI usage	Prophylactic for GERD-induced gastritis	714 (70.90)
	IBS	417 (41.11)
	Prophylactic for NSAID-induced ulcers	457 (45.40)
	Peptic ulcer disease	588 (58.39)
	Gastroparesis	468 (46.47)
Commonly reported symptoms with long-term PPI use	Abnormal bowel habits	641 (63.65)
	Flatulence	450 (44.69)
	Bloating	500 (49.65)
	Abdominal pain and discomfort	417 (41.41)
	Micronutrient deficiencies, for example, vitamin B_{12}, calcium, magnesium, etc.	466 (46.28)

Data presented as *n* (%); GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton-pump inhibitor

Discussion

There has been a surge in PPI utilization driven by patients' availability of over-the-counter medications and self-administration. Studies in primary care and emergency settings revealed that PPIs are frequently prescribed without evident clinical rationale, encompassing approximately 14.6–54% of instances.[8,9] While the direct individual harm risk associated with PPIs remains minimal, their extensive and prolonged usage can lead to adverse effects, resulting in notable detrimental consequences.

The prescription pattern of PPIs and the potential utilization of probiotics as adjuncts to PPIs in diverse clinical indications represent important considerations in the healthcare system. This discussion aimed to comprehend the national pattern regarding PPI prescriptions and disseminate evidence-based recommendations for probiotic use in India.

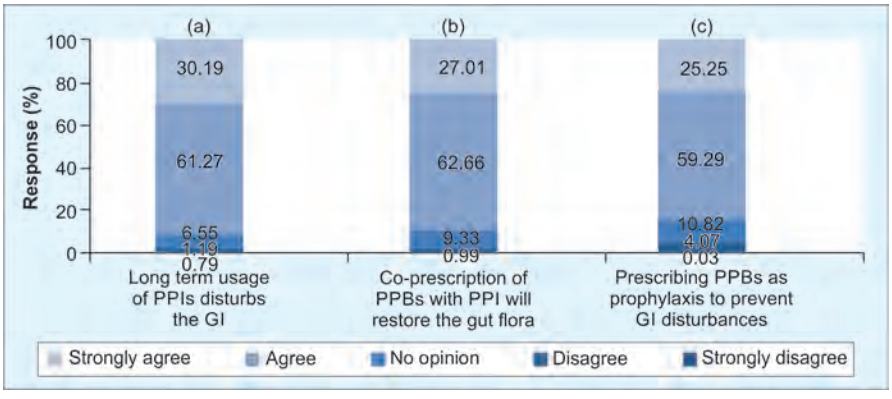


Fig. 1: Summary of prescription pattern; GI, gastrointestinal; PPI, proton-pump inhibitor; PPB, pre- and probiotic.

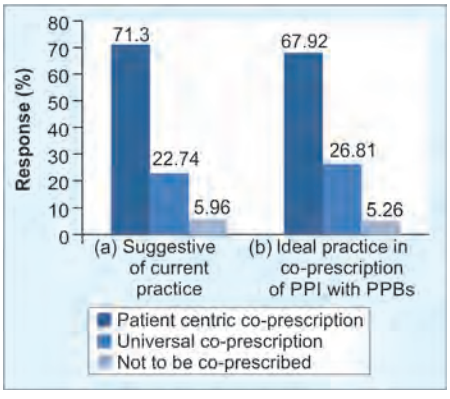


Fig. 2: Summary of opinion on prescription pattern PPI with pre- and probiotics

Table 2: Responses for the questions related to prescription pattern of pre- and probiotics

Questions	*Opinion options*	*Response*
Indications you prefer for using a pre- and probiotic	AAD	786 (78.05)
	Acute infectious diarrhea	625 (62.07)
	IBD/IBD-like symptoms	520 (51.64)
	Diabetes mellitus	289 (28.7)
	Hepatic encephalopathy	188 (18.67)
Preferred duration of co-prescription of pre and probiotics with PPI to prevent GI disturbances	Short-term PPI use (>1 month)	356 (35.35)
	Midterm PPI use (>3 months)	339 (33.66)
	Long-term PPI use (>6 months)	211 (20.95)
	Need more evidence	73 (7.25)
	Should not be added	28 (2.78)
Duration of pre- and probiotic treatment when co-prescribed with PPI	Exactly equal to the duration of PPI	282 (28.00)
	More than the duration of PPI	354 (35.15)
	Less than the duration of PPI	210 (20.85)
	Any other	46 (4.57)
	Need more evidence	115 (11.42)
Clinical improvement observed when pre- and probiotics are co-prescribed in patients with chronic PPI usage	1–4 weeks	500 (49.65)
	4–8 weeks	352 (34.96)
	8–10 weeks	104 (10.33)
	10–12 weeks	35 (3.48)
	>12 weeks	16 (1.59)

Data represented as *n* (%); AAD, antibiotic-associated diarrhea; IBD, irritable bowel disease; PPI, proton-pump inhibitor

Table 3: Five commandments

1	Perform a thorough clinical evaluation before prescribing PPIs (level 1)
2	Prescribe PPIs for a short-term duration (≤8 weeks). If long-term therapy is prescribed, reassess the need for continuation periodically and attempt to taper or discontinue if possible (level 2)
3	Educate patients about the potential side effects associated with long-term PPI use, especially regarding abnormal bowel habits, bloating, micronutrient deficiencies, flatulence, and abdominal pain (level 2)
4	Co-prescribe pre- and probiotics with PPIs when managing patients with AAD, and in patients experiencing abnormal bowel habits, bloating (level 1), micronutrient deficiencies, flatulence, and abdominal pain (level 2)
5	Consider co-prescribing pre- and probiotics for >3 months to achieve favorable outcomes and improve overall QoL (level 1), while monitoring and assessing their effectiveness regularly

PPI, proton-pump inhibitor; QoL, quality of life; level 1: >50% agreed; level 2, 30–50% HCPs agreed

Among the surveyed HCPs, the responses revealed a diverse distribution of PPI prescriptions within the 3–6 months' timeframe. The largest proportion of HCPs (43%) reported prescribing PPIs to 10–30% of their patients for this duration, indicating a common practice. Ideally, the recommended duration of PPI usage primarily ranges from 8 to 16 weeks. However, the definition of long-term PPI use varies, ranging from >2 weeks to >7 years.[10] Overall, the results indicate that chronic PPI use can be particularly beneficial for preventing GERD-induced gastritis and NSAID-induced gastritis and managing peptic ulcer disease. According to a systematic review of global trends, prophylactic prescription of PPIs was notably prominent for NSAIDs, antiplatelet therapy, aspirin, corticosteroids, and chemotherapy, representing the prevailing indication. In addition, dyspepsia and GERD emerged as the second most prevalent reasons for prescription, applicable to both the broader spectrum of users and those newly embarking on treatment regimens.[8] In India, PPIs are primarily used for prophylactic purposes rather than therapeutic ones.

The majority of contributors/HCPs agreed that long-term PPI use disturbs the GI flora. This recognition aligns with the growing concern over the consequences of prolonged PPI administration. Notably, PPI users present an altered and less healthy gut microbiome when compared to nonusers. A striking hallmark of this dysbiosis is the pronounced elevation in *Enterococcus*, *Streptococcus*, *Staphylococcus*, and *Escherichia coli*—bacterial strains linked to various health issues.[5] Abnormal bowel habits (64%) were the most commonly reported symptoms with long-term use of PPI, followed by bloating, micronutrient deficiencies, flatulence, and abdominal pain and discomfort. The high prevalence of abnormal bowel habits and various digestive symptoms associated with long-term PPI use underscores the importance of monitoring and managing these side effects to ensure optimal patient care and treatment outcomes. According to the survey results, AAD (78%) was the most preferred indication for using pre- and probiotics. Studies have shown promising outcomes for using probiotics in preventing AAD.[11,12] Research suggests that incorporating pre- and probiotics alongside antibiotics can help reduce the incidence and severity of diarrhea by promoting beneficial microbial populations and inhibiting the growth of harmful bacteria.[13]

The panel is convinced that sufficient evidence has accumulated to support the concept of "Gut Guardianship," which refers to the practices, behaviors, and activities individuals may adopt or engage in to attain and sustain a healthy gut and gut microbiome. Probiotics, on the other hand, are live microorganisms that confer health benefits when consumed in adequate amounts by positively influencing the gut microbiota composition and function. Integrating probiotics into one's gut guardianship strategy can significantly support gut health, foster a balanced microbiome, and promote overall well-being.[14]

The combination of probiotics with PPIs could potentially offer beneficial strategies. This approach could facilitate probiotic colonization and counteract the microbial perturbation induced by PPIs. A significant proportion of contributors/HCPs believe that co-prescribing pre- and probiotics with a PPI can lead to favorable outcomes and ultimately improve overall QoL. Results indicate a positive outlook on the therapeutic effects of this combination in managing various GI issues and its potential to enhance overall patient well-being. Panelists also recommended considering pre- and probiotics for individuals experiencing GI symptoms.

Furthermore, probiotics can be safely used in various conditions, serving as a co-prescription alongside certain medications, particularly in diabetes, hypertension, and coronary artery disease. Their consideration is even more pronounced for individuals taking PPIs and those with metabolic syndrome. According to survey results, prolonged usage of

PPIs can disrupt the balance of gut microbiota, increasing vulnerability to infections and intestinal diseases. Recent suggestions propose incorporating probiotic supplementation during PPI therapy to enhance its effects and mitigate potential complications. Apart from augmenting the efficacy of PPIs, probiotics have the potential to counteract intestinal dysbiosis and alleviate the side effects associated with prolonged PPI use. Indeed, the study by Belei et al., where they supplemented the probiotic *Lactobacillus reuteri* DSM 17938 along with 12 weeks of PPI treatment for children with GERD, demonstrated a significant difference. While 56.2% of the children not receiving the probiotic experienced intestinal dysbiosis, a mere 6.2% of those who received the probiotic encountered dysbiosis.[7] This underscores the potential of combining a probiotic with PPI therapy to substantially reduce the incidence of dysbiosis.

Understanding the appropriate duration of co-prescribing PPI with pre- and probiotics is crucial for preventing GI disturbances. In the present survey, approximately 55% of contributors/HCPs consider that co-prescription of PPI with pre- and probiotics is needed for >3 months to prevent GI disturbances. This suggests that many practitioners are utilizing this combination therapy to address GI issues and potentially improve gut health in their patients.

The majority of contributors/HCPs (50%) believe that co-prescribing pre- and probiotics with PPIs for 1–4 weeks could lead to clinical improvement. In a study conducted by Kwak et al., 53 patients with chronic hepatic disease were administered *Bifidobacterium bifidum*, *Bifidobacterium lactis*, *Bifidobacterium longum*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, and *Streptococcus thermophilus* over 4 weeks.[15] The study assessed changes in fecal bacterial composition, small intestinal bacterial overgrowth (SIBO), and intestinal permeability. The results indicated that the short-term usage of probiotics effectively alleviated SIBO.[15] Similarly, a pilot study by Khalighi et al. showed that probiotic therapy for SIBO effectively mitigated side effects associated with PPI treatment.[16] PPI use alters the composition of the gut microbiome by changing pH and affecting immune response modulation, potentially leading to SIBO. Therefore, probiotics could help inhibit PPI-induced intestinal dysbiosis and alleviate associated side effects.

Conclusion

The findings indicated that the majority of HCPs commonly prescribed PPIs for the prophylaxis of GERD-induced gastritis, peptic ulcer disease, and various GI conditions. A significant proportion of contributors acknowledged the disruptive impact of long-term PPI use on GI flora. A notable consensus emerged among contributors that co-prescribing pre- and probiotics with PPIs could yield favorable outcomes, thereby enhancing overall QoL. The study emphasized the growing trend of patient-centered co-prescription of PPIs and pre-/probiotics, with a majority of contributors favoring this approach. The results underscore the importance of co-prescription of pre- and probiotics to mitigate potential side effects associated with long-term PPI use and optimize patient well-being. By bridging the gap between research and practice, this study provides valuable insights to guide clinical decision-making and improve patient care.

Funding

This initiative was funded by USV Pvt. Ltd., Mumbai.

Acknowledgments

The medical writing support was provided by Snehal Khanolkar (Sqarona Medical Communications LLP, Pune) and paid by USV Pvt. Ltd.

References

1. Desai A, Anand SS. Clinical practice of prescribing proton pump inhibitors by physicians: an Indian perspective. J Indian Med Assoc 2021;119(6):91–96.
2. Bhatia S, Shukla A, Johnson D, et al. An expert review and recommendations on the rational use of proton pump inhibitors: Indian perspective. J Assoc Physicians India 2019;67(4):88–96.
3. Takagi T, Naito Y, Inoue R, et al. The influence of long-term use of proton pump inhibitors on the gut microbiota: an age-sex-matched case-control study. J Clin Biochem Nutr 2018;62(1):100–105.
4. Freedberg DE, Lebwohl B, Abrams JA. The impact of proton pump inhibitors on the human gastrointestinal microbiome. Clin Lab Med 2014;34(4):771–785.
5. Imhann F, Bonder MJ, Vich Vila A, et al. Proton pump inhibitors affect the gut microbiome. Gut 2016;65(5):740–748.
6. Wang X, Zhang P, Zhang X. Probiotics regulate gut microbiota: an effective method to improve immunity. Molecules 2021;26(19):6076.
7. Belei O, Olariu L, Dobrescu A, et al. Is it useful to administer probiotics together with proton pump inhibitors in children with gastroesophageal reflux? J Neurogastroenterol Motil 2018;24(1):51–57.
8. Shanika LGT, Reynolds A, Pattison S, et al. Proton pump inhibitor use: systematic review of global trends and practices. Eur J Clin Pharmacol 2023;79(9):1159–1172.
9. Batuwitage BT, Kingham JG, Morgan NE, et al. Inappropriate prescribing of proton pump inhibitors in primary care. Postgrad Med J 2007;83(975):66–68.
10. Haastrup PF, Jarbøl DE, Thompson W, et al. When does proton pump inhibitor treatment become long term? A scoping review. BMJ Open Gastroenterol 2021;8(1):e000563.
11. Blaabjerg S, Artzi DM, Aabenhus R. Probiotics for the prevention of antibiotic-associated diarrhea in outpatients-a systematic review and meta-analysis. Antibiotics (Basel) 2017;6(4):21.
12. Zhang L, Zeng X, Guo D, et al. Early use of probiotics might prevent antibiotic-associated diarrhea in elderly (>65 years): a systematic review and meta-analysis. BMC Geriatr 2022;22(1):562.
13. Kopacz K, Phadtare S. Probiotics for the prevention of antibiotic-associated diarrhea. Healthcare (Basel) 2022;10(8):1450.
14. Sanjay Kalra, Pawan Rawal, Navneet Agrawal. Gut guardianship. J Pak Med Assoc [Ahead of publication].
15. Kwak DS, Jun DW, Seo JG, et al. Short-term probiotic therapy alleviates small intestinal bacterial overgrowth, but does not improve intestinal permeability in chronic liver disease. Eur J Gastroenterol Hepatol 2014;26(12):1353–1359.
16. Khalighi AR, Khalighi MR, Behdani R, et al. Evaluating the efficacy of probiotic on treatment in patients with small intestinal bacterial overgrowth (SIBO)–a pilot study. Indian J Med Res 2014;140(5):604–608.

ORIGINAL ARTICLE

Glycemic Variability and Its Correlation with Large for Gestation-age Babies in Gestational Diabetic Pregnancies

Anamika Baghel[1], Aruna Nigam[2*], Nidhi Gupta[3]

Received: 02 June 2023; *Revised:* 24 August 2023; *Accepted:* 15 September 2023

Abstract

Background: Although glycemic variability (GV) has been shown to be associated with endothelial dysfunction in diabetes mellitus (DM), there is a dearth of literature on its correlation in gestational diabetic pregnancies.

Aim: To compare GV and 24-hour ambulatory glucose profile (AGP) in gestational diabetic pregnancies with and without large for gestation-age (LGA) babies.

Materials and methods: It was a cross-sectional observational study. A total of 40 pregnant females between 19 and 35 years with gestational DM (GDM) controlled on pharmacotherapy fulfilling inclusion criteria were recruited. A flash glucose monitor (FGM) was used to record AGP between 32 and 36 weeks of gestation in these women. A total of 400 patient days with 38,400 glucose values in the study group were analyzed. Various glucose measures were compared between the GDM pregnancies with or without LGA babies.

Results: The incidence of LGA was 15% in these pregnant women who were on pharmacotherapy and apparently controlled as evidenced by self-monitoring of blood sugar values. All the parameters of 24-hour AGP except dinner values were significantly high in the LGA group when compared with the non-LGA group [mean amplitude of glycemic excursion (MAGE) LGA vs non-LGA 74.58 ± 16.83 vs 49.86 ± 12.83 mg/dL, $p = 0.002$; standard deviation (SD) LGA vs non-LGA 30.19 ± 9.69 vs 20.10 ± 5.97 mg/dL, $p = 0.001$]. Variables of GV: MAGE and SD were significantly high in the LGA group ($p < 0.001$). Time below range (TBR) and time above range (TAR) were also significantly altered in the LGA group ($p < 0.001$).

Conclusion: High GV and time in the range are the important parameters that can be well correlated with LGA babies in gestational diabetic pregnancies on pharmacotherapy. An FGM is a good monitoring device to measure this parameter and can be used as an adjunct to modify measures to control the glucose values within range in these pregnancies.

Journal of the Association of Physicians of India (2023): 10.59556/japi.71.0412

Introduction

Glycemic variability (GV) is characterized by extreme glucose excursions. It includes variations in blood glucose that occur at the same time on different days as well as variations in blood glucose that occur throughout the day, such as hypoglycemic periods and postprandial increases.[1] Glycemic fluctuations can result in endothelial dysfunction, which causes vascular complications. Experimental studies have shown that intermittent high blood glucose exposure is more harmful than constant high blood glucose exposure.[2]

Various measures of GV can be estimated by flash glucose monitor (FGM) that measures ambulatory glucose profile (AGP) 24 hours a day. It also measures hypo- and hyperglycemic episodes that would otherwise go unnoticed in routine intermittent monitoring. An added advantage of FGM is a measurement of time in range (TIR) which is defined as the time spent in an individual's target glucose range.

Although GV has been studied and correlated with outcomes in the nonpregnant diabetic population, there is a dearth of literature on the pregnant diabetic population, especially in gestational diabetes mellitus (GDM). Therefore, we planned to compare GV and 24-hour AGP in GDM women in gestational diabetic pregnancies (on pharmacotherapy) with and without large for gestation-age (LGA) babies.

Materials and Methods

It was a cross-sectional observational study conducted between January 2021 and July 2022 in the Department of Obstetrics and Gynecology of Hamdard Institute of Medical Sciences & Research (HIMSR), Delhi, India after obtaining permission from the Ethics Committee, Jamia Hamdard.

Subject Selection

All pregnant women who were diagnosed with GDM were screened for recruitment in the study as per inclusion criteria. The inclusion criteria included singleton pregnancy between 28 and 36 weeks taking metformin/insulin with apparent control of blood glucose values as assessed by self-monitoring of blood glucose (SMBG).

Exclusion criteria were GDM on a diet, twin pregnancy, patient with autoimmune disease, patient with current tuberculosis, patient with diabetes diagnosed before pregnancy, and patients on steroids. A written informed consent was obtained from all study participants.

Sample Size Calculation

The sample size was calculated assuming GDM prevalence to be 14% in North India[3] and 44.8% among them requiring pharmacotherapy[4] making a prevalence of 5% of pregnant women with GDM on pharmacotherapy.

Where n is the sample size, p = prevalence, p = 5%, Zα = confidence level according to the standard normal distribution (for a level of confidence of 95%, z =1.96), d = precision (tolerated margin of error), that is, 10%.

Accordingly, 40 pregnant women with GDM on drugs were recruited after written informed consent. A complete general physical, systemic, and obstetric examination was performed for each subject enrolled in the study. Information was collected and recorded on a prestructured proforma, devised as per the requirement of the study including the patient's details, demographic profile, and obstetrics history. Patients were given a proforma to record their meals and drug timings.

A flash glucose monitor (FGM) (Abbott FreeStyle Libre Pro) was used to assess AGP which is inserted on the upper arm. The device was approved by the Food and Drug Administration for continuous glucose monitoring in 2017.[5] It uses a wired glucose oxidase enzyme coimmobilized on an electrochemical sensor that is worn on the arm

[1]Postgraduate Resident; [2]Professor and Head of the Department; [3]Associate Professor, Department of Obstetrics and Gynecology, Hamdard Institute of Medical Sciences & Research (HIMSR), Jamia Hamdard University (Deemed to be University), Delhi, India; *Corresponding Author

How to cite this article: Baghel A, Nigam A, Gupta N. Glycemic Variability and Its Correlation with Large for Gestation-age Babies in Gestational Diabetic Pregnancies. J Assoc Physicians India 2023;71(12):32–35.

for up to 14 days. The sensor is about the size of a coin and has a short filament (4 mm long) that is inserted into the subcutaneous tissue. It gives glucose values every 15 minutes. Glucose values can be downloaded at any time from the reader available along with it. Data is presented in a simple form and includes the AGP, which combines all the data from the sensor over a period of 14 days and gives a summarized visual display of glycemic patterns.

In the current study, it was applied between 32 and 34 weeks for 2 weeks in apparently controlled GDM women on pharmacotherapy. Though FGM recorded data for 14 days, only 10 days of data entries were considered. Data from the first 2 days following insertion and the last 2 days was not taken into analysis as it usually takes 2 days for the monitor to stabilize. Patients were called on the 7th and 14th day to check for the functioning of the monitor and removal was done after day 14. The treatment was not modified according to the readings. SMBG was advised as per hospital protocol, that is, twice a week. FGM gives one value every 15 minutes. Therefore, it recorded 96 data points per day making 960 data points for every patient for 10 days. A total of 400 patient days with 38,400 glucose values in the study were analyzed.

All the patients were followed till delivery and the fetomaternal outcome was noted, that is, mode of delivery, difficult labor/shoulder dystocia, baby weight, baby outcome—Apgar score, neonatal intensive care unit admission, and postpartum complications.

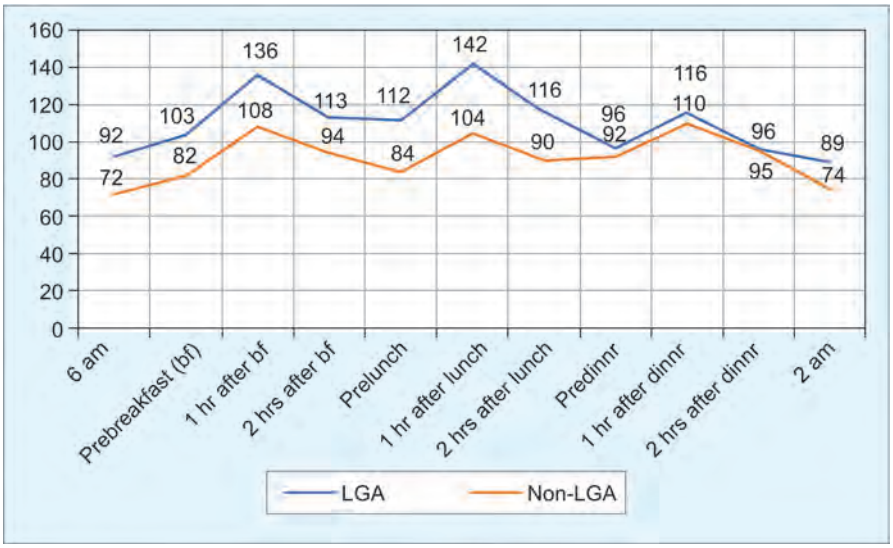


Fig. 1: The X-axis represents the timing of the day; Y-axis represents glucose values in mg/dL

Table 1: Baseline characteristics of study participants

	Study group (n = 40)
Age (years)	29.65 (4.38)
Body mass index (kg/m^2)	30.25
Family history of DM	60% (24)
Period of gestation at which FGM inserted	33.15 weeks
H/o GDM in a previous pregnancy	32%
Multigravida	85%
Primigravida	15%
Oral glucose tolerance test (0/1/2 hour values) in mg/dL	115.03/200.60/162.18

Statistical Analysis

The collected data were tabulated on Statistical Package for the Social Sciences version 20. Data were evaluated descriptively and arranged graphically for a better understanding of the variation in blood glucose profile in 24-hour time intervals. GV was calculated using GV easy version 9.0.R2. The $p < 0.05$ was taken as significant.

Result

The characteristics of the 40 women recruited into the study are displayed in Table 1.

The average birth weight in the study group was 3.08 kg. The incidence of LGA (birth weight > 90th centile) was 12.5% and one patient had macrosomia (birth weight > 4 kg). A comparison of AGP was done between the LGA + macrosomia ($N = 6$) and non-LGA babies ($N = 34$).

Table 2 delineates AGP in relation to meals between the LGA and non-LGA groups and reveals a statistically significant difference in the glucose values of the two groups with the LGA group having much higher values. Figure 1

Table 2: Comparison of AGP between the GDM pregnancies complicated by LGA vs non-LGA babies

Average glucose values in relation to meals (mg/dL)	*LGA (N = 60 patient days)*	*Non-LGA (N = 330 patient days)*	*p-value*
Total glucose values evaluated	5760	31680	
6 am	92 (16.85)	72 (12.65)	**0.0017**
Prebreakfast	103 (22.83)	82 (18.76)	**0.019**
Postbreakfast after 1 hours	136 (20.86)	108 (16.94)	**0.0009**
Postbreakfast after 2 hours	113 (22.63)	94 (15.86)	**0.0159**
Prelunch	112 (18.95)	84 (14.66)	**0.0002**
Postlunch after 1 hour	142 (20.93)	104 (16.46)	**0.001**
Postlunch after 2 hours	116 (18.47)	90 (14.27)	**0.004**
Predinner	96 (26.94)	92 (20.26)	0.6744
Postdinner after 1 hour	116 (28.59)	110 (18.80)	0.5116
Postdinner after 2 hours	96 (20.47)	95 (15.27)	0.8893
2 am	89 (18.36)	74 (12.76)	**0.018**
Mean	103.36 (26.52)	84.67 (18.92)	0.0432

Values are mean (SD); Bold values are considered as significant (*p*-value <0.05 is significant)

Table 3: Comparison of GV between the GDM pregnancies complicated by LGA vs non-LGA babies

Measure of GV (mg/dL)	*SD*	*CONGA*	*MAGE*	*J index*	*HBGI*
LGA	30.19 (9.69)	77.55 (14.87)	74.58 (16.83)	5803.79 (1500.52)	279.27 (36.82)
Non-LGA	20.10 (5.97)	67.02 (10.59)	49.86 (12.83)	3615.87 (1272.62)	241.13 (24.83)
p-value	**0.001**	**0.042**	**0.002**	**0.006**	**0.0027**

CONGA, continuous overall net glycemic action; HBGI, high blood glucose index; MAGE, mean amplitude of glucose excursion; SD, standard deviation; Bold values are considered as significant (*p*-value <0.05 is significant)

Table 4: Comparison of TIR, TBR, and TAR between LGA and non-LGA group

%	*Mean (SD)*		*p-value*
	LGA (N = 60 patient days)	*Non-LGA (N = 330 patient days)*	
TIR	50.85 (13.40)	49.36 (19.15)	0.85
TBR	32.15 (16.70)	47.95 (21.78)	**<0.001**
TAR	15.71 (6.48)	2.69 (5.32)	**<0.001**

Bold values are considered as significant (*p*-value <0.05 is significant)

depicts 24-hour AGP between LGA and non-LGA groups.

Table 3 compares GV between the LGA and non-LGA groups in which all the measures of GV are statistically significantly higher in the LGA group.

Table 4 compares TIR, time below range (TBR), and time above range (TAR) between LGA and non-LGA groups where TAR and TBR values were statistically significant between the two groups which signifies that there were more hypoglycemic and hyperglycemic time periods in LGA group.

Discussion

The current study provides evidence regarding GV and various parameters evaluated using FGM in pregnant women with GDM. The study results are derived in the Indian population where the burden of GDM is high but good quality data in pregnancies complicated by GDM using FGM are limited. Sensor-derived average blood glucose levels, time spent in euglycemic (TIR—the percentage of time spent between 60 and 140 mg/dL), hypoglycemic (TBR—<60 mg/dL), and hyperglycemic state (TAR > 140 mg/dL), and several GV indices were assessed in the current study.

As evident from Tables 2 and 3, the glucose values in GDM pregnancies were significantly deranged despite apparent control which can be well correlated with adverse fetal outcomes six out of 40 babies showed complications like LGA and macrosomia.

The peak postprandial glucose rise occurred later in pregnant women than in the nonpregnant state at 60 vs 30 minutes and is an important contributor to the risk of fetal overgrowth.[6] Our study shows a stark difference between postmeal rise in between LGA and non-LGA groups. The average postprandial increase in blood glucose in the LGA group was 30 mg/dL compared to 20 mg/dL in the non-LGA group. This finding has an important place in the management of hyperglycemia in pregnancy—as both the American College of Obstetricians and Gynaecologists and the National Institute for Health and Care Excellence guidelines recommend MBG at 1 hour after the meal to capture this peak.[7]

Apart from hyperglycemia, another major concern in GDM women is the risk of hypoglycemia. The need to avoid hypoglycemia is a limiting factor to achieving target glucose values in GDM patients. Yogev et al. conducted a study enrolling 117 patients (82 GDM vs 35 normoglycemic pregnant) and found that there were frequent asymptomatic hypoglycemic episodes detected by using continuous glucose monitoring (CGM) in the GDM group compared to the controls ($p < 0.001$).[8] Our study had similar findings with GDM patients spending an average of 9.96% of their time in a hyperglycemic state and 42.15% time in a hypoglycemic state, of which most episodes were asymptomatic.

The usefulness of GV has been studied in adult and pediatric patients affected by diabetes. Despite being approved for use in pregnancy, studies and trials related to FGM and GV and their effect on GDM-related complications are limited. Available evidence strongly suggests that glucose values obtained from SMBG only offer a myopic view of blood glucose variation as it fails to consider glucose oscillations, which have important pathophysiological implications. Moreover, transient hyperglycemic spikes as well as rapid glucose excursions from peaks to nadirs which occur more frequently in pregnant women with diabetes are associated with a higher incidence of fetal overweight, *via* a mechanism that is not only related to persistent hyperglycemia. It has been postulated that there is an association between maternal hyperglycemia-induced oxygen-free radical overproduction and fetal abnormalities, with the onset of diabetes-related embryopathy.

Leksic et al. also showed a significant association of increased GV with LGA babies (36%) in pregnancies with type 1 DM ($N = 66$).[9] Incidence of LGA in our study was 15%. There were differences in the GV parameters (MBG, SD, MAGE, continuous overall net glycemic action, high blood glucose index, J index) between the LGA and non-LGA groups, with the latter having GV on the lower side as shown in Table 2. Glucose fluctuations were calculated both inter and intraday using the FGM sensor data. In order to gain insight into rapid glucose excursions, intraday glucose variability was measured according to the SD of daily glucose values. The MAGE is designed to capture mealtime-related glucose excursions. It is considered the gold standard for GV determination. Mothers having LGA babies had an average MAGE of 74.55 ± 14.87 mg/dL whereas the average MAGE of non-LGA group was 49.86 mg/dL ± 12.83 which was statistically significant. Yu et al. had similar findings with MAGE strongly associated with birth weight percentile ($p < 0.001$).[10] They also found that MAGE was an independent determinant of birth weight and customized birth weight centile. Monnier et al. proposed that the target level of MAGE for normal GV should not be >40 mg/dL.[11] In our study, MAGE was as high as 87.77 mg/dL in women with macrosomic babies (weight 4.6 kg) which is more than twice the normal value. GV can be used as a new parameter related to poor fetal outcome as shown in the study and timely intervention can prevent LGA and other adverse outcomes. However, the correlation between GV and fetal outcomes was not found in women with GDM controlled by diet and lifestyle modifications.[12] The substantial effect of GV in the process of fetal overgrowth is also supported by earlier studies showing that glucose excursions have a greater impact on LGA development than chronic hyperglycemia per se. Fetal hyperinsulinemia is the main driver of fetal overgrowth, whereas, fetal insulin secretion is possibly suppressed by chronic hyperglycemia and stimulated by short glucose fluctuations.[13]

Nevertheless, our results confirm that higher GV in GDM pregnancies is a significant risk factor for LGA. The current study also demonstrated the importance of GV in glycemic control in the third trimester.

Freinkel proposed the concept of glucose-mediated teratogenesis, hypothesizing that glucose of maternal origin can influence fetus development with subsequent long-term effects later in life.[14] Placenta exposed to fluctuating blood glucose levels have been shown to exhibit modifications in DNA methylation at the leptin and adiponectin genes. These epigenetic markers are functional and are supposed to have long-lasting effects on the regulation of energy metabolism in offspring and are able to trigger the development of chronic metabolic diseases such as obesity and metabolic syndrome.[15] This risk of developing chronic diseases after exposure to altered blood glucose levels in utero conditions is the basis of the fetal metabolic programming hypothesis known as Barker's hypothesis.[16] Thus GV is not only a contributing factor in the development of LGA, it also has detrimental effects in the future, forming a vicious cycle of transgenerational transmission of diabetes. This further necessitates the need to know and control GV in GDM pregnancies. Results of the current study provide an opportunity for future studies to determine whether targeting GV and TIR and timely intervention could reduce fetal overgrowth in GDM pregnancies.

Strengths and Limitations

There is a dearth of studies on GV correlating with LGA babies in the GDM population in a published literature, moreover, there are no studies correlating the same from this part of the continent where the GDM prevalence is very high.

More insight into the GV could have been obtained if the treatment had been modified according to the obtained data to see the effect of the intervention. This limitation can be overcome in future studies.

Conclusion

Glycemic variability (GV) is an important parameter that is closely associated with LGA babies in gestational diabetic pregnancies on pharmacotherapy. FGM is a good monitoring device to measure GV as well as TIR, TBR, and TAR values in these pregnancies. This can be integrated into the routine management protocols so as to decrease the complications.

Ethical Approval

Approved by Institutional Ethical Committee, Jamia Hamdard University (Deemed to be University), Delhi, India.

Acknowledgment

We are thankful to the Delhi diabetic forum for providing the AGP monitors to conduct the study.

Synopsis

High GV and TIR are important parameters that can be well correlated with LGA babies in gestational diabetic pregnancies on pharmacotherapy.

Contribution to Authorship

- Anamika Baghel: Contributed to the planning, carrying out, analyzing, and writing of the work.
- Aruna Nigam: Contributed to the conception, planning, carrying out, analyzing, and writing up of the work.
- Nidhi Gupta: Contributed to planning, carrying out, and analyzing the study.

References

1. Suh S, Kim JH. Glycemic variability: how do we measure it and why is it important? Diabetes Metab J 2015;39(4):273–282.
2. Satya Krishna SV, Kota SK, Modi KD. Glycemic variability: clinical implications. Indian J Endocrinol Metab 2013;17(4):611–619.
3. Agrawal S, Das V, Agarwal A, et al. Prevalence of gestational glucose intolerance and gestational diabetes in a tertiary care centre in Northern India. J Clin Diagn Res 2018,12(8):QC04–QC06.
4. Zhang Y, Shao J, Li F, et al. Factors in gestational diabetes mellitus predicting the needs for insulin therapy. Int J Endocrinol 2016;2016:4858976.
5. Nigam A, Sharma S, Varun N, et al. Comparative analysis of 2-week glycaemic profile of healthy versus mild gestational diabetic pregnant women using flash glucose monitoring system: an observational study. BJOG 2019;126(S4):27–33.
6. Ben-Haroush A, Yogev Y, Chen R, et al. The postprandial glucose profile in the diabetic pregnancy. Am J Obstet Gynecol 2004;191(2):576–581.
7. National Institute for Health and Care Excellence. Diabetes in Pregnancy: Management of Diabetes and Its Complications from Preconception to the Postnatal Period. 2018;131:e49–e64.
8. Yogev Y, Ben-Haroush A, Chen R, et al. Continuous glucose monitoring for treatment adjustment in diabetic pregnancies—a pilot study. Diabet Med 2003;20(7):558–562.
9. Leksic G, Baretić M, Gudelj L, et al. Glycemic variability in type 1 diabetes mellitus pregnancies-novel parameters in predicting large-for-gestational-age neonates: a prospective cohort study. Biomedicines 2022;10(9):2175.
10. Yu F, Lv L, Liang Z, et al. Continuous glucose monitoring effects on maternal glycemic control and pregnancy outcomes in patients with gestational diabetes mellitus: a prospective cohort study. J Clin Endocrinol Metab 2014;99(12):4674–4682.
11. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 2006;295(14):1681–1687.
12. Panyakat WS, Phatihattakorn C, Sriwijitkamol A, et al. Correlation between third trimester glycemic variability in non-insulin-dependent gestational diabetes mellitus and adverse pregnancy and fetal outcomes. J Diabetes Sci Technol 2018;12(3):622–629.
13. Desoye G, Nolan C. The fetal glucose steal: an underappreciated phenomenon in diabetic pregnancy. Diabetologia 2016;59(6):1089–1094.
14. Freinkel N. Banting lecture 1980. of pregnancy and progeny. Diabetes 1980;29(12):1023–1035.
15. Ruchat SM, Hivert MF, Bouchard L. Epigenetic programming of obesity and diabetes by in utero exposure to gestational diabetes mellitus. Nutr Rev 2013;71(Suppl 1):S88–S94.
16. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia 1992;35(7):595–601.

REVIEW ARTICLE

Role and Significance of Dietary Protein in the Management of Type 2 Diabetes and Its Complications in India: An Expert Opinion

Viswanathan Mohan[1], Anoop Misra[2], Anil Bhansali[3], Awadhesh Kumar Singh[4], Brij Makkar[5], Dharini Krishnan[6], Manoj Chadha[7], Parag Shah[8], Ritika Samaddar[9], Ravi Kant Saraogi[10], Saptarshi Bhattacharya[11], Sheryl Salis[12*], Sri Nagesh[13], Umesh Khanna[14]

Received: 05 May 2023; *Accepted:* 27 May 2023

Abstract

Background: Obesity, prediabetes, and type 2 diabetes mellitus (T2DM) pose a triple burden in India. Almost two-thirds of people with diabetes (PWD) in India are found to have suboptimal glycemic, blood pressure, and lipid control. Medical nutrition therapy (MNT) in diabetes has emphasized on the amount and type of carbohydrates for years. However, protein, an important macronutrient in diabetes management, needs to be focused upon, especially in India, where the consumption is found to be lower than the recommendations provided by most guidelines.

Aim: An expert committee attempted to review the role of dietary protein in the management of T2DM, arrive at a consensus on the significance of increasing dietary protein for various benefits, and offer practical guidance on ways to improve protein intake among Indians.

Methodology: A total of 10 endocrinologists and diabetologists, one nephrologist, and three registered dietitians representing four zones of India formed the expert committee. An in-depth review of literature in the Indian context was carried out, and the draft document was shared with the expert committee, and their views were incorporated into the same. The expert committee then assembled virtually to deliberate on various aspects of the role of protein in T2DM management. The experts from various specialties gave their valuable inputs and suggestions from their extensive personal clinical experience and research work, which helped to reach a consensus on the role and significance of protein in the management of T2DM and its complications in India.

Results: There is abundant evidence that MNT is essential for the prevention and management of T2DM and its complications. Experts agreed that increasing protein intake offers myriad health benefits, namely reducing glycemic variability, improving glycemic control, increasing insulin sensitivity, improvement in lipid profile and immunity, and helping in weight management and preservation of muscle mass in PWD. The expert committee suggested aiming for an increase in protein intake by at least 5–10% of the current intake in lieu of carbohydrates in PWD. Experts also highlighted the need for more data quantifying the unmet protein needs in the Indian PWD, especially among vegetarians. Randomized controlled trials to study the effect of protein in diabetes complications such as cardiovascular disease (CVD) and diabetic kidney disease (DKD) and comorbid conditions such as sarcopenia among the Indian population are also warranted.

Conclusion: Increasing protein quantity and quality in the diets of Indian PWD could significantly contribute to positive health outcomes. Increased protein intake, preferably through dietary sources to meet the requirements and, when required using diabetes-specific protein supplements (DSPS), is recommended in the prevention and control of T2DM.

Journal of the Association of Physicians of India (2023): 10.59556/japi.71.0339

Introduction

There is a persistent rise in the incidence of obesity, especially abdominal obesity, and as a result, prediabetes and type 2 diabetes mellitus (T2DM) in India. The prevalence of obesity and diabetes is higher in urban areas than in rural areas.[1,2] In a study conducted in 15 states of India, the prevalence of prediabetes was found to be 24.7% [as per the American Diabetes Association (ADA) criteria].[3] The growing incidence of diabetes globally and in India is also reported in the latest edition (tenth edition, 2021) of the International Diabetes Federation (IDF) Atlas. According to this report, India houses around 74 million people with diabetes (PWD), of whom approximately one in two adults are undiagnosed.[4] About 63.7% of PWD have suboptimal blood glucose control, as revealed by the latest ICMR-INDIAB-13 study.[5] Thus, in addition to the increasing burden of diabesity, a significant proportion of the diagnosed population has uncontrolled diabetes. This increases the susceptibility to disabling and life-threatening complications of diabetes. Most prominent of these are microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular complications leading to a twofold to fourfold increased risk of CVDs.[6] The risk of complications can be minimized or delayed by lifestyle modification, dietary, and pharmacological therapy.

Asian Indian dietary patterns are typically high in carbohydrates. A slow transition from the consumption of coarse grains to refined grains owing to socioeconomic, cultural, and other factors has been observed over the last few years.[7–9] Increased consumption of sugar, sugar-sweetened beverages, trans fats, and processed foods have also been reported. India has a substantial population

[1]Chairman, Dr Mohan's Diabetes Specialities Centre (IDF Centre of Excellence in Diabetes Care); Madras Diabetes Research Foundation (ICMR Centre for Advanced Research on Diabetes), Chennai, Tamil Nadu; [2]Chairman, Fortis CDOC Centre of Excellence for Diabetes Metabolic Diseases and Endocrinology; Director, National Diabetes, Obesity and Cholesterol Foundation and Diabetes Foundation, Delhi; [3]Endocrinologist and Medical Director, Gini Health, Mohali, Punjab; [4]Consultant Endocrinologist and Diabetologist and Head, Department of Endocrinology, GD Hospital and Diabetes Institute, Kolkata, West Bengal; [5]Senior Diabetes and Bariatric Physician and Director, Dr Makkar's Diabetes and Obesity Centre, Delhi; [6]Director and Consultant Dietician, DV Living Science Enterprises Pvt Ltd, Chennai, Tamil Nadu; [7]Consultant Endocrinologist, PD Hinduja Hospital and Research Centre, Mumbai; Founder; Hope & Care Centre, Navi Mumbai, Maharashtra; [8]Endocrinologist, Gujarat Endocrine Centre, Ahmedabad, Gujarat; [9]Regional Head, Department of Dietetics, Max Healthcare, Delhi; [10]Consultant Endocrinologist, Diabetes and Endocrine Clinic, Kolkata, West Bengal; [11]Endocrinologist and Diabetologist, Apollo Hospital, Delhi; [12]Registered Dietician and Founder, Nurture Health Solutions, Mumbai, Maharashtra; [13]Consultant Endocrinologist and Diabetologist, Srinagesh Diabetes Thyroid Endocrine Clinic, Hyderabad,Telengana; [14]Consultant Nephrologist and Transplant Physician, Lancelot Kidney and GI Centre, Mumbai, Maharashtra, India; *Corresponding Author

How to cite this article: Mohan V, Misra A, Bhansali A, *et al.* Role and Significance of Dietary Protein in the Management of Type 2 Diabetes and Its Complications in India: An Expert Opinion. J Assoc Physicians India 2023;71(12):36–46.

of vegetarians as compared to the Western population.[10] Cereal grains, followed by pulses and legumes, are the main sources of protein in Indian diets, even among nonvegetarians as the frequency of flesh foods consumption is found to be low. Hence, both the quantity and quality of dietary protein are low in India, resulting in the loss of skeletal muscle mass and function (also called sarcopenia).[7,8]

Medical nutrition therapy (MNT) and lifestyle modification are indispensable components of diabetes management which have proven to improve metabolic control and prevent micro- and macrovascular complications.[11,12] Till recently, MNT in PWD was mostly focused on the amount and type of carbohydrates. However, protein is an important macronutrient and deserves special attention, more so in India, where protein consumption is found to be lower than the recommended intake. Dietary protein has various health benefits for PWD, in addition to its key role in bodily processes, and as described in this article, can play an important role both in the prevention and control of diabetes.

Why is an Expert Consensus on Dietary Protein for PWD Required for India?

The following reasons necessitate a consensus on dietary protein for PWD:

- The latest ICMR-INDIAB study reported that glycemic control, blood pressure, and lipid management among PWD remains suboptimal.[5] This warrants the need for reviewing and revising macronutrient recommendations for PWDs.
- There is growing evidence about the significant role of dietary protein and its associated health benefits, especially in diabetes management. Improved insulin sensitivity with increased dietary protein intake has been reported in individuals with T2DM.[13]
- People with T2DM in India have been found to have lower protein intake.[14] They are also more prone to sarcopenia (loss of muscle mass), which necessitates increasing dietary protein intake. Sarcopenia is reported to be higher in South Asians as compared to Whites, Caucasians, and Blacks.[15–17]
- Various guidelines that focus on PWD differ in their recommendations for protein intake. ADA Standards of Care 2023 mentions that research is inconclusive on the ideal amount of protein needed for glycemic management, and therefore, it should be individualized based on current eating patterns.[10] The dietary guidelines for Asian Indians (National Dietary Guidelines Consensus Group, 2011) suggest energy from protein as 10–15%,[18] the Indian Council of Medical Research (ICMR) 2018 guidelines suggest 12–15%,[19] while the recent Research Society for the Study of Diabetes in India (RSSDI) 2022 recommends 15%.[20] Recently derived macronutrient recommendation using a data-driven optimization model from the ICMR-INDIAB (2022) study suggests increasing protein intake to 19–20% of energy for T2DM remission in newly diagnosed PWD.[21]
- There is a need for a ready reckoner enlisting the role of dietary protein, its requirements, sources, and ways to incorporate it in the diets of Indian PWD, which can be referred to by nutritionists, healthcare professionals, and the general population at large.

Methodology

Our objective was to arrive at a consensus on the role of dietary protein in the management of T2DM and its complications in India and offer practical guidance on meeting the protein requirements. Fourteen key opinion leaders who have extensive expertise in the related domain, representing four zones of India, formed the Expert Committee. This Expert Committee included 10 endocrinologists and diabetologists, one nephrologist, and three registered dietitians. A literature search was carried out using Google Scholar, PubMed, and ResearchGate from the year 2000 using the keywords: "T2DM," "protein," "glycemic control," "muscle mass," "sarcopenia," "DKD," and "CVD." A preread document based on a detailed literature review on the role of dietary protein in T2DM was prepared well in advance for the Expert Committee Meeting and was shared with the experts for their inputs and comments. The Expert Committee assembled virtually to deliberate on the data presented in the literature review and arrived at a consensus. After the meeting, feedback and responses from the experts were compiled into a manuscript, and the draft was shared for review. An in-depth review of literature in the Indian context and the clinical and research experiences of the experts from various specialties helped to reach a consensus on the role and significance of dietary protein in the management of T2DM and its complications in India.

This article summarizes the opinions expressed by the Expert Committee that can serve as a useful tool for improving protein intake in individuals with T2DM in India. The following topics were discussed to arrive at a consensus.

Dietary Protein: Role and Types

Nutritionally, dietary proteins are divided into the following two categories:

- Complete proteins: These protein sources contain all of the essential amino acids in adequate proportions required by the human body. Eggs, flesh foods, milk and milk products, and soybean are examples of complete proteins.
- Incomplete proteins: These protein sources are limited in one or more essential amino acids, for example, wheat and rice are deficient in lysine and threonine and pulses in methionine.

Physiological Effects of Dietary Protein

The physiological effects of dietary protein are depicted in Flowchart 1.

Muscle protein synthesis (MPS): MPS is stimulated by protein or amino acid ingestion both at rest and during exercise recovery. MPS from protein is described in Flowchart 2.

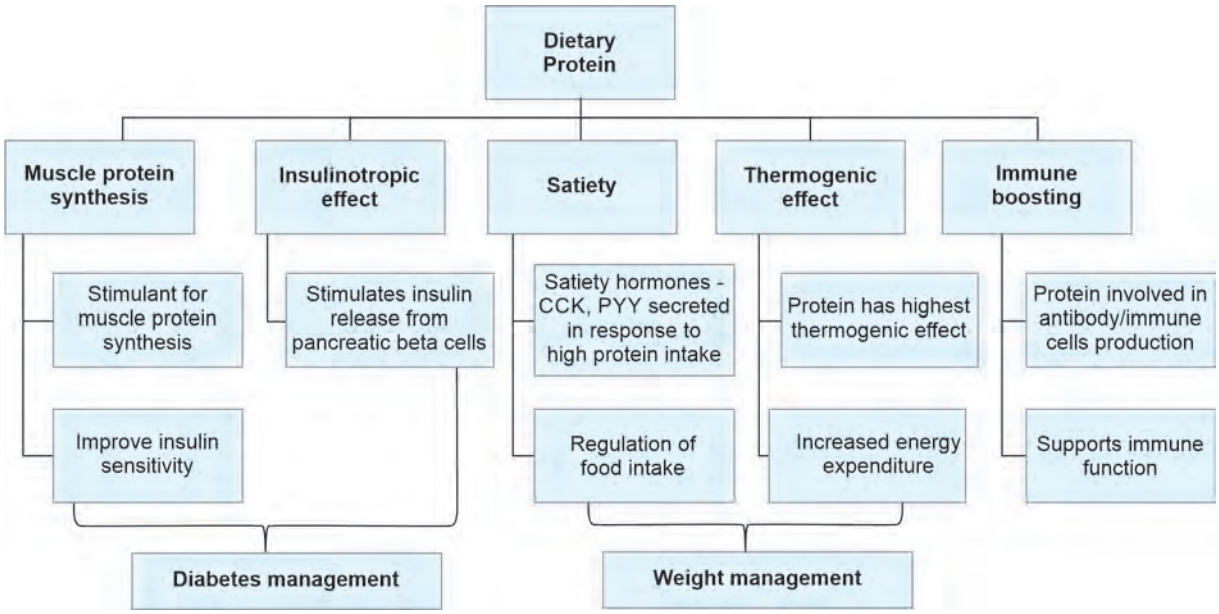
Thus, protein consumption is important for maintaining skeletal muscle mass. It also plays an important role in improving insulin sensitivity in T2DM.[22] Amino acids such as glycine, serine, glutamine, and asparagine have been seen to improve insulin sensitivity.[23] Several dietary factors influence amino acid availability, including the protein source, the amount consumed, time, pattern, and macronutrient coingestion.[24]

Insulinotropic effect: Protein ingestion stimulates incretin peptide secretion, such as glucagon-like peptide-1 (GLP-1). GLP-1 stimulates the secretion of insulin from pancreatic β-cells, enhancing insulin release. Amino acids also function as a substrate to increase adenosine triphosphate/adenosine diphosphate (ATP/ADP) ratio, which leads to insulin exocytosis.[25]

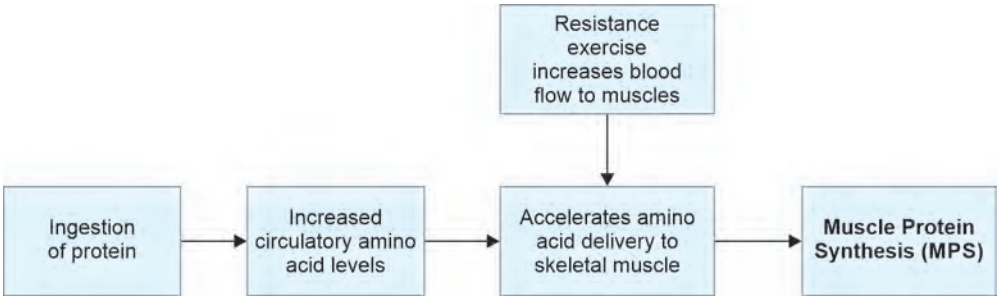
Satiety: Protein is the most effective macronutrient in providing a satiating effect. In response to a high-protein meal, satiety hormones [cholecystokinin (CCK) and pancreatic peptide YY (PYY)] are released from the small intestine. Foods high in protein induce satiety and may aid in the regulation of food intake, resulting in weight loss and maintenance in the long run.[26]

Thermogenic effect: Protein has the highest thermogenic effect.[27] Diet-induced thermogenesis increases by 20–30% after protein ingestion but only 5–10% after carbohydrates and 0–5% after fat ingestion.[28] Thus, increased protein consumption may boost energy expenditure and metabolism, resulting in weight loss.[21]

Flowchart 1: Physiological effects of dietary protein



Flowchart 2: The role of amino acid availability in regulating muscle protein synthesis with amino acid/protein ingestion and exercise



Immune function: Proteins are needed for tissue healing, body defense system structure, as well as mechanisms. Protein is broken down into amino acids and then reassembled into antibodies and complement proteins, which are majorly involved in the immune function. Amino acids are involved in the activation of macrophages, natural killer cells, and B and T lymphocytes. They also regulate key metabolic pathways of the immune response against pathogens. Thus, protein deficiency has been shown to impair immune system functioning.[29]

Beneficial Role of Dietary Protein in T2DM

- Increasing dietary protein intake has shown to help in the reduction of the glycemic index (GI) of a meal, thereby stabilizing blood glucose levels and improving postprandial insulin response and glycemic variability by regulating 24-hour mean glucose values.[30–32] Reducing the GI of the meal has shown several benefits, such as prevention and control of diabetes, thereby decreasing mortality risk.[33] A high-protein diet has also been shown to improve insulin sensitivity, which could be due to reduced carbohydrate intake and low glycemic load.[33] High-protein diet helps lower blood glucose postprandially and improves overall blood glucose control.[29–34] Increasing dietary protein also contributes to weight and dyslipidemia management in T2DM.[30,31] The clinical evidence about the above-discussed roles of high-protein diets in T2DM is described in Annexure 1.
- Consuming protein first, followed by carbohydrates in a meal, has shown to confer better control on postprandial glucose excursions. A surge in postprandial glucose was minimized if chicken, fish, paneer, or pulses were consumed first, followed by rice or chapatti.[35] Consumption of whey protein prior to a meal has been shown to reduce postprandial glucose excursion as well as stimulate insulin and incretin hormone secretion, thereby slowing down gastric emptying rate.[36] Thus, the correct food order plays an important role in facilitating an improved glucose profile.

Types of protein also have a varied effect on glycemic control as discussed in Table 1.

Role of Dietary Protein in Other Health Conditions

Weight management: Increasing protein intake provides satiety, increases energy expenditure due to its high thermogenic effect, and helps in the maintenance and synthesis of muscle protein in T2DM. Increasing protein intake along with regular physical activity helps to preserve muscle mass during weight loss in older adults with obesity and T2DM.[32] Increasing protein by up to 25–29% of Energy in overweight/obese Asian Indians has been shown to significantly reduce weight, waist circumference, and body mass index (BMI).[52,53] Protein intake of 1.0–1.2 gm/kg body weight (BW) in overweight and obese individuals with prediabetes and T2DM is shown to be associated with a reduction in fat mass, waist circumference, insulin resistance, and preservation of muscle mass.[11]

Gestational diabetes mellitus (GDM): Dietary protein is necessary for the synthesis of maternal, fetal, and placental tissues.[54] Most guidelines of various scientific bodies

Table 1: Types of protein and their role in glycemic control

Type	*Role in glycemic control*
Dairy protein	Dairy protein contains fast-acting whey and slow-acting casein protein, both of which have been shown to play unique roles in weight loss and improving muscle mass when combined with physical activity.[37,38] This is especially beneficial for individuals with T2DM.
Dairy whey	Whey protein contains 50–70% higher leucine concentration than soy or casein.[39] Leucine is a potent stimulator of muscle protein synthesis.[14] Whey protein when taken premeal or along with a high glycemic index meal has been shown to stimulate insulin release thereby reducing post-prandial blood glucose excursions. It has also been shown to increase satiety, thus aiding in weight loss in T2DM.[40,41] A dose-dependent reduction in glucose excursion is also observed when whey protein is consumed along with a carbohydrate-containing diet. A 20 gm dose of whey protein showed a greater reduction in the incremental area under the glucose curve (AUC) than 5 and 10 gm doses.[42]
Dairy casein	Casein coingested with carbohydrates or with leucine has been shown to significantly increase insulin response reducing the postprandial blood glucose rise associated with carbohydrate intake in T2DM.[43,44]
Soy	Soy is low in carbohydrates and high in protein as compared to other plant sources: dals and legumes making it a choice of protein for PWDs.[45] Soy protein supplementation has been shown to improve fasting blood glucose levels, fasting serum insulin and insulin resistance, LDL-cholesterol, and C-reactive protein levels in diabetes.[46] Soy protein in combination with exercise has also been shown to improve muscle mass and strength,[47] thus playing an important role in the management of T2DM and associated sarcopenia.
Egg and flesh foods	Considering the high protein content and virtually no carbohydrate in eggs, chicken (lean), and fish, an increased intake of these within the recommended amounts would necessarily lead to increased protein intake, without increasing the carbohydrate content of the meal. Replacing carbohydrate-rich foods with protein-rich foods is crucial for long-term weight maintenance and will be beneficial in PWD, especially in a high carbohydrate-consuming country like India.[21] Energy-restricted dietary pattern comprising egg or fish intake, along with adequate fiber contributed from whole-grain cereals, fruit, and vegetables, has been shown to be effective in diabetes management.[48,49] It has been shown to reduce fasting blood glucose, postprandial glucose AUC and improve insulin sensitivity by increasing the insulin AUC.[50,51]

suggest that protein should account for 20% of total calories in GDM.[55,56] Adequate protein intake with every meal has been suggested as it helps lower postprandial glucose spikes by flattening the glycemic response of food.[57]

Diabetic kidney disease (DKD): A low-protein diet (LPD) (0.6–0.8 gm/kg BW) minimizes intraglomerular pressure, which reduces nitrogen waste products causing less strain on the kidney and potentially protects the kidneys, especially in patients with impaired nephron function.[58] It has beneficial metabolic actions that can help to maintain kidney function and reduce uremic symptoms. However, in India, the protein intake is around 0.6 gm/kg BW/day in adults,[59] which is considered as LPD. Emphasizing reducing dietary proteins will further lower protein intake, increase malnutrition, and lead to poor prognosis. A study conducted on patients with chronic kidney disease (CKD) [stages IIIb/IV as per Kidney Disease: Improving Global Outcomes (KDIGO) guidelines], who followed LPD for 6 weeks with protein intake of 0.7 gm/kg/ideal body weight/day found to have a significant decrease in serum albumin values ($p = 0.039$) and increase in C-reactive protein. Thus, LPD slows the progression of kidney disease but may worsen patients' nutritional status.[60] Plant proteins have been found to be safe as compared to animal proteins in those with DKD.[61] Hence, appropriate advice on protein intake must be individualized and should be given considering the current dietary patterns and clinical implications. Protein intake should be reduced gradually depending on severity, progression of CKD, and the individual's nutritional status, with a target of 0.6–0.8 gm/kg/day in most individuals with eGFR <45 mL/minute/1.73 m^2.[62]

Cardiovascular diseases (CVD): Individuals with T2DM are twice as likely to have CVD.[63] Studies have shown that whey and soy protein have an antihypertensive effect.[64–66] Consumption of soy protein has also been shown to have a lowering effect on total cholesterol (TC), low-density lipoprotein cholesterol (LDL cholesterol), and triglycerides (TG) among PWD.[67] Pooled analysis of studies showed a lower risk of CVD and mortality with a higher intake of fish, which is also rich in Omega-3 fatty acids (n-3 FA).[68] However, more robust Indian data is needed to establish the significant role of dietary protein in various cardiac conditions.

Intercurrent illnesses: PWD are more prone to infections due to hyperglycemia as compared to those without diabetes. They have an increased risk of intercurrent illnesses due to bacterial and fungal infections. Pneumonia, tuberculosis, urinary tract infections, and diabetic foot infections are a few common infections seen in PWD.[69] Improving protein intake in PWD has beneficial effects on the prevention and treatment of infections through innate and adaptive immune response modulation or direct effects on viral enzymes or the rate of cell entrance.[70] In addition, dietary protein plays a vital role in weight restoration and muscle regain in chronic infections associated with undernutrition.[71] Therefore, among PWD, increasing protein intake is associated with positive outcomes during infections.

Diabetes and associated sarcopenia: Diabetes mellitus is associated with inflammation, insulin resistance, increased oxidative stress, and accumulation of advanced glycosylated end products. These factors result in cellular dysfunction and death of myocytes leading to the loss of skeletal muscle mass, strength, and function (sarcopenia).[72] This acceleration of loss of muscle mass and function in T2DM could be due to insulin resistance of protein anabolism concurrent with insufficient protein consumption and low physical activity levels.[73] Hence, PWD have a higher prevalence of sarcopenia than the general population,[74] and special focus on maintaining muscle health *via* adequate protein intake (diet and/or supplementation) is important. The International Clinical Practice Guideline for Sarcopenia (ICFSR) recommends a protein-rich diet or protein supplementation, ensuring optimal protein intake of 1–1.2 gm/kg BW/day along with physical activity in sarcopenia.[75] In addition to protein, the beneficial role of vitamin D has also been reported in individuals with insufficient levels. PWD are often seen to have low vitamin D levels. PROVIDE study found the benefits of a 13-week intervention with vitamin D and leucine-enriched whey protein oral nutritional supplements in improving muscle mass and lower-extremity function among older sarcopenic adults.[76] Thus, vitamin D supplementation may also

help in preventing or slowing down diabetes-associated sarcopenia. An increase in protein intake with resistance exercises in Asian Indians can help improve metabolic status.[14] Protein supplementation in combination with exercise in PWDs has shown a significant increase in appendicular muscle mass, total lean mass, and insulin sensitivity (Matsuda index) as well.[32]

Recommendations for Protein

Recommendations for protein (% energy) as stated by various scientific bodies from India, the United States of America, and Canada have been summarized in Table 2.

A recent consensus on MNT for diabesity in South Asian adults suggested a protein increment by 10% of the current protein intake to a maximum of 1 gm/kg BW/day.[1] Macronutrient recommendation using a data-driven optimization model in the latest ICMR-INDIAB (2022) study has highlighted the reduction in dietary carbohydrate and increase in protein intake for both T2DM remission and for prevention of progression to T2DM in prediabetes and normal glucose tolerance. The daily energy from protein recommended for diabetes remission in newly diagnosed diabetes is 19–20%, while for prediabetes remission, it is 18–20%.[21]

Gap in Protein Intake in India

Diets consumed by Asian Indians are high in refined carbohydrates, saturated fat (SFA) and trans-fats, salt, and sugar, and low in protein, fiber, and n-3 polyunsaturated fatty acid (PUFA).[79–81] The protein quantity and quality are also affected by the cost-to-nutrient ratio.[10] The Starch study (Study To Assess the dietaRy CarboHydrate content of Indian type-2 diabetes population) revealed that individuals with T2DM in India consume higher than recommended amounts of carbohydrates and lower amounts of protein.[82] Nutrient intake analysis in another study (n = 1,000) conducted in PWD across India reported that only 14.8% were meeting their protein requirements.[12] As per the National Institute of Nutrition-Indian Council of Medical Research (NIN-ICMR) What India Eats Report, only 5% of rural and 18% of the urban population were consuming recommended food groups (>66% protein from pulses, legumes, nuts, milk, and flesh foods) as a good source of protein.[83]

Thus, the dietary protein needs are not being met by healthy individuals as well as those with diabetes in India, and the dietary protein quality is also low. Some of the reasons cited for this are lack of awareness, nutritional transition, and the high cost of protein-rich foods.[84]

Ways to Improve Protein Intake among Indians

Considering the poor protein intake in India and its health benefits, PWD should be guided to include adequate protein in their diets, particularly from high biological value sources. It is challenging to meet the dietary protein requirement adequately in a typical Indian vegetarian menu. Incorporating a source of protein in every meal would help to meet the requirements and improve overall protein intake. Table 3 enlists sources of protein in the Indian diet and its macronutrient content.

These sources of protein need to be evenly distributed in all the main meals to meet the protein requirement as well as to obtain the benefit of postprandial glucose control. Milk and milk products, dals, and pulses are good sources of protein to increase protein intake in a vegetarian diet. However, these foods are also a source of carbohydrates, and their addition implies increase in the total carbohydrate content of a meal. Milk and milk products such as paneer and curd can only be used up to a limited quantity in T2DM as they are also sources of SFA. Increasing the portion of dals/pulses may cause increased bloating and flatulence.

In a nonvegetarian menu, adding egg or lean chicken or fish is a way to increase the protein content of the meal. However, the frequency and quantity of nonvegetarian foods would determine the adequacy of protein consumption. Animal protein sources such as lean meats (fish, poultry) are low or devoid of carbohydrates and a source of high biological value protein. The inclusion of these sources in a meal can improve protein intake without increasing carbohydrates. Hence, they are also one of the recommended sources of protein for PWD.[46] Here, caution is necessary, as these are also sources of cholesterol and SFAs, and nonvegetarian preparations in Indian households are often with rich gravies or fried, therefore high in visible fat. Table 4 elucidates examples of ways to incorporate protein at every meal.

Table 2: Recommendation for dietary protein intake

ADA (2023)[10]	*Indian Council of Medical Research guidelines for T2DM (2018)*[16]	*Research Society for the Study of Diabetes in India (RSSDI 2022)*[17]	*Canadian Diabetes Association Clinical Practice Guidelines (2018)*[77]
No ideal macronutrient distribution	12–15% calories from protein	15% calories from protein	15–20% calories from protein OR 1–1.5 g/kg BW

Table 3: Dietary sources of protein[85]

Source	*Amount*	*Protein (gm)*	*Carbohydrate (gm)*	*Energy (kcal)*
Milk (cow's)	150 mL	4.8	7.4	110
Curd	100 gm (5½ tbsp)	3.1	3	60
Paneer	50 gm	9.4	6.2	130
Cheese	25 gm (one cube cheese)	5.8	0.6	85
Greek yogurt	85 gm	6.1	4	55
Egg	One whole/two egg whites	Whole—6.5 White—6.0	0	Whole—90 White—30
Chicken/fish	100 gm	18–21	0	100
Soybean	25 gm	9.4	2.5	95
Soya chunks	30 gm (3/4 cup)	15.6	9.9	100
Soy paneer (tofu)	100 gm	9.4	2.3	95
Pulses (green gram, kidney beans, and chickpeas)	30 gm (one fistful, raw)	7.0	14	100

Table 4: Ways to incorporate protein at every meal[82]

Meal	*Protein source*
Breakfast (7–14 gm protein)	One cup curd/50 gm paneer/one cup skimmed milk/one egg/one cup sprouts*/one cup kidney beans*/chickpeas*/soyabean*/green gram* (either steamed or made into patties)
Lunch (7–20 gm protein)	One cup curd/one cup dal*/sprouts*/50 gm paneer/one cup soya granules*/100 gm chicken or fish
Evening (6–7 gm protein)	One cup chana* chaat/sprouts* chaat/one egg omelette
Dinner (7–20 gm protein)	One cup curd/one cup dal*/sprouts*/50 gm paneer/one cup soya granules*/100 gm chicken or fish

*Cooked portions, one cup = 200 mL

Table 5: Protein complementation

Food	*Limiting amino acid*	*Complement*
Beans/legumes	Methionine	Grains, dairy
Grains	Lysine, threonine	Legumes, dairy
Nuts	Methionine	Grains, dairy

Sample meal plans achieving a total of 60 gm of protein per day are detailed in Annexure 2.

Improving Dietary Protein Quality

The composition of essential amino acids to meet physiological needs determines the quality of protein in a food. Animal proteins have all the amino acids, and a higher protein digestibility corrected amino acid score (PDCAAS), but they are also high in SFA and cholesterol content. In contrast, plant proteins have low-fat content and no cholesterol, but the PDCAAS is lower in comparison to animal proteins.[14] To improve the protein quality of a meal, protein complementation can be done. Combining two plant sources of proteins, for instance, legumes and grains, or combining plant and animal sources of protein would provide all the nine essential amino acids. This is known as protein complementation. Protein complementation can help improve protein quality in the diets of PWD. Different ways of protein complementation have been described in Table 5,[86] and a few examples belonging to traditional Indian cuisine are detailed out in Annexure 3.

Furthermore, the common Indian preparations can be modified to improve the protein quality and quantity. This can be done without affecting palatability and making major changes in the individuals' eating preferences. The addition of pulses, nuts, dairy products like curd, cottage cheese (paneer), buttermilk, or cheese to cereal preparations can further enhance the protein content of the meal as well as improve protein quality. For instance, the addition of peanuts and peas to poha or the addition of soya chunks and paneer to vegetable pulao.

Challenges in Improving Protein Quantity and Quality in Daily Diets

The following factors are seen as barriers to improving protein intake in PWD:

- Availability and accessibility to good sources of protein foods.
- High cost of these foods.
- Unawareness and misconceptions about protein and its sources, for example, a false belief that it damages the kidney.

Bridging the Protein Gap with Diabetes-Specific Protein Supplement (DSPS)

Diabetes-specific protein supplements (DSPS) are a combination of macro and micronutrients specially designed to help bridge the nutritional gaps and aid in the nutritional management of diabetes for better clinical outcomes. These supplements are high in protein and fiber, and low in fat, especially SFA, source of vitamins and minerals. They usually have a low GI and complement dietary recommendations for PWD. DSPS can be a convenient way to improve protein intake when the normal diet is unable to meet the requirements. Their usage is determined by dietary intake, and clinical requirements and is presented at the discretion of prescribing healthcare professionals.[87] These supplements can play a significant role in meeting the nutritional, especially protein requirements in PWD.

Diabetes-specific Protein Supplement (DSPS) Helps to[88–95]:

- Reduce glycemic excursions.
- Reduce fasting and postprandial glucose and glycated hemoglobin (HbA1c) levels.
- Improve glycemic control in hospitalized individuals.
- Improve satiety.
- Correct dyslipidemia.
- Reduce weight (if used as a meal replacement).

Role of DSPS in Diabetes

Undernourished individuals with diabetes: For individuals with low body mass index (BMI), poor dietary intake, sarcopenia, and elderly individuals, energy and protein supplementation can be advised for gain in weight and muscle mass, improvement of nutritional deficiencies, and prevention of diabetes-related complications.[96,97]

Individuals with diabesity (T2DM + obesity): For individuals with T2DM and obesity, DSPS included along with diet and lifestyle modification could be beneficial in weight loss, improving metabolic control, and reducing the risk of various micronutrient (vitamins/minerals) deficiencies which may be due to calorie restriction.[78] DSPS can be used as a partial or total meal or snack replacement in low-calorie diets for individuals with diabesity.

Summary

- All the experts were in agreement that protein is an essential nutrient in diabetes management.
- Individuals with T2DM in India are required to increase their protein intake both in terms of quantity and quality and simultaneously reduce their carbohydrate intake.
- Lean muscle mass and MPS rates are seen to be lower in PWD, and the Indian sarcopenic phenotype further necessitates optimal protein consumption along with regular physical activity.
- A 5–10% increase in protein energy over and above the current intake, if possible, bringing it up to 19–20%, could help flatten the diabetes epidemic in India.
- To implement this on a population level, awareness programs need to be conducted, and policies need to be put in place.
- Special focus on including a source of protein at every meal must be underlined. A combination of plant and/or animal sources can help meet both the quality and quantity of protein.
- Diabetes-specific protein supplements (DSPS) can be advised in conditions where dietary sources are unable to meet the increased protein requirements. DSPS plays an important role in improving nutritional status, glycemic control, managing diabesity, reducing the risk of complications, preserving lean body mass, and accelerating wound healing in diabetic foot ulcers. However, renal insufficiency must be considered while prescribing

DSPS or higher protein intake, especially when using protein from animal sources.

Conclusion

Adequate protein in the diet of PWD is crucial for the management of T2DM. Targeting an increment of 5–10% of protein energy in lieu of carbohydrates in Indian PWD could ensure significant positive health outcomes such as reduced glycemic variability, improved glycemic control, insulin sensitivity, and lipid profile, immunity, and help in weight management and preservation of muscle mass apart from preventing diabetes. Increasing both protein quantity and quality, preferably through dietary sources or where needed through DSPS, is recommended for PWD.

Limitations

The focus of this consensus document is to give detailed information about the role of protein in the management of T2DM and its associated complications. Yet, due to a lack of sufficient Indian data, certain questions remain unanswered, like protein recommendations for CVD and DKD in the Indian PWDs. More research is also warranted to evaluate the need for protein quantity and timing with respect to meals and physical activity in Indian PWD.

Funding

The writing and publishing services for the paper have been funded by Nutricia International Private Limited (Danone), India.

Acknowledgements

The author's responsibilities were as follows—Dr VM and Dr AM contributed to the content of the consensus and gave their valuable feedback; all the authors contributed to reviewing and interpretation of the available data on the role of protein in T2DM during the advisory board meeting; and approved the final version of this manuscript for publication. None of the authors had any conflicts of interest to disclose. The framework creation, drafting of the consensus document for the Expert Committee Meeting, and manuscript preparation was supported by the team of Nutritionists at Nurture Health Solutions, Mumbai and Danone Medical Team. The authors would also like to acknowledge Nutricia International Private Limited (Danone), India for leading the project.

References

1. Mathur P, Kulothungan V, Leburu S, et al. National non-communicable disease monitoring survey (NNMS) in India: Estimating risk factor prevalence in the adult population. PLoS ONE 2021;16(3):e0246712.
2. Gupta S, Bansal S. Does a rise in BMI cause an increased risk of diabetes?: evidence from India. PLoS ONE 2020;15(4):e0229716.
3. Anjana RM, Deepa M, Pradeepa R, et al. For the ICMR–INDIAB Collaborative study group. Prevalence of diabetes and prediabetes in 15 states of India: results from the ICMR–INDIAB population-based cross-sectional study. Lancet Diabetes Endocrinol 2017;5:585–596.
4. International Diabetes Federation. IDF. Diabetes Atlas, 10th edition. Brussels, Belgium: 2021. Available from: https://www.diabetesatlas.org
5. Anjana RM, Unnikrishnan R, Deepa M, et al. Achievement of guideline recommended diabetes treatment targets and health habits in people with self-reported diabetes in India (ICMR-INDIAB-13): a national cross-sectional study. Lancet Diabetes Endocrinology 2022;10(6):430–441.
6. Goyal R, Jialal I. Diabetes mellitus type 2. [Updated 2021 Sep 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Jan 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513253/
7. Sachdev M, Misra A. Heterogeneity of dietary practices in India: current status and implications for the prevention and control of type 2 diabetes. Eur J Clin Nutr 2022.
8. Mohan V, Radhika G, Vijayalakshmi P, et al. Can the diabetes/cardiovascular disease epidemic in India be explained, at least in part, by excess refined grain (rice) intake? Indian J Med Res 2010;131:369–347.
9. Mohan V, Radhika G, Sathya RM, et al. Dietary carbohydrates, glycaemic load, food groups and newly detected type 2 diabetes among urban Asian Indian population in Chennai, India (Chennai Urban Rural Epidemiology Study 59). Br J Nutr 2009;102(10):1498–1506.
10. Gopalan HS, Misra A, Jayawardena R. Nutrition and diabetes in South Asia. Eur J Clin Nutr 2018;72(9):1267–1273.
11. Viswanathan V, Krishnan D, Kalra S, et al. Insights on medical nutrition therapy for type 2 diabetes mellitus: an Indian Perspective. Adv Ther 2019;36(3):520–547.
12. Facilitating positive health behaviors and well-being to improve health outcomes: standards of care in diabetes—2023. Diabetes Care 2023;46(Supplement_1):S68–S96.
13. Akhavan NS, Pourafshar S, Johnson SA, et al. The relationship between protein intake and source on factors associated with glycaemic control in individuals with prediabetes and type 2 diabetes. Nutrients 2020;12(7):2031.
14. Padmanabh P, Marathe M. Awareness and perception of diet and nutrition in individuals with diabetes mellitus. IJAIR 2021;7(6):V7I6–1248.
15. Ntuk UE, Celis-Morales CA, Mackay DF, et al. Association between grip strength and diabetes prevalence in black, South-Asian, and white European ethnic groups: a cross-sectional analysis of 418,656 participants in the UK biobank study. Diabet Med 2017;34:1120–1128.
16. Gulati S, Misra A. Dietary proteins, metabolic syndrome, and sarcopenia: focus on Asian Indians. Diabetes Metab Syndr 2019;13(6):3091–3092.
17. Anbalagan VP, Venkataraman V, Pradeepa R, et al. The prevalence of presarcopenia in Asian Indian individuals with and without type 2 diabetes. Diabetes Technol Ther 2013;15:768–775.
18. Misra A, Sharma R, Gulati S, et al. Consensus dietary guidelines for healthy living and prevention of obesity, the metabolic syndrome, diabetes, and related disorders in Asian Indians. Diabetes Technol Ther 2011;13(6):683–694.
19. ICMR Guidelines for Management of Type 2 Diabetes 2018. Available from: https://main.icmr.nic.in/sites/default/files/guidelines/ICMR_GuidelinesType2diabetes2018_0.pdf.
20. RSSDI Clinical Practice Recommendations for the Management of Type 2 Diabetes Mellitus 2022. Int J Diabetes Dev Ctries 2022;42(Suppl 1):1–143.
21. Anjana RM, Srinivasan S, Sudha V, et al. ICMR-INDIAB collaborative study group. Macronutrient recommendations for remission and prevention of diabetes in Asian Indians based on a data-driven optimization model: the ICMR-INDIAB National Study. Diabetes Care 2022;45:2883–2891.
22. Marco-Benedí V, Pérez-Calahorra S, Bea AM, et al. High-protein energy-restricted diets induce greater improvement in glucose homeostasis but not in adipokines comparing to standard-protein diets in early-onset diabetic adults with overweight or obesity. Clin Nutr 2020;39(5):1354–1363.
23. Vangipurapu J, Stancáková A, Smith U, et al. Nine amino acids are associated with decreased insulin secretion and elevated glucose levels in a 7.4-year follow-up study of 5,181 Finnish men. Diabetes 2019;68(6):1353–1358.
24. Witard O, Wardle S, Macnaughton L, et al. Protein considerations for optimising skeletal muscle mass in healthy young and older adults. Nutrients 2016;8(4):181.
25. Manders RJ, Little JP, Forbes SC, et al. Insulinotropic and muscle protein synthetic effects of branched-chain amino acids: potential therapy for type 2 diabetes and sarcopenia. Nutrients 2012;4(11):1664–1678.
26. Morell P, Fiszman S. Revisiting the role of protein-induced satiation and satiety. Food Hydrocolloids 2017;68:199–210.
27. Veldhorst MAB, Westerterp KR, van Vught, et al. Presence or absence of carbohydrates and the proportion of fat in a high-protein diet affect appetite suppression but not energy expenditure in normal-weight human subjects fed in energy balance. Br J Nutr 2010;104(9):1395–1405.
28. Keller U. Dietary proteins in obesity and in diabetes. Int J Vitam Nutr Res 2011;81(2-3):125–133.
29. Calcuttawala F. Nutrition as a key to boost immunity against COVID-19. Clin Nutr ESPEN 2022;49:17–23.
30. Layman DK, Shiue H, Sather C, et al. Increased dietary protein modifies glucose and insulin homeostasis in adult women during weight loss. J Nutr 2003;133(2):405–410.
31. Boden G, Sargrad K, Homko C, et al. Effect of a low-carbohydrate diet on appetite, blood glucose levels, and insulin resistance in obese patients with type 2 diabetes. Ann Intern Med 2005;142(6):403.
32. Thomsen MN, Skytte MJ, Astrup A, et al. The clinical effects of a carbohydrate-reduced high-protein diet on glycaemic variability in metformin-treated patients with type 2 diabetes mellitus: A randomised controlled study. Clin Nutr ESPEN 2020;39:46–52.
33. Jenkins DJA, Dehghan M, Mente A, et al. PURE study investigators. glycemic index, glycemic load, and cardiovascular disease and mortality. N Engl J Med 2021;384(14):1312–1322.
34. Mohan V, Spiegelman D, Sudha V, et al. Effect of brown rice, white rice, and brown rice with legumes on blood glucose and insulin responses in overweight asian indians: a randomized controlled trial. Diabetes Technol Ther 2014;16:317–325.
35. Shukla AP, Iliescu RG, Thomas CE, et al. Food order has a significant impact on postprandial glucose and insulin levels. Diabetes Care 2015;38(7):e98–e99.
36. Ma J, Stevens JE, Cukier K, et al. Effects of a protein preload on gastric emptying, glycemia, and gut hormones after a carbohydrate meal in diet-controlled type 2 diabetes. Diabetes Care 2009;32(9):1600–1602.
37. Karlsson HKR, Nilsson P, Nilsson J, et al. Branched-chain amino acids increase p70S6k phosphorylation in human skeletal muscle after resistance exercise. Am J Physiol Endocrinol Metab 2004;287(1):E1–E7.
38. Kimball SR, Jefferson LS. Signaling pathways and molecular mechanisms through which branched-chain amino acids mediate translational control of protein synthesis. J Nutr 2006;136(1):227S–231S.
39. Clark DC. Association of dairy protein intake during pregnancy with birth weight. Food Nutr Bull 2018;39(2_suppl):S54–S59.
40. Frid AH, Nilsson M, Holst JJ, et al. Effect of whey on blood glucose and insulin responses to composite breakfast and lunch meals in type 2 diabetic subjects. Am J Clin Nutr 2005;82(1):69–75.
41. King DG, Walker M, Campbell MD, et al. A small dose of whey protein co-ingested with mixed-macronutrient

breakfast and lunch meals improves postprandial glycemia and suppresses appetite in men with type 2 diabetes: a randomized controlled trial. Am J Clin Nutr 2018;107(4):550–557.
42. Petersen BL, Ward LS, Bastian ED, et al. A whey protein supplement decreases post-prandial glycemia. Nutr J 2009;8(1).
43. Manders RJ, Praet SF, Meex RC, et al. Protein hydrolysate/leucine co-ingestion reduces the prevalence of hyperglycemia in type 2 diabetic patients. Diabetes Care 2006;29:2721–2722.
44. Pasin G, Comerford KB. Dairy foods and dairy proteins in the management of type 2 diabetes: a systematic review of the clinical evidence. Adv Nutr 2015;6(3):245–259.
45. Longvah T, Anantan I, Bhaskarachary K, et al. Indian food composition tables. Hyderabad: National Institute of Nutrition, Indian Council of Medical Research; 2017.
46. Zhang X, Zhang Y, Chi M. Soy protein supplementation reduces clinical indices in type 2 diabetes and metabolic syndrome. Yonsei Med J 2016;57(3):681.
47. Hashimoto R, Sakai A, Murayama M, et al. Effects of dietary soy protein on skeletal muscle volume and strength in humans with various physical activities. J Med Invest 2015;62(3.4):177–183.
48. Esposito K, Kastorini C, Panagiotakos DB, et al. Prevention of type 2 diabetes by dietary patterns: a systematic review of prospective studies and meta-analysis. Metab Syndr Relat Disord 2010;8(6):471–476.
49. Marangoni F, Corsello G, Cricelli C, et al. Role of poultry meat in a balanced diet aimed at maintaining health and wellbeing: an Italian consensus document. Food Nutr Res 2015;59(1):27606.
50. Karlström BE, Järvi AE, Byberg L, et al. Fatty fish in the diet of patients with type 2 diabetes: comparison of the metabolic effects of foods rich in n–3 and n–6 fatty acids. Am J Clin Nutr 2011;94(1):26–33.
51. Smith JD, Hou T, Ludwig DS, et al. Changes in intake of protein foods, carbohydrate amount and quality, and long-term weight change: results from 3 prospective cohorts. Am J Clin Nutr 2015;101(6):1216–1224.
52. Bhardwaj S, Misra A, Gulati S, et al. A randomized controlled trial to evaluate the effects of high protein complete (IActo) VEgetaRian (PACER) diet in non-diabetic obese Asian Indians in North India. Heliyon 2017;3(12):e00472.
53. Gulati S, Misra A, Tiwari R, et al. Effect of high-protein meal replacement on weight and cardiometabolic profile in overweight/obese Asian Indians in North India. Br J Nutr 2017;117(11):1531–1540.
54. Rasmussen L, Poulsen CW, Kampmann U, et al. Diet and healthy lifestyle in the management of gestational diabetes mellitus. Nutrients 2020;12(10):3050.
55. Celeste D, Nathan D, Werner E, et al. Gestational diabetes mellitus: glucose management and maternal prognosis. Available at https://www.uptodate.com/contents/gestational-diabetes-mellitus-glucose-management-and-maternal-prognosis#disclaimerContent. Last updated Mar 18, 2022.
56. Kapur K, Kapur A, Hod M. Nutrition management of gestational diabetes mellitus. Ann Nutr Metab 2020;76(Suppl. 3):17–29.
57. Salis S, Vora N, Syed S, et al. Management of gestational diabetes mellitus with medical nutrition therapy: a comprehensive review. J Diabetol 2021;12Suppl S1:52–58
58. Ko GJ, Obi Y, Tortorici AR, et al. Dietary protein intake and chronic kidney disease. Curr Opin Clin Nutr Metab Care 2017;20(1):77–85.
59. Suri S. India's protein deficiency and the need to address the problem. Observer. Researcher's Foundation, Healthexpress. Available from: https://www.orfonline.org/expert-speak/indias-protein-deficiency-and-the-need-to-address-the-problem/#:~:text=India's%20protein%20consumption%20is%20much,gm%20per%20kg%20body%20weight.
60. Noce A, Vidiri MF, Marrone G, et al. Is low-protein diet a possible risk factor of malnutrition in chronic kidney disease patients? Cell Death Discov 2016;2:16026.
61. Viswanathan V, Snehalatha C, Varadharani MP, et al. Prevalence of albuminuria among vegetarian and non-vegetarian south Indian diabetic patients. Indian J Nephrol 2002;12:73–76.
62. Wang M, Chou J, Chang Y, et al. The role of low protein diet in ameliorating proteinuria and deferring dialysis initiation: what is old and what is new. Panminerva Med 2017;59(2):157–165.
63. Diabetes undefined. Centre for disease control. Available from: https://www.cdc.gov/diabetes/library/features/diabetes-and-heart.html.
64. Price D, Jackson KG, Lovegrove JA, et al. The effects of whey proteins, their peptides and amino acids on vascular function. Nutr Bull 2022;47:9–26.
65. Pal S, Ellis V. The chronic effects of whey proteins on blood pressure, vascular function, and inflammatory markers in overweight individuals. Obesity 2010;18:1354–1359.
66. Messina M. Soy and health update: evaluation of the clinical and epidemiologic literature. Nutrients 2016;8(12):754.
67. Yang B, Chen Y, Xu T, et al. Systematic review and meta-analysis of soy products consumption in patients with type 2 diabetes mellitus. Asia Pac J Clin Nutr 2011;20(4):593–602.
68. Mohan D, Mente A, Dehghan M, et al. Associations of fish consumption with risk of cardiovascular disease and mortality among individuals with or without vascular disease from 58 countries. JAMA Intern Med 2021;181(5):631.
69. Toniolo A, Cassani G, Puggioni A, et al. The diabetes pandemic and associated infections: suggestions for clinical microbiology. Rev Med Microbiol 2019;30(1):1–17.
70. Mahluji S, Jalili M, Ostadrahimi A, et al. Nutritional management of diabetes mellitus during the pandemic of COVID-19: a comprehensive narrative review. J Diabetes Metab Disord 2021;20(1):963–972.
71. Carbone JW, Pasiakos SM. Dietary protein and muscle mass: translating science to application and health benefit. Nutrients 2019;11(5):1136.
72. Madhu SV. Muscle health—the expanding horizon of diabetes care. Int J Diabetes Dev Ctries 2022;42:175–177.
73. Bassil MS, Gougeon R. Muscle protein anabolism in type 2 diabetes. Curr Opin Clin Nutr Metab Care 2013;16(1):83–88.
74. Trierweiler H, Kisielewicz G, Hoffmann Jonasson, et al. Sarcopenia: a chronic complication of type 2 diabetes mellitus. Diabetol Metab Syndr 2018;10:25.
75. Lim WS. Sarcopenia: update on diagnosis and treatment in an Asian community setting, 2021 update: malnutrition, muscle loss and sarcopenia. Singapore Fam Physician 2021;47(6):5–12.
76. Bauer JM, Verlaan S, Bautmans I, et al. Effects of a vitamin D and leucine-enriched whey protein nutritional supplement on measures of sarcopenia in older adults, the PROVIDE study: a randomized, double-blind, placebo-controlled trial. J Am Med Dir Assoc 2015;16(9):740–747.
77. Diabetes Canada. Clinical practice guidelines. Can J Diabetes 2018;42(Suppl 1):S1–S325.
78. Kapoor N, Sahay R, Kalra S, et al. Consensus on medical nutrition therapy for diabesity (CoMeND) in adults: a South Asian perspective. Diabetes Metab Syndr Obes 2021;14:1703–1728.
79. Gulati S, Misra A. Sugar intake, obesity, and diabetes in India. Nutrients 2014;6(12):5955–5974.
80. Narasimhan S, Nagarajan L, Vaidya R, et al. Dietary fat intake and its association with risk of selected components of the metabolic syndrome among rural South Indians. Indian J Endocrinol Metab 2016;20:47–54.
81. Dehghan M, Mente A, Zhang X, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. Lancet 2017;390(10107):2050–2062.
82. Joshi SR, Bhansali A, Bajaj S, et al. Results from a dietary survey in an Indian T2DM population: a STARCH study. BMJ Open 2014;4(10):e005138.
83. Hemlatha A, Laxmaiah A, et al. What India eats. ICMR-National Institute of Nutrition. Available at: https://www.millets.res.in/pdf/what_india_eats.pdf.
84. Mohan V, Sudha V, Shobana S, et al. Are unhealthy diets contributing to the rapid rise of type 2 diabetes in India? J Nutr 2023;153(4):940–948.
85. Longvah T, Ananthan R, Bhaskar K, et al. Indian food composition tables. National Institute of Nutrition 2017.
86. Protein Complementation, American Society for Nutrition, 2011. Available at: https://nutrition.org/protein-complementation/.
87. Mechanick JI, Marchetti A, Hegazi R, et al. Diabetes-specific nutrition formulas in the management of patients with diabetes and cardiometabolic risk. Nutrients 2020;12(12):3616.
88. Devitt AA, Oliver JS, Hegazi RA, et al. Glycemia targeted specialized nutrition (GTSN) improves postprandial glycemia and GLP-1 with similar appetitive responses compared to a healthful whole food breakfast in persons with type 2 diabetes: a randomized, controlled trial. J Diab Res Clin Met 2012;1(1):20.
89. de Luis, Izaola O, de la, et al. Blood glucose and insulin responses to two hypocaloric enteral formulas in patients with diabetes mellitus type 2. Nutr Hosp 2013;28(3):600–696.
90. Elia M, Ceriello A, Laube H, et al. Enteral nutritional support and use of diabetes-specific formulas for patients with diabetes. Diabetes Care 2005;28(9):2267–2279.
91. Ojo O, Brooke J. Evaluation of the role of enteral nutrition in managing patients with diabetes: a systematic review. Nutrients 2014;6(11):5142–5152.
92. Ojo O, Weldon SM, Thompson T, et al. The effect of diabetes-specific enteral nutrition formula on cardiometabolic parameters in patients with type 2 diabetes: a systematicreview and meta-analysis of randomised controlled trials . Nutrients 2019;11(8):1905.
93. Bhoite R, Chandrasekaran A, Pratti VL, et al. Effect of a high-protein high-fibre nutritional supplement on lipid profile in overweight/obese adults with type 2 diabetes mellitus: a 24-week randomized controlled trial. J Nutr Metab 2021;2021:6634225.
94. Alish CJ, Garvey WT, Maki KC, et al. A diabetes-specific enteral formula improves glycemic variability in patients with type 2 diabetes. Diabetes Technol Ther 2010;12(6):419–425.
95. Mori Y, Ohta T, Tanaka T, et al. Effects of a low-carbohydrate diabetes-specific formula in type 2 diabetic patients during tube feeding evaluated by continuous glucose monitoring. e-SPEN European J Clin Nutr Metab 2011;6(2):e68–e73.
96. Sanz-Paris A, Boj-Carceller D, Lardies-Sanchez B, et al. Health-care costs, glycemic control and nutritional status in malnourished older diabetics treated with a hypercaloric diabetes-specific enteral nutritional formula. Nutrients 2016;8(3):153.
97. Mechanick JI, Marchetti AE, Apovian C, et al. Diabetes-specific nutrition algorithm: a transcultural program to optimize diabetes and prediabetes care. Curr Diab Rep 2012;12(2):180–194.
98. Gannon MC, Nuttall FQ, Saeed A, et al. An increase in dietary protein improves the blood glucose response in persons with type 2 diabetes. Am J Clin Nutr 2003;78(4):734–741.
99. Bhoite R, Chandrasekaran A, Aacharya S, et al. Effect of high-protein high-fibre supplement on glycaemic control in overweight and obese Indian adults with type 2 diabetes mellitus: a 24-week, randomized, controlled trial. J Diabetes Metab 2020;11:846.
100. Luger M, Holstein B, Schindler K, et al. Feasibility and efficacy of an isocaloric high-protein vs. standard diet on insulin requirement, body weight and metabolic parameters in patients with type 2 diabetes on insulin therapy. Exp Clin Endocrinol Diabetes 2013;121(5):286–294.
101. Memelink RG, Pasman WJ, Bongers A, et al. Effect of an enriched protein drink on muscle mass and glycemic control during combined lifestyle intervention in older adults with obesity and type 2 diabetes: a double-blind RCT. Nutrients 2020;13(1):64.

Annexure 1: Role of high protein diet in T2DM

Beneficial effects	*Author/year*	*Subjects*	*Dietary intervention*	*Results*
Glycaemic control	Gannon et al. 2003[98]	12 subjects with mild, untreated type 2 diabetes (age range 39–79 years)	Control diet: protein to carbohydrate to fat ratio 15:55:30 high protein diet the ratio was 30:40:30 5-week intervention, separated by a 2–5-week washout period	Glycated hemoglobin significantly decreased with the high-protein diet (0.8%) as compared to the control diet (0.3%) ($p < 0.05$) After ingestion of a high-protein diet, the glucose concentration was consistently lower compared to the control group. The rate of decline was also significantly greater after the high-protein diet ($p < 0.001$)
	Bhoite et al. 2020[99]	100 overweight/obese Indian adults with T2DM (aged 30–65 years)	Intervention group: standard care of T2DM + 25 g high protein high fiber nutritional supplement), twice daily for 6 months Control group: standard care of T2DM for 6 months	Mean (SE) change in iAUC for the intervention group was significantly lower (23.0 mg–15 minutes/dL) compared to control group (168.0 mg–15 minutes/dL), $p = 0.008$ Significant reductions in the intervention group for HbA1c (-0.3, $p = 0.03$) and FBS (-16 mg/dl, $p = 0.01$) level compared to the control group
Dyslipidaemia management	Bhoite et al. 2021[93]	100 overweight/obese Indian adults with T2DM (aged 30–65 years)	Intervention group: standard care of T2DM + 25 g high protein high fiber nutritional supplement), twice daily Control group: standard care of T2DM, for 6 months	Significant increase in HDL-C (4 mg/dL, $p = 0.04$) in the intervention group compared to the control group A significant decrease in the T Chol/HDL-C ratio ($p = 0.03$) was observed within the intervention group
Glycaemic control and weight management	Luger et al. 2013[100]	44 T2DM individuals on insulin therapy	High protein diet (HP, experimental grp) ($n = 22$): energy distribution as 30% protein, 40% carbs, and 30% fats Standard diet (control, $n = 22$): energy distribution as 15% protein, 55% carbs, 30% fat for 12 weeks	HP diet: significant decrease in insulin requirement (9.4 ± 16.3 vs + 0.8 ± 4.8 IU, mean ± SD; $p = 0.007$), fasting plasma glucose (41.7 ± 62.5 vs 2.1 ± 39.0 mg dl^{-1}; $p = 0.02$), body mass index (1.1 ± 0.8 vs 0.3 ± 0.7 kg m^{-2}; $p = 0.003$), fat-free (0.8 ± 0.5 vs 0.2 ± 0.5 kg; $p = 0.001$), fat mass (2.6 ± 1.7 vs 0.8 ± 1.6 kg; $p = 0.001$) compared to the standard diet
Improving skeletal muscle mass	Memelink, et al. 2021[101]	123 older adults (≥55 years) with obesity and type 2 diabetes	13-week lifestyle intervention with dietary advice and exercise, receiving either the enriched protein drink (test, protein 1.15 ± 0.31 g/kg BW/d) or an isocaloric control (control)	Significant increase in appendicular muscle mass (+0.36 kg; 95% CI, 0.005–0.71) and total lean mass (+0.92 kg; 95% CI, 0.19–1.65) in test vs control

Annexure 2: Sample meal plans achieving a total of 60 g of protein per day are explained below

Menu plan for lower income group (60 g protein, 1600 kcal)		
	Menu	*Amounts*
Breakfast	Tea/coffee (without sugar)	1 cup
	+	
	Egg/sprouts	1 whole/½ cup
	+	
	Veg poha	1 cup
Mid-morning	Orange	1 portion
	+	
	Peanuts	1 handful
Lunch	Salad (tomato/onion/cucumber/carrot/ radish)	100 g
	+	
	Curd/buttermilk	1 cup/1 glass
	+	
	Dal/whole pulses preparations	1 cup
	+	
	Vegetable	1 cup
	+	
	Chapati/ rice	2 no./1½ cup
Snacks	Tea/coffee (without sugar)	1 cup
	+	
	Roasted chana with peanuts	½ cup
Dinner	Salad (tomato/ onion/ cucumber/carrot/radish)	100 g
	+	
	Curd/buttermilk	1 cup/1 glass
	+	
	Dal/whole pulses preparations	1 cup
	+	
	Vegetable	1 cup
	+	
	Chapati	2 no.
Menu plan for higher income group: (60 g protein, 1600 kcal)		
	Menu	*Amounts*
Breakfast	Tea/coffee (without sugar)	1 cup
	+	
	Egg wrap	1 no.
	or	
	Moong dosa/besan chilla (crepe)	2 no.
Mid-morning	Apple	1 portion
	+	
	Almonds	10–15 no.
Lunch	Salad (tomato/ onion/cucumber/carrot/other vegetables)	100 g
	+	
	Curd/buttermilk	1 cup/1 glass
	+	
	Dal/paneer/tofu	1 cup/50 g/100 g
	+	
	Vegetable	1 cup
	+	
	Chapati/rice	2 no./1 ½ cup
Snacks	Tea/coffee/green tea (without sugar)	1 cup
	+	
	Beans salad (add veggies)/egg vegetable omelet	1 cup/1 no.
Dinner	Salad (tomato/onion/ cucumber/carrot/other vegetables)	100 g
	+	
	Curd	1 cup/1 glass
	+	
	Dal/paneer/tofu	1 cup/50 g/100 g
	+	
	Vegetable	1 cup
	+	
	Chapati	2 no.

Annexure 3: Examples of protein complementation belonging to our traditional Indian cuisine are explained below

- Dal with chawal/chapati: In Indian cuisine, dals are dry, split pulses (such as lentils, peas, and beans). The most popular way to prepare dal is as a soup, which can also include onions, tomatoes, and different spices. Dal is usually consumed with flatbreads like roti/chapati or rice (chawal).
- Rajma chawal: Rajma (kidney beans) are used to make a popular curry originating from North India. It usually has a tomato base and is spiced with various herbs. It is traditionally served with a steaming hot plate of chawal (rice), hence the name rajma chawal.
- Dal baati: Dal bati has its roots in Rajasthan. Dal *viz* a lentil-based soup is consumed with baati which are baked whole wheat bread balls.
- Idli/dosa with sambhar: The classic South Indian breakfast dish known as "idli sambar" combines fluffy, soft idli (a savory steamed cake made of rice and black gram dal) with hot sambar (vegetable lentil stew). It creates a satisfying, filling, flavourful, and protein-rich meal. Dosas are delicate crepes prepared from fermented rice and black gram lentil batter (urad dal).
- Thalipeeth: Thalipeeth is a savory flatbread popular in western India, mainly Maharashtra. The flour for Thalipeeth is called bhajanee, which is prepared from roasted grains, legumes, and spices.
- Dal dhokli: A traditional Gujarati one-pot meal recipe made with toor dal (pigeon pea) and wheat dough. It is made by boiling kneaded and rolled wheat flour pieces in a lentil stew.
- Khichdi: Khichdi is one of the most common comfort foods in India. It is a steam-cooked dish, made from rice and a mix of different dals, usually moong dal (split green gram) or masoor dal (split red lentil), and cooked till it reaches a soft mushy texture. It is usually topped with a small dollop of ghee.
- Soya pulao, paneer pulao: Pulao is a one-pot dish that is mostly rice-based. It involves adding spices, vegetables, paneer (cottage cheese) and soya.
- Pitla bhakri: A typical Maharashtrian dish called pithla is made using besan or chickpea flour, having a consistency similar to paste. Garlic, green chilies, onions, curry/coriander leaves, and other spices are used for a delightful taste. For a complete dinner, it is served with a spicy condiment called thecha and rustic traditional Indian bread like jowar (sorghum) or bajra (pearl millet) roti.
- Handvo: Handvo is a savory vegetable cake originating from Gujarat, made with a combination of lentils and rice, vegetables, and spices (green chili, ginger, cumin, mustard, and sesame seeds).
- Dal paratha: The stuffed paratha known as a "dal paratha" is comprised of unleavened whole wheat dough, chana dal (Bengal gram), and spices. Popular in Punjabi homes, this stuffed paratha is typically prepared for breakfast.
- Dahi chawal: Dahi chawal is a south Indian dish. Soft-cooked mushy rice is mixed with dahi (curd) and salt. It is also further tempered with different whole spices and curry leaves.

REVIEW ARTICLE

Dehydration in Elderly: Revisiting the Assessment and Management Strategies

Minakshi Dhar[1*], Kartik Mittal[2], Monika Pathania[3], Sanjay Kalra[4]

Received: 11 January 2023; *Accepted:* 03 April 2023

Abstract

Dehydration, like many other aspects of an aging body, is often neglected by patients and physicians alike. Not only does it sometimes become difficult to clinically assess and identify dehydration in the elderly, but it also becomes difficult to attribute gross changes in functioning to something as simple as water depletion. This can be counterproductive to the overall health and even survival of elderly patients if diagnosis is delayed. We propose a comprehensive hydration stewardship program, with public health and clinical interventions, to prevent dehydration and its complications in vulnerable segments of society, such as the elderly. This short review summarizes current evidence available for the diagnosis and identification of dehydration in the elderly and shares preventive strategies to prevent its occurrence and complications.

Journal of the Association of Physicians of India (2023): 10.59556/japi.71.0332

Definition

Dehydration is a multifactorial and multifaceted syndrome, that is, a constellation of symptoms, signs, and laboratory abnormalities, which may be organ or life-threatening. There is no universally accepted definition for dehydration.[1] For all practical purposes, it is defined as "depletion in total body water (TBW) content caused by pathological fluid losses, diminished water intake, or a combination of both."

Epidemiology

The burden of dehydration among older adults has been described across the world using different nonstandardized diagnosing criteria. These include classical clinical findings, biomarkers [like blood urea nitrogen (BUN) to creatinine ratio, electrolytes, and specific gravity], and measurements of the adequacy of fluid intake.[2] Paulis et al., in a systematic review of nineteen studies, found wide variation in various prevalence studies, mainly due to differing definitions of dehydration used by authors.[3] This suggests a lack of standard consensus criteria to diagnose such cases, more so in the elderly population. The lack of a standard operational definition for dehydration prevents the comparability of research findings and prevalence results.

Lesnik et al. studied 410 patients, 65 years and older from Slovenia, where they used biochemical parameters like osmolality, electrolytes, and BUN to creatinine ratio to screen for dehydration.[4] The prevalence of dehydration ranged from 51 to 41.3%, depending on whether the patient was institutionalized or in the community, respectively. Schettino et al. carried out a systematic review of the literature associated with stroke, dehydration, and dysphagia and found prevalence of dehydration in poststroke patients during hospitalization was up to 66%.[5] They also noted that dehydration, defined using the biochemical parameters, was associated with the development of venous thromboembolism during the course of their stay in the hospital. This reinforces previous studies that show dehydration rates worsen rather than improve after hospital admission, suggesting a strong need for effective hydration stewardship.

The main causes of death among the elderly during high ambient temperatures include severe dehydration, heat-related pathologies (hyperthermia, heat syncope, and heat stroke), acute cardiovascular events, including heart failure in preexisting compromised heart patients, prerenal failure, the rapid development of delirium, and subsequent chest infections, with one organ failure precipitating multi-organ failure, characteristic of geriatric patients.[6,7] Thus dehydration becomes a cause of mortality in these patients This is precipitated by impaired thermoregulatory mechanisms, that is inevitable with aging. The elderly population, especially those with premorbid frailty, with or without underlying debilitating comorbidities, and use of dehydration-precipitating drugs like diuretics or sedatives, had the highest death rate in France and Italy during the 2003 heat wave. The age-associated physiology makes it even more important for the caregiver to get involved in the hydration maintenance of such individuals before any complication occurs. Once hospitalization is required occurs, bringing the patient back to the premorbid state of functioning becomes quite a daunting task for any healthcare facility.[6,7]

Salam et al., in a 4-year prospective study, observed the effects of meteorological factors and their association with seasonal stroke risk.[8] They demonstrated a seasonal pattern in the incidence of stroke with a higher risk of both ischemic as well as hemorrhagic stroke during the summer months, with higher solar radiations, irrespective of temperature rise. Such studies point to heat-related mechanisms in addition to dehydration in the causation of these events.

Etiopathogenesis

Older individuals are at increased risk for dehydration, and multiple reasons converge to increase this risk. These are listed in Table 1.

Several studies prove this by demonstrating that in healthy elders, even if the water and temperature regulating mechanisms function normally in the controlled, nonvarying environment, they become impaired as soon as the excessive physical stress of temperatures ensues. At these extremes, compensation is ineffective, and this becomes apparent earlier in elders with chronic comorbidities. Elders, with increasing comorbidities, are highly vulnerable, and this lands them with various geriatric giants, which increases their risk of acute diseases and mortality.[9,10]

Screening for Dehydration

Screening can be done using clinical and/or biochemical parameters. Validated scales have been created for use in ambulatory as

[1]Junior Resident; [2,3]Additional Professor, Department of Geriatric Medicine, All India Institute of Medical Sciences, Rishikesh, Uttarakhand; [4]Senior Consultant, Department of Endocrinology, Bharti Hospital, Karnal, Haryana, India; *Corresponding Author

How to cite this article: Dhar M, Mittal K, Pathania M, *et al.* Dehydration in Elderly: Revisiting the Assessment and Management Strategies. J Assoc Physicians India 2023;71(12):47–50.

well as hospitalized patients by medical and nursing staff. Some useful screening tools are listed in Table 2.

Screening Tools[11–15]

The orthostatic blood pressure changes and skin turgor, though good clinical makers of acute dehydration, are of less diagnostic value in chronically dehydrated elderly and thus are not included in most of these screening tools.

Diagnosis of Dehydration

Lacey et al. published a multidisciplinary consensus statement on the definition and diagnostic methods of dehydration, and the key findings suggested by them were that there is no universally accepted definition for dehydration.[15] For all practical purposes, dehydration is defined as "depletion in TBW content caused by pathological fluid losses, diminished water intake, or a combination of both."

Direct measurement of plasma osmolarity is the gold standard for determining dehydration. Underhydration is a precursory condition to dehydration associated with a more insidious onset of clinical features but a similar poor outcome.

Changes in skin turgor, sunken eyes, and dry mucosal membranes are of more clinical value in younger individuals. For older adults, due to age-related changes in skin and mucosa, the diagnostic value of such clinical findings becomes less marked. Thus, making a diagnosis, and more so, guiding fluids based on skin/mucosal changes, would not be recommended.

Assessing skin turgor at the sternal level is widely used, but like measurement of skin turgor at any other level might become comprised due to age-related changes in skin tissue. From a systematic review, Hooper et al. found that the clinical symptoms of "expressing fatigue" and "missing drinks between meals" were the only measures with the ability to identify those at greatest risk of impending dehydration.[12]

Table 3 shows various methods of diagnosing hydration status in the elderly with their merits and demerits.

Studies have found urine color and specific gravity to be easy, low-cost, and effective indicators of hydration status in older individuals with adequate renal function. They can be used as useful measures to monitor hydration in nursing

Table 3: Diagnosis of hydration status

Different methods to diagnose dehydration in elderly	*Merits*	*Demerits*
Serum osmolality	Gold standard recommended by European Society for Clinical Nutrition and Metabolism.	
Serum sodium		Only slight alteration in mild dehydration.
Urine specific gravity Urine osmolarity Urine output		Affected by comorbidities and drugs.
Urine color charting	Easy and reliable. Self-monitoring at home is possible.	
Saliva flow rate Saliva osmolality		Difficult to collect and send Diurnal variations.
Clinical signs: Skin turgor/ Sunken eyes/ Mucosal membranes	Early sensitive indicators as compared to blood parameters. Skin turgor is best assessed at the sternal level in the elderly.	Age-related changes in skin elasticity and poor oral health make these less reliable in elderly.
Combination of clinical and lab parameters	Best recommended approach.	

Table 1: Etiopathogenetic factors of dehydration

- Lack of thirst due to changes in hypothalamic thirst receptors as well as peripheral baroreceptors, which diminishes their ability to sense volume deficit.
- Differences in body composition, including loss of muscle tissue and increase in fat content.
- Poor thermoregulatory response to rise in environmental temperature changes.
- Changes in kidney physiology, including age-related loss of regulating fluids and ability to handle excess sodium.
- Elderly individuals have cellular water content, which jeopardizes thermoregulation through less sweat generation and a diminished ability to dissipate body heat via dehydrated skin.
- It also depends on the underlying chronic hydration status of the patient, as those with some form of chronic water diminution will more likely to be affected by acute water loss, which in turn depends on drinking habits, cognition, and the involvement of caregiver in overall maintained of patients general health.[8,9]

Table 2: Screening tools for dehydration

- The dehydration risk appraisal checklist keeps the risk population at higher score, including those >85 years of age, females, those with significant medical/or neuropsychiatric conditions, poor hydration behaviors, those taking medications with risk of diuresis or water loss, and also includes biochemical parameters like urine osmolality, urine color, hematocrit, BUN/creatinine ratio, serum sodium, serum osmolality.
- Dehydration screening tool (DST) designed by Vivanti et al. Gives a fair idea about hydration in hospitalized elderly people. It is composed by the most promising 11 items based only on history taking alone.[4]
- The geriatric DST, a comprehensive toolkit, is divided into three sections:
  - Section 1: Demographics linked to dehydration (age/gender/education/comorbidities).
  - Section 2: Physical signs of dehydration (tongue hydration/weight-body mass index/axillary hydration).
  - Section 3: Lab parameters (hematocrit/blood urea/serum osmolarity).
- The Northumbria assessment of hydration is a simple, nurse-guided screening tool to identify and stratify elderly patients according to their risk of dehydration, which can be easily used for daily charting by nursing staff in the ward.

homes (by nurses) and at home (by patient and his/her caregivers).[11]

Limitations in using urine indices to estimate specific gravity include the following:

- Medications and foods have the ability to change urine color.
- Motivation of staff or caregiver and ability of the patient to diligently monitor or chart correctly identified findings of urine color.
- Compromised renal function in chronic kidney disease.
- Timing of collection of urine.

In a recent study of younger adults, Perrier et al. found that a late afternoon (between 4:00 and 8:00 p.m.) specimen best reflected overall hydration status as measured by urine osmolality when compared to a 24-hour urine collection. This would need to be tested with a sample of older adults. Rodrigues et al. found a 24-hour urine osmolality was negatively associated with hydration score.[12] Johnson et al. created a composite index, the fluid retention index, which includes urine color, specific gravity, and urine creatinine. They proposed that the renal system is more responsive to water deficiency as compared to blood levels, and thus urine indicators are better than serum for biochemical diagnosis of dehydration.

Salivary osmolality is coming up as a novel indicator of dehydration, both in water and water-solute type of dehydration, the only limitation being sample collection on a regular basis for monitoring, and those patients with poor health, in which case, the sensitivity of the test might get affected.[1]

Another very good modality being used in the geriatric clinic is bioelectrical impedance analysis (BIA), which has the ability to screen for sarcopenia/muscle mass, body composition, and total water content in the body. Upcoming research may strengthen the utility of BIA in both outpatient and inpatient settings.

Hooper et al. demonstrated that serial measurement of history of fatigue grading, the number of missed drinks between meals, and BIA resistance of 50 hz has good sensitivity in diagnosing impending and ongoing dehydrated patients. These simple tests become more important at the community level for timely diagnosis of dehydration and appropriate education so as to prevent decompensation and disease.

Dehydration Prevention Stewardship[16–18]

Dehydration should be considered a chronic disease, and water intake a medical therapeutic priority in geriatric practice. Preventing dehydration, or managing it in its early stages, is the key to ensuring geriatric health. Prevention of dehydration can be ensured by appropriate public health messaging, as well as counseling and clinical interventions.

Defining Adequate Daily Fluid Intake Goal

An evidence-based nursing review concluded that all older adults should have an individualized fluid goal determined based on a documented standard for daily fluid intake. Numerous standards have been developed, several based on liquid intake, while others are based on water intake that is inclusive of food and fluid. Gaspar et al. provide a rationale for the use of the following formula as a recommended water intake standard (from food to fluid): 1600 mL/m^2 × 0.75. This formula provides the most individualized approach to the establishment of a water intake recommendation and should be attainable. The National Institute of Nutrition, Hyderabad, has also recommended daily allowances for water intake in various age groups I, II, and III.

Dehydration Preventive Strategies: Current Evidence

At the National level

At the government level, taking cues from various European countries, a mass information dissemination system must be put in place. This can include electronic alert notices, early warning systems, and mass media use to make dehydration stewardship a priority. Mitigative strategies like urban design modifications (Table 4) to include more green spaces, reflective material use on the road, and clothing and dietary advisory for the elderly must be implemented. Extensive preventive planning is needed to translate scientific evidence base into action at a mass level.

At the Community Level

Community plays a huge role in the overall well-being of the older adult, whether it involves the dissemination of vital information regarding good hydration practices or during the time of emergencies, where support from the hospital might be essential. Individual outreach programs, where a home visit to every elderly person for regular monitoring of well-being, should include a short history of water intake practices. Such initiatives might seem very nonspecific, and the necessity of such measures might seem quite futile to physicians, but such preventive measures form the basis of future medicine. Prevention might actually be a better cure: the elderly are made to realize the importance of drinking water, and dehydration and its downstream complications can be prevented.

At the Healthcare Level

Physicians, both generalists, and specialists, should be trained in recognizing and promptly treating such cases. At the index outpatient visit, they should advise the elderly of suitable water intake amounts based on comorbidities, complications, and concomitant medications and guide the patient so that he/she becomes a champion of his/her own fluid needs. For those with severe frailty, caregivers should be properly instructed to monitor urine color and common signs of poor hydration status such that management can be appropriately instituted at the home level itself, obviating the need for hospitalization. Simple techniques like regular monitoring of weight and urine color diary can also go a long way in improving the overall quality of life.

Drugs that can affect the thermoregulatory compensation, like β-blockers, diuretics, and sodium-glucose cotransporter-2 inhibitors, should be titrated accordingly. Like in any frail elderly, drugs that affect cognition should be omitted whenever feasible. Kidney disease and hydration in itself is a very specific issue, where

Table 4: Environmental modifications and hydration stewardship

- Use of air cooling systems like air-conditioners (ACs) or water coolers might be very beneficial for individuals per se. From an environmental perspective, water coolers have an edge over ACs.
- Improvement in civil engineering design of building materials to include more insulation materials and urban home designing to promote cooling, with special emphasis on roof flooring.
- Paint should be reflective and free from toxins, with regular repainting to ensure continued insulation.
- Using appliances that pollute less and emit less heat.
- Everyone should be promoted to use public transport, and these should be made accessible and affordable to the elderly to promote better utilization.

a very attentive approach to intake, output, and insensible losses should be observed carefully; a similar approach is required for heart and hepatic conditions, which have an easy tendency of decompensating or worsening if a tight fluid control strategy is not followed.

Authors Contribution

Minakshi Dhar conceived the idea, formulated the methodology, wrote the protocol, and edited the final manuscript; Kartik Mittal did the review search and helped in writing the review; Monika and Sanjay helped in the review of studies, edited the manuscript, and all authors approved the manuscript.

References

1. Walsh NP, Laing SJ, Oliver SJ, et al. Saliva parameters as potential indices of hydration status during acute dehydration. Med Sci Sports Exerc 2004;36(9):1535–42.
2. Picetti D, Foster S, Pangle AK, et al. Hydration health literacy in the elderly. Nutr Healthy Aging 2017;4(3):227–237.
3. Paulis SJC, Everink IHJ, Halfens RJG, et al. Prevalence and risk factors of dehydration among nursing home residents: a systematic review. J Am Med Dir Assoc 2018;19(8):646–657.
4. Lešnik A, Piko N, Železnik D, et al. Dehydration of older patients in institutional care and the home environment. Res Gerontol Nurs 2017;10(6):260–266.
5. Schettino MSTB, Silva DCC, Pereira-Carvalho NAV, et al. Desidratação, acidente vascular cerebral e disfagia: revisão sistemática da literatura TT - dehydration, stroke and dysphagia: systematic review. Audiol Commun Res 2020;24.
6. Rikkert MG, Melis RJ, Claassen JA. Heat waves and dehydration in the elderly. BMJ 2009;339:b2663.
7. Johnson RJ, Sánchez-Lozada LG, Newman LS, et al. Climate change and the kidney. Ann Nutr Metab 2019;74(Suppl 3):38–44.
8. Salam A, Kamran S, Bibi R, et al. Meteorological factors and seasonal stroke rates: a four-year comprehensive study. J Stroke Cerebrovasc Dis 2019;28(8):2324–2331.
9. Marra MV, Simmons SF, Shotwell MS, et al. Elevated serum osmolality and total water deficit indicate impaired hydration status in residents of long-term care facilities regardless of low or high body mass index. J Acad Nutr Diet 2016;116(5):828.e2–836.e2.
10. Mentes JC, Wang J. Measuring risk for dehydration in nursing home residents. Res Gerontol Nurs 2011;4(2):148–156.
11. Rodrigues S, Silva J, Severo M, et al. Validation analysis of a geriatric dehydration screening tool in community-dwelling and institutionalized elderly people. Int J Environ Res Public Health 2015;12(3):2700–2717.
12. Hooper L, Abdelhamid A, Attreed NJ, et al. Clinical symptoms, signs and tests for identification of impending and current water-loss dehydration in older people. Cochrane Database Syst Rev 2015;2015(4):CD009647
13. Kinoshita K, Hattori K, Ota Y, et al. The measurement of axillary moisture for the assessment of dehydration among older patients: a pilot study. Exp Gerontol 2013;48(2):255–258.
14. Burgos R, Bretón I, Cereda E, et al. ESPEN guideline clinical nutrition in neurology. Clin Nutr 2018;37(1):354–396.
15. Lacey J, Corbett J, Forni L, et al. A multidisciplinary consensus on dehydration: definitions, diagnostic methods and clinical implications. Ann Med 2019;51(3–4):232–251.
16. Huang JJ, Desai C, Singh N, et al. Summer syncope syndrome redux. Am J Med 2015;128(10):1140–1143.
17. Gaspar PM. Comparison of four standards for determining adequate water intake of nursing home residents. Res Theory Nurs Pract 2011;25(1):11–22
18. Schols JM, De Groot CP, van der Cammen TJ, et al. Preventing and treating dehydration in the elderly during periods of illness and warm weather. J Nutr Health Aging 2009;13(2):150–157.

Ref.
1. Clamp, L. et al. Enhanced insulin sensitivity in successful, long-term weight loss maintainers compared with matched controls with no weight loss history. Nutr. Diabetes 7, e282 (2017)
2. Hu Y. Advances in reducing cardiovascular risk in the management of patients with type 2 diabetes mellitus. Chronic Dis Transl Med. 2019 Mar 15;5(1):25-36.

REVIEW ARTICLE

Telmisartan Plus Amlodipine as the Preferred Initial Combination in Newly Diagnosed Indian Patients with Hypertension: An Expert Consensus Statements

Jamshed Dalal[1], Santanu Guha[2], Yerramareddy Vijaya Chandra Reddy[3], Chandrashekhar K Ponde[4], Sameer Shrivastava[5], Rajesh Badani[6*], Shashank Joshi[7], Arindam Pande[8], Viveka Kumar[9], Neeraj Bhalla[10], Akshyaya Pradhan[11], Asha Mahilmaran[12], Nirmal Kumar[13], Sivaramakrishnan Manoj[14], Toutem Sashikant[15], Mainak Mukhopadhyay[16], Mangesh Tiwaskar[17]

Received: 09 May 2023; *Accepted:* 10 October 2023

Abstract

Introduction: Hypertension (HTN) remains one of the most important risk factors for cardiovascular (CV) diseases and a leading cause of mortality worldwide. Despite improvement in detection and treatment, poor blood pressure (BP) control rates are observed globally. The situation in India is alarming with only 22.5% of patients maintaining their BP under control. Initiating early and effective treatment for HTN helps control BP within normal limits and reduces associated health risks. In India, currently, there are no guidelines on the choice of dual combination treatment that can be considered an initial treatment for newly diagnosed HTN patients to achieve effective BP control and reduce CV risks.

Objective: To provide consensus recommendations for preferred initial combinations in newly diagnosed Indian patients with HTN.

Methodology: A core group of 100 experts with HTN expertise conceptualized and formulated the four key questions based on answerability, effectiveness, potential for translation to clinical practice, novelty, and potential impact on the healthcare burden. A mix of Delphi and Child Health and Nutrition Research Initiative (CHNRI) methods was adopted for acceptance or refusal of recommendations. Likert scale 1–9 was used for scoring. A score of ≥7 was considered "statement accepted," >6.50 "near to acceptance" and <6.50 "not accepted." A vote of ≥7 by at least two-thirds of the experts (66.66%) was mandatory for acceptance of the recommendation.

Conclusion: Combination therapy could be necessary for a majority of newly diagnosed Indian patients for effective BP control. It can manage HTN with better clinical outcomes. Based on mean rating scores from experts, telmisartan plus amlodipine can be considered the preferred initial combination in the management of newly diagnosed Indian patients with HTN to achieve better BP control and improve CV outcomes.

Journal of the Association of Physicians of India (2023): 10.59556/japi.71.0407

Introduction

Hypertension (HTN) continues to remain one of the most important risk factors for cardiovascular (CV) diseases and a leading cause of mortality worldwide. The recent reports present alarming data of 8.5 million deaths from stroke, ischemic heart disease, other vascular diseases, and renal disease worldwide as a result of HTN.[1]

Despite improvement in detection, treatment, and control rates, more people did not achieve effective control in 2019. The global age-standardized prevalence of HTN in adults aged 30–79 years is reported as 32% [95% confidence interval (CI) 30–34] among women and 34% (95% CI 32–37) among men. Less than half of those treated (47% women and 38% men) had achieved HTN control, leading to global control rates of only 23% (20–27) for women and 18% (16–21) for men with HTN.[2]

The situation in India is far more alarming. Only 22.5% of hypertensive patients in India had their blood pressure (BP) under control from 2016 to 2020. The poor BP control rate is a matter of concern as not only increases the burden of disease but also increases the morbi-mortality associated with HTN and its subsequent effects on CV and renal health.[3] Research shows that 50% of hypertensive patients are not aware of their BP status. This makes the population demographics of the 15–49-year age-group highly vulnerable during the most productive years of their life.[4] The data of 2020 is similar to the one that was reported in 2012 with 55.7% (95% CI 54.9–56.5%) diagnosed patients, only 38.9% (95% CI 38.1–39.6%) took antihypertensive medication, and 31.7% (95% CI 31.0–32.4%) achieved BP control.[3,4]

A systematic search (PROSPERO No.: CRD42021239800) between April 2013 and March 2021 has reported the pooled prevalence of controlled HTN as 15% (95% CI—12–19%) across geographic regions of India from 19 studies with 44,994 hypertensive population. The control rate among those under treatment was 46% (95% CI—40–52%). The authors have reported control status among patients with HTN was significantly higher in Southern

[1]Consulting Cardiologist, Department of Cardiac Sciences, Kokilaben Dhirubhai Ambani Hospital & Medical Research Institute, Mumbai, Maharashtra; [2]Consulting Cardiologist, Department of Cardiology, Medical College, Kolkata, West Bengal; [3]Consulting Cardiologist, Department of Cardiology, Apollo Main Hospitals, Chennai, Tamil Nadu; [4]Consulting Cardiologist, Department of Cardiology, PD Hinduja National Hospital, Mumbai, Maharashtra; [5]Consulting Cardiologist, Department of Cardiology, Max Superspecialty Hospital, Saket, Delhi; [6]Consulting Cardiologist, Department of Cardiology, Aditya Birla Memorial Hospital, Pune; [7]Consultant Endocrinologist, Lilavati Hospital and Research Centre, Mumbai, Maharashtra; [8]Consulting Cardiologist, Department of Cardiology, Medica Superspecialty Hospital, Kolkata, West Bengal; [9]Consulting Cardiologist, Department of Cardiology, Max Super Specialty Hospital, Saket; [10]Consulting Cardiologist, Department of Cardiology, BLK Super Specialty Hospital, New Delhi; [11]Additional Professor, Department of Cardiology, King George's Medical University, Lucknow, Uttar Pradesh; [12]Interventional Cardiologist, Department of Cardiology, Apollo Hospitals, Chennai, Tamil Nadu; [13]Consulting Cardiologist, Department of Cardiology, Care Hospitals, Hyderabad, Telangana; [14]Consulting Cardiologist, Department of Cardiology, Kauvery Hospital, Chennai, Tamil Nadu; [15]Consulting Cardiologist, Department of Cardiology, Yashoda Hospital, Secunderabad, Telangana; [16]Consulting Cardiologist, Department of Cardiology, AMRI Hospital, Kolkata, West Bengal; [17]Consultant Physician and Diabetologist, Shilpa Medical Research Centre Mumbai, Maharashtra, India; *Corresponding Author

How to cite this article: Dalal J, Guha S, Reddy YVC, *et al.* Telmisartan Plus Amlodipine as the Preferred Initial Combination in Newly Diagnosed Indian Patients with Hypertension: An Expert Consensus Statements. J Assoc Physicians India 2023;71(12):56–61.

India at 23% (95% CI—16–31%) followed by Western 13% (95% CI—4–16%), Northern 12% (95% C—8–16%), and Eastern India 5% (95% CI—4–5%).[5] HTN is treatable and needs to be managed with lifestyle measures and by introducing pharmacological interventions. Therefore, in order to provide India-specific treatment guidelines, these consensus recommendations are proposed.

Need for Consensus

The HTN diagnosis, treatment, and control continue to remain a challenge across sociodemographic groups and geographic areas within India. These poor control rates and lack of awareness are worrying and need immediate correction. Although there is a marginal improvement in the control rate compared to previous years, there are several socioeconomic and infrastructural differences. The several lifestyle risk factors and social determinants relevant to HTN control in India need immediate attention. India needs to develop and evaluate sustainable, community-based strategies, and programs to improve HTN control rates. Against this backdrop, pharmacological intervention for uncontrolled HTN is the most practical and implementable solution. Fortunately, almost all BP-reducing medicinal products are available in India. The government of India continues to relentlessly work on controlling the prices of these medicines so as to make treatment accessible and affordable to patients. Systematic guidance on the need for controlling BP among newly diagnosed patients at the initiation of the treatment can bring in change and help achieve reasonable treatment and HTN control goals. Effective treatment in the early stage can help reduce CV risks in patients. With the growing prevalence of HTN in early youth, initiation of effective treatment can control HTN and can help prevent associated complications.

Expert Panel

A core group of 100 experts was involved in conceptualizing and recommending these guidelines. The core group identified the need to reduce CV risks in newly diagnosed hypertensive patients by attaining early BP control during initial HTN management. There is no consensus available currently for the most preferred combination therapy as initial treatment management for newly diagnosed hypertensive patients. The initial literature search as well as all the global guidelines do recommend two-drug therapy in patients with stage 2 HTN and above and also for any stage 1 hypertensive patients with at least one CV risk factor such as diabetes mellitus (DM), smoking, family history, etc. Thus, experts deliberated on the class of antihypertensive medicines that can be considered the preferred initial combination. In order to set up the consensus, the core group consisted of eminent cardiologists, physicians, and specialists actively involved in HTN clinics/managing HTN for at least 10 years and above. To advance this concept, the core group identified other experts across the country from specialties including cardiology, nephrology, endocrinology, and internal medicine. Overall, 100 experts participated in four round table meetings conducted across the country and provided their recommendations on specific consensus statements. The meetings were video recorded as well and minutes of proceedings were taken. Based on the deliberations followed by voting, the proposed recommendations were finalized. The approach to consensus development is presented as a schematic diagram (Fig. 1).

Approach to Consensus Statement

To begin with, the approach and methodology for consensus development was discussed. The 2018 guidelines on the management of HTN from the European Society of Cardiology and European Society of HTN (ESC/ESH) as well as the 2019 HTN guidelines were referred to decide key questions/statements. The American College of Cardiology and American Heart Association (ACC/AHA) guidelines were also referred.[6] Four key questions were identified to undertake deliberations within the group to provide consensus recommendations.

For accepting or refuting the consensus on the four key recommendations, a mix of Delphi and Child Health and Nutrition Research Initiative (CHNRI) methods was adopted. As recommended in the CHNRI method, all the experts contributing to the consensus had expertise in HTN management. All four key questions were formulated based on the criteria of answerability, effectiveness, the potential for translation to clinical practice, novelty, and potential impact on the healthcare burden. After discussing each key question, the experts provided their opinion which was scored on a Likert scale ranging from 1 to 9. The CHNRI method was developed to address research gaps and aid decision-making. The Likert score of 7 and above was considered <statement (accepted); >6.50 [near to acceptance and <6.50 (not accepted)]. Also, a vote of ≥7 by at least two-thirds of the experts (66.66%) was mandatory for the statement to be considered accepted. All the key statements and relevant literature were shared with all expert panel members before the meetings to form informed opinions. During each meeting, two experts moderated the discussion by highlighting the key questions along with supporting evidence. The manuscript draft incorporating all the consensus statements was sent to all the experts who provided their comments. The final draft of the manuscript was reviewed, edited, and finalized by the core group experts.

Consensus Recommendations

A discussion of the consensus recommendations from the expert panel is provided in the following sections. Table 1 summarizes all the expert recommendations and presents their mean scores on the Likert scale.

The majority of patients newly diagnosed with HTN in India require initial combination drug treatment.

The HTN has achieved epidemic proportion in India and the reported

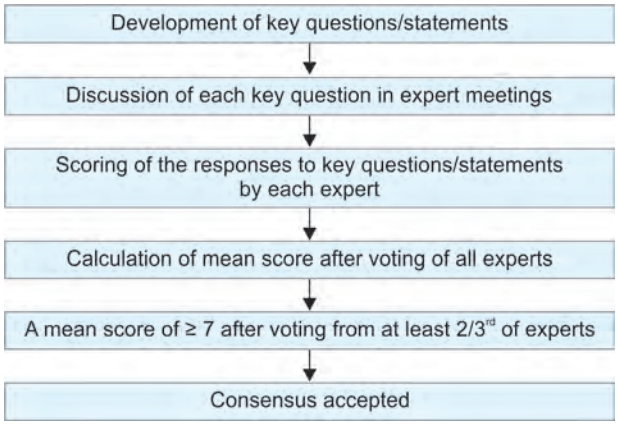


Fig. 1: Approach to consensus development

Table 1: Final consensus recommendations

S. no.	Key questions	Mean score
1	Majority of patients newly diagnosed with HTN in India require initial combination drug treatment	7.8
2	Initial combination therapy can provide better outcomes in the management of Indian patients with HTN	6.9
3	ARB + CCB can be considered the first line initial combination in the management of HTN	8.1
4	Telmisartan plus amlodipine can be considered the preferred initial combination in the management of newly diagnosed Indian patients with HTN	7.9

prevalence from various studies is around 29.8%.[7] The attributable disease burden in terms of disease-adjusted life years to HTN alone is estimated to be 39 million in 2016.[8] Among the patients receiving treatment, it is reported that only 8% of hypertensive patients are able to attain target BP control thus leaving the majority of patients remaining with raised BP readings.[9] About 33% of urban and 25% of rural Indians are hypertensive and only one-tenth of rural and one-fifth of urban Indian hypertensive population have their BP under control. All these figures are alarming.[7]

Experts expressed their concerns as many patients continue to remain with elevated HTN over long periods of time and consequently, it proportionally increases their CV risk. Therefore, it is of utmost necessity to bring the elevated BP to near normal at the earliest. All-cause and CV mortality in subjects with different grades of HTN has been well demonstrated in several research findings. The disease prevalence data shows that HTN seems to strike at a young age with an approximate prevalence of 12% population of aged between 30 and 40 years and 24% population of 41–50 years. Thus ~40% young Indian population below 50 years is hypertensive. HTN on average gets diagnosed at an average age of 51 years with almost 64% prevalence above 50 years of age. Association of both stages I and II HTN with CV mortality has been reported in India. The subsequent follow-up over 5 years has further demonstrated that the subjects with stage II HTN have had greater risk of death from hypertensive heart disease [heart rate (HR) men 2.77, 95% CI 1.75–4.40; HR women 3.04, 95% CI 1.73–5.35), ischemic heart disease (HR men 1.87, 95% CI 1.54–2.28; HR women 1.85, 95% CI 1.29–2.65), and cerebrovascular diseases (HR men 3.50, 95% CI 2.42–5.05; HR women 3.09, 95% CI 1.77–5.39). This evidence suggests that uncontrolled HTN is associated with higher CV risk and the risk is higher for patients with stage II HTN.[8–10]

In Mumbai city alone, HTN continues to be of high magnitude with 74.4% of the population <55 years of age being affected. It is also reported higher among women (57.2%) than men (44.2%).[10] With such a propensity for disease and its severity, effective treatment to achieve control is essential. Despite being on medication, patients do not achieve control possibly because they are undertreated and/or there are treatment compliance issues or both. Effective treatment for HTN is now available with many different medicines with varied mechanisms of action that provide complementary and synergistic actions to reduce elevated BP. Patients who are unable to achieve BP control with monotherapy should be considered immediately for combination treatment to achieve BP control at the earliest. In fact, most of the treatment guidelines for HTN recommend adding dual therapy to achieve a BP reduction of a minimum 20 mm Hg systolic/10 mm Hg diastolic BP reading in patients. This is applicable to known as well as newly diagnosed hypertensive patients. It is estimated that approximately one-third of patients require two drugs to achieve BP control, defined as <140/90 mm Hg. One-third of patients require three or more antihypertensive agents.

The experts discussed several reasons that are responsible for the failure to achieve BP control targets. One of the important reasons is the "therapeutic inertia," that is, unwillingness and/or apprehension by the clinicians to increase the dosage and/or to add an additional antihypertensive medication to the treatment. A few of the other reasons include the low efficacy of monotherapy and the underuse of combination therapies. Lack of faith in dual therapy due to the availability of irrational combinations in the Indian market cannot be denied. Nonadherence to the treatment and compliance issues from the patients are also responsible for not achieving the target goal of controlling the elevated BP. The clinician's prescription pattern also influences the treatment considered for the patient. Experts opined that the specialist would usually add on additional medicines without hesitation and provide combination therapy unlike few of the primary physicians who may not consider the same. Though all newly diagnosed patients may not need dual treatment initially, there is always a possibility of using dual therapy in a few newly diagnosed cases.

Recommendation

The majority of patients newly diagnosed with HTN in India may require initial combination drug treatment (score 7.8 accepted).

Initial combination therapy can provide better outcomes in the management of Indian patients with HTN.

A lot of evidence is available today that endorses the use of combination therapy as it offers BP control and helps in preventing CV events among patients. Combination treatment is endorsed by all global HTN treatment guidelines.[11,12] Clinical trials suggest that the time to BP control is an important determinant of long-term outcomes. Gradman et al. evaluated the effects of initial vs delayed treatment with a drug combination on BP control and the risk of CV events in 1,762 hypertensive patients. Initial combination therapy was found to be associated with a significant risk reduction of CV events or death [hazard ratio, 0.77 (95% CI, 0.61–0.96); $p = 0.0223$]. Achieving rapid BP reduction and achieving the target BP are the main factors in the estimated risk reduction.[13]

Corrao et al. in a population-based, nested case-control study with a cohort of 209,650 patients demonstrated that a combination of antihypertensive drugs is associated with a great reduction of CV risk. Patients starting on combination therapy had an 11% CV risk reduction with respect to those starting on monotherapy (95% CI—5–16%).[14] In a meta-analysis comprising 42 trials (10,968 participants), BP reduction from combining drugs from four classes, namely thiazide diuretics (DU), β-blockers (BB), angiotensin-converting enzyme inhibitors (ACEI), and calcium channel blockers (CCBs), is discussed based on their additive effects. When one combines two different classes of antihypertensive drugs, the additive effect is magnified and is approximately five times greater than doubling the dose of one drug.[15] When one introduces combination treatment in the early treatment part of the ailment, the benefits are higher, and associated CV risks are lowered.

Clinicians seem to prefer initial single-pill combination therapy in stage II hypertensive patients rather than giving free combinations to improve adherence to the treatment and compliance with the prescription. The study by Egan et al. justified this principle where stage II hypertensive patients (N-9194) received single pill combinations/fixed dose combinations (FDC). Higher use of single-pill

combinations as initial therapy improved HTN control and CV outcomes early during the treatment.[16] Meta-analysis from Salam et al. compared standard dose monotherapy with low-to-standard dose dual combination therapy comprising 13,095 patients from 33 trials. Initiating treatment with low-to-standard dose dual combination therapy was found to be more efficacious with fewer side effects and better patient compliance.[17] SPRINT study showed that among adults with HTN but without diabetes, lowering systolic BP to a target goal of <120 mm Hg, compared with the standard goal of <140 mm Hg, resulted in significantly lower rates of fatal and nonfatal CV events and death from any cause.[18] All this evidence is in favor of use of the combination therapy in the early stage of the disease.

Recommendation

Initial combination therapy can provide better outcomes in the management of Indian patients with HTN (score 6.9—near acceptance).

Angiotensin receptor blockers (ARB) + CCB can be considered the preferred initial combination in the management of HTN.

The current HTN treatment guidelines (Figs 2 and 3) recommend treatment with antihypertensive drugs along with lifestyle interventions for patients with grade II or III HTN, patients with grade I HTN at high risk, or with HTN-mediated organ damage.[19]

The ESC/ESH 2018 as well as the International Society for Hypertension (ISH) guidelines 2020 provide clear guidance to start dual low-dose combination therapy as the first step toward pharmacological intervention for HTN management. These guidelines further advise the choice of pharmacological agents that can be considered between ACEIs, ARBs, CCBs, and DUs. BB is to be considered specifically with comorbidities such as heart failure (HF), coronary artery disease (CAD), atrial fibrillation, and also in young women and those planning pregnancies.

Experts discussed these guideline recommendations and agreed to the use of ARB + CCB as one of the initial combinations for the management of HTN. Experts also opined that there is vast evidence available with ARBs/ACEI and CCBs. Cumulative evidence from LIFE, ASCOT, CAFE, ACCOMPLISH, and VALUE trials strongly support the view that in hypertensive patients, combination therapy with CCB/ARB or CCB/ACEI is likely to be associated with better CV outcomes including myocardial infarction (MI) and stroke than regimens containing BB and DU. Cost-effectiveness analysis from the NICE guidelines clearly demonstrates that CCBs and ARBs or ACEIs are more cost-effective treatment choices than BB or thiazide DU.

Bangalore et al. has conducted a meta-analysis of randomized trials of ACEIs and ARBs compared with placebo or active controls and corroborated with head-to-head trials of ARBs vs ACEIs. Outcomes measured included all-cause mortality, CV death, MI, angina, stroke, HF, revascularization, and new-onset diabetes. Head-to-head comparison trials of ARBs vs ACEIs exhibited no difference in outcomes

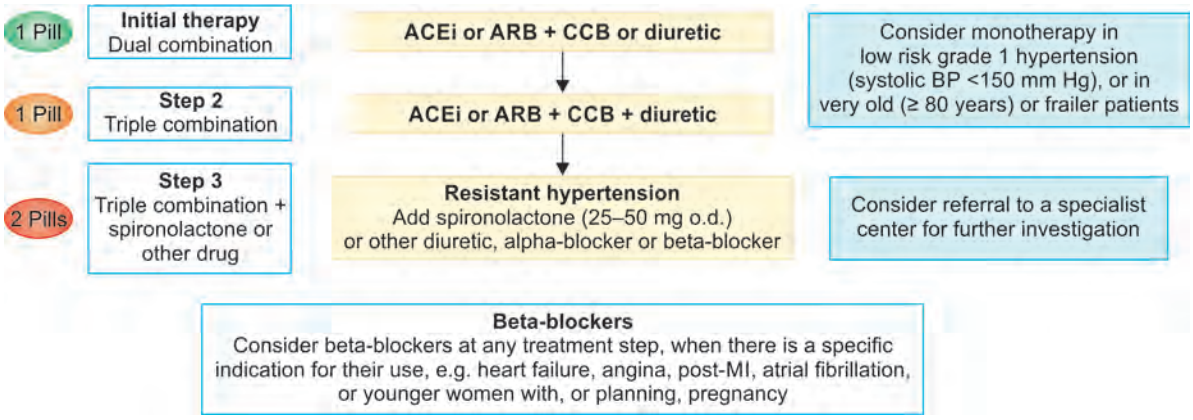


Fig. 2: 2018 ESC/ESH targets: uncomplicated HTN (ESC guidelines)[19]

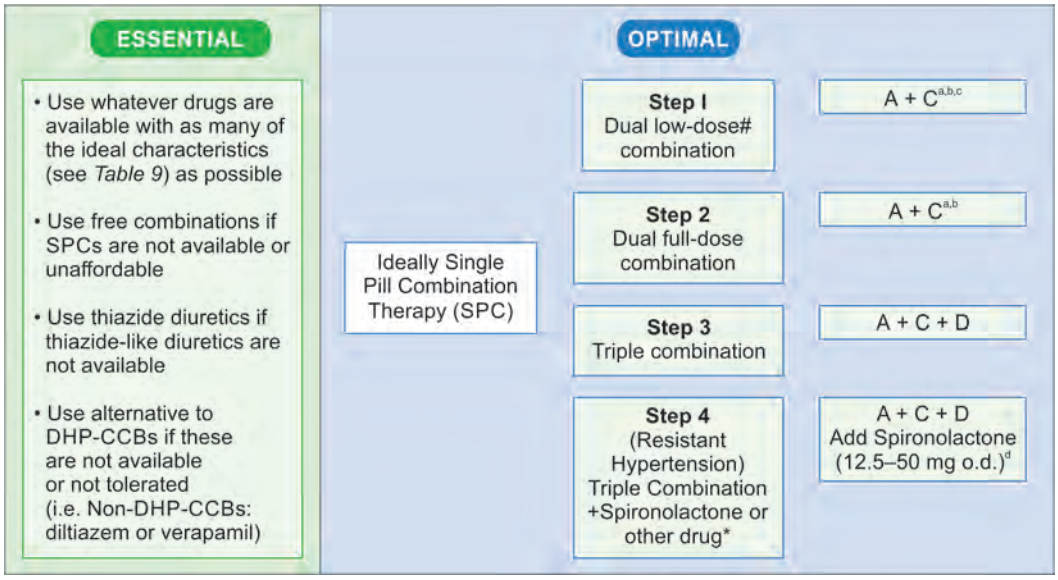


Fig. 3: 2020 ISH Global HTN Practice guidelines (Unger et al.)[12]

except for a lower risk of drug withdrawal due to adverse effects with ARBs (RR, 0.72; 95% CI, 0.65–0.81). This meta-analysis suggests ARBs to be as efficacious and safe as ACEIs, with the added advantage of better tolerability among patients without HF.[20] Additionally, the use of CCB and ARBs in the SPRINT study has already demonstrated that lowering the systolic BP below 120 mm Hg helped reduce CV events by 25% and reduced the overall risk of death by 27%. The currently available evidence on ARB + CCB combination favors its use in HTN management as an initial combination to initiate the treatment.

Recommendation

Angiotensin receptor blockers (ARB) + CCB can be considered the preferred initial combination in the management of HTN (score 8.1 accepted).

Telmisartan plus amlodipine can be considered the preferred initial combination in the management of newly diagnosed Indian patients with HTN.

ONTARGET study compared the ACEI ramipril and the ARB telmisartan and their dual combination in patients with vascular disease or high-risk diabetes. Telmisartan was found to be equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less angioedema. The combination of the two drugs was associated with more adverse events without an increase in benefits. The combination therapy demonstrated a significant BP reduction than either of the monotherapies.[21]

The INNOVATION study determined the clinical efficacy and safety of telmisartan in delaying the progression of renal disease from incipient nephropathy to overt nephropathy in hypertensive or normotensive Japanese patients with type 2 DM. The study demonstrated the prevention of the progression of microalbuminuria in normotensive Japanese patients with type 2 diabetes with telmisartan with good safety and tolerability.[22]

Amlodipine is a highly investigated and well-known CCB that has been widely used in HTN management. Specialists do use the latest generation CCBs such as cilnidipine. Amlodipine has wide use in India with only concern of pedal edema at high doses. It has been well-investigated with its combinations with ACEIs and ARBs. Amlodipine apart from BP reduction has been demonstrated to slow down the atherosclerosis progression in the intravascular ultrasound sub-study of CAMELOT.[23]

The ACCOMPLISH trial demonstrated a 20% advantage in CV risk reduction when BP was lowered using the single-pill combination of benazepril-amlodipine compared to benazepril-hydrochlorothiazide. Additionally, in patients with HTN and CAD, the ACCOMPLISH sub-study has demonstrated that the combination of ACEI + CCB provides better mortality benefits than the combination of ACEI + DU.[24,25] Based on the results, the American Society of HTN position paper and the European HTN Society guidelines endorsed such combinations as a first-line agent for patients with stage II HTN.[26] Following this, the combination of amlodipine + olmesartan was also found to be efficacious, safe, and well-tolerated in the COACH study.[27]

The TEAMSTA-5 study evaluated the single-pill combinations of telmisartan 40 or 80 mg/amlodipine 5 mg (T40/A5 or T80/A5) vs monotherapy with amlodipine 5 or 10 mg (A10) in 1,097 patients with uncontrolled HTN (diastolic BP ≥90 mm Hg).[28] Telmisartan + amlodipine combinations produced significantly higher reductions ($p < 0.0001$) in systolic/diastolic BP vs A5 (−7.4/−3.6; −8.8/−4.9 mm Hg). A greater ($p < 0.001$) proportion of patients from both the combination groups achieved target BP compared to the monotherapy. The study demonstrated that a single-pill combination of telmisartan 40/amlodipine 5 or telmisartan 80/amlodipine 5 had been a better treatment option than up-titration to full-dose monotherapy with amlodipine 10 that was associated with side effects. The advantages of switching patients from monotherapy to combination therapy with dual low-dose therapy, thereby achieving target BP control as well as lowering the side effects of high doses of monotherapy and improving compliance have been demonstrated in this study.[29] The experts discussed the advantages of dual therapy and also agreed that wherever possible and FDC is available they are preferred but if not, combination therapy is certainly helpful in achieving BP control which is most desirous to reduce any CV events. Based on the current evidence, telmisartan and amlodipine can be considered the preferred first-line treatment for HTN in India.

Recommendation

Telmisartan plus amlodipine can be considered the preferred initial combination in the management of newly diagnosed Indian patients with HTN (score 8.1 accepted).

Strengths and Limitations

These recommendations are proposed with the intention of providing guidance to clinicians on the medications that can be considered initial therapy for hypertensive patients. The recommended medicines belong to the class of BP-lowering medications that are endorsed and suggested by all international guidelines. Both amlodipine and telmisartan have a long history of use and are backed up by evidence that has been generated worldwide with randomized controlled trials, and large observational cohort studies. Both these medications have proven safety and efficacy. As far as India is concerned, amlodipine has been used for >30 years, and telmisartan for >15 years. Both these individual medications as well as their FDCs are widely used and prescribed. Providing the recommendation as initial therapy is an attempt to provide guidance to the primary physicians who probably would consider beginning only with monotherapy. Low-dose dual drug therapy has established its use in reducing elevated BP rapidly and sustaining the BP within range as well as reducing CV risk for the patients. This recommendation should be considered a first attempt to introduce the treatment guidelines along with the choice of drugs.

The recommendations are based on available published literature as well as global clinical treatment guidelines issued by ESC/ESH, ISH, JNC VII, and ACC/AHA guidelines. The majority of patients are expected to tolerate both amlodipine and telmisartan. There could be some random cases, wherein patients could be hypersensitive and/or may not be able to tolerate these medicines. Few cases of resistant HTN and/or complicated cases will require customization and specific treatment.

Conclusion

Approximately 1 billion adults worldwide have HTN. Preventive as well as effective treatment strategies are essential and are customized based on socioeconomic issues as well as regional health infrastructure. The diversity of India requires customization and simplification of strategies that are easy to implement and follow. As observed with mean rating scores from experts for each recommendation, telmisartan plus amlodipine can be considered the preferred initial combination in the management of newly diagnosed Indian patients with HTN to achieve better control of BP and to reduce CV outcomes.

Acknowledgments

We thank Auriga Research Private Limited, Dr Manjusha Rajarshi, Dr Mayur Jadhav, Dr Sachin Suryawanshi, and Dr Hanmant Barkate for drafting the manuscript. We thank Dr Jaspal Arneja, Dr Anil Damle, Dr Ashok Punjabi, Dr G R Kane, Dr Zakia Khan, Dr Sandeep fulpagare, Dr G P Ratnaparkhi, Dr Nilesh Gautam, Dr Nitin Gokhale, Dr Sunil Washimkar,

Dr Pramod Gandhi, Dr Sarita Rao, Dr Smit Shrivastav, Dr Mohan Magdum, Dr Sunil Sathe, Dr Abhijeet Vaidhya, Dr Nitin Patki, Dr Ramesh Goyal, Dr TR. Muralidharan, Dr Sridhar Kasturi, Dr Shailender Singh, Dr VS Ramachandra, Dr KAV Subramanyam, Dr John Satish, Dr CS Dwarakanath, Dr TK Venkatesh, Dr A Gopi, Dr Manohar Surangi, Dr Siva Prasad, Dr Prabhanini Gupta, Dr Mini G Pillai, Dr CG Sajeev, Dr A Sreenivas kumar, Dr Prasanth mappa, Dr Asit Khanna, Dr Sandeep Chopra, Dr Sameer Mehrotra, Dr Amit Pendharkar, Dr C M Batra, Dr R K Marya, Dr Dharmendra jain, Dr Karan Bahal, Dr Rishi Gupta, Dr Sanjeev Syal, Dr Rajeev Rajput, Dr Surya Kant Mathur, Dr Ripen Gupta, Dr Gaurav Minocha, Dr Dipankar Ghoshdostider, Dr Bappaditya Kumar, Dr Arnab Dutta, Dr Soumya Kanti Dutta, Dr Biswajit Majumder, Dr Lipika Adhikary, Dr B P Pande, Dr Tirthankar Chowdhury, Dr Ghanshyam Goyel, Dr B B Bharti, Dr Abhinav Bhagat, Dr. Rajiv Krishna, Dr M P Tripathy, Dr Somnath Mukhopadhyay, and Dr Debasis Ghosh for providing their expert opinion to develop this consensus document.

References

1. NCD Risk Factor Collaboration (NCD-RisC). Long-term and recent trends in hypertension awareness, treatment, and control in 12 high-income countries: an analysis of 123 nationally representative surveys. Lancet 2019;394(10199):639–651.
2. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet 2021;398(10324):957–980.
3. Koya SF, Pilakkadavath Z, Chandran P, et al. Hypertension control rate in India: systematic review and meta-analysis of population-level non-interventional studies, 2001–2022. Lancet Reg Health Southeast Asia 2022;9:100113.
4. Ghosh S, Kumar M. Prevalence and associated risk factors of hypertension among persons aged 15-49 in India: a cross-sectional study. BMJ Open 2019;9(12):e029714.
5. Kumar SM, Anandraj J, Sivanatham P, et al. Control status of hypertension in India: systematic review and meta-analysis. J Hypertens 2023;41(5):687–698.
6. Whelton PK, Carey RM, Mancia G, et al. Harmonization of the American College of Cardiology/American Heart Association and European Society of Cardiology/European Society of Hypertension Blood Pressure/Hypertension guidelines: comparisons, reflections, and recommendations. J Am Coll Cardiol 2022;80(12):1192–1201.
7. Anchala R, Kannuri NK, Pant H, et al. Hypertension in India: a systematic review and meta-analysis of prevalence, awareness, and control of hypertension. J Hypertens 2014;32(6):1170–1177.
8. Gupta R, Gaur K, S Ram CV. Emerging trends in hypertension epidemiology in India. J Hum Hypertens 2019;33(8):575–587.
9. Prenissl J, Manne-Goehler J, Jaacks LM, et al. Hypertension screening, awareness, treatment, and control in India: A nationally representative cross-sectional study among individuals aged 15 to 49 years. PLoS Med 2019;16(5):e1002801.
10. Pednekar MS, Gupta R, Gupta PC. Association of blood pressure and cardiovascular mortality in India: Mumbai cohort study. Am J Hypertens 2009;22(10):1076–1084.
11. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 2003;289(19): 2560–2572.
12. Unger T, Borghi C, Charchar F, et al. 2020 international society of hypertension global hypertension practice guidelines. Hypertension 2020;75(6):1334–1357.
13. Gradman AH, Parisé H, Lefebvre P, et al. Initial combination therapy reduces the risk of cardiovascular events in hypertensive patients: a matched cohort study. Hypertension 2013;61(2):309–318.
14. Corrao G, Nicotra F, Parodi A, et al. Cardiovascular protection by initial and subsequent combination of antihypertensive drugs in daily life practice. Hypertension 2011;58(4):566–572.
15. Wald DS, Law M, Morris JK, et al. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med 2019;122(3):290–300.
16. Egan BM, Bandyopadhyay D, Shaftman SR, et al. Initial monotherapy and combination therapy and hypertension control the first year. Hypertension 2012;59(6):1124–1131.
17. Salam A, Kanukula R, Atkins E, et al. Efficacy and safety of dual combination therapy of blood pressure-lowering drugs as initial treatment for hypertension: a systematic review and meta-analysis of randomized controlled trials. J Hypertens 2019;37(9):1768–1774.
18. SPRINT Research Group, Wright JT Jr,Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373(22):2103–2116.
19. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39(33):3021–3104.
20. Bangalore S, Fakheri R, Toklu B, et al. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients without heart failure? insights from 254,301 patients from randomized trials. Mayo Clin Proc 2016;91(1):51–60.
21. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358(15):1547–1559.
22. Makino H, Haneda M, Babazono T, et al. The telmisartan renoprotective study from incipient nephropathy to overt nephropathy–rationale, study design, treatment plan and baseline characteristics of the incipient to overt: angiotensin II receptor blocker, telmisartan, investigation on type 2 diabetic nephropathy (INNOVATION) study. J Int Med Res 2005;33(6):677–686.
23. Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. JAMA 2004;292(18):2217–2225.
24. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 2008;359(23):2417–2428.
25. Bakris G, Hester A, Weber M, et al. The diabetes subgroup baseline characteristics of the avoiding cardiovascular events through combination therapy in patients living with systolic hypertension (ACCOMPLISH) trial. J Cardiometab Syndr 2008;3(4):229–233.
26. Byrd JB, Bakris G, Jamerson K. The contribution of the ACCOMPLISH trial to the treatment of stage 2 hypertension. Curr Hypertens Rep 2014;16(3):419.
27. Oparil S, Lee J, Karki S, et al. Subgroup analyses of an efficacy and safety study of concomitant administration of amlodipine besylate and olmesartan medoxomil: evaluation by baseline hypertension stage and prior antihypertensive medication use. J Cardiovasc Pharmacol 2009;54(5):427–436.
28. Neldam S, Edwards C, Jones R, et al. Switching patients with uncontrolled hypertension on amlodipine 10 mg to single-pill combinations of telmisartan and amlodipine: results of the TEAMSTA-10 study. Curr Med Res Opin 2011;27(11):2145–2153.
29. Neldam S, Lang M, Jones R, et al. Telmisartan and amlodipine single-pill combinations vs amlodipine monotherapy for superior blood pressure lowering and improved tolerability in patients with uncontrolled hypertension: results of the TEAMSTA-5 study. J Clin Hypertens (Greenwich) 2011;13(7):459–466.

REVIEW ARTICLE

SGLT2i as a First-line Antihyperglycemic in the Management of Type 2 Diabetes in the Context of Indians: A Systematic Review and Consensus

Awadhesh Kumar Singh[1*], Anoop Misra[2], Ashok Kumar Das[3], Anish Behl[4], Ankit Srivastava[5], Arunachalam Paneerselvam[6], Balaji Chidambaram[7], Banshi Saboo[8], Bipin Sethi[9], Brij Mohan Makkar[10], Ganapathi Bantwal[11], Hemant Thacker[12], Jayant Panda[13], Jothydev Kesavadev[14], Krishna G Seshadri[15], Mangesh Tiwaskar[16], Minakshisundaram Shunmugavelu[17], Rakesh Sahay[18], Sambit Das[19], Sanjay Agarwal[20], Shehla Shaikh[21], Surendra Kumar Sharma[22], Sunil Gupta[23], Supratik Bhattacharyya[24], Viswanathan Mohan[25], Vijaya Kumar Gunupati[26]

Received: 05 October 2023; *Accepted:* 10 October 2023

Abstract

Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been used for almost a decade and have proven to be effective not only in managing Type 2 diabetes (T2D), but their cardio and renal protective features make them very useful in managing patients with risk of multiple comorbidities. This systematic review was undertaken by the authors because there is no evidence currently available in India that has studied the suitability of SGLT2i as a first-line agent in patients newly diagnosed with T2D in India.

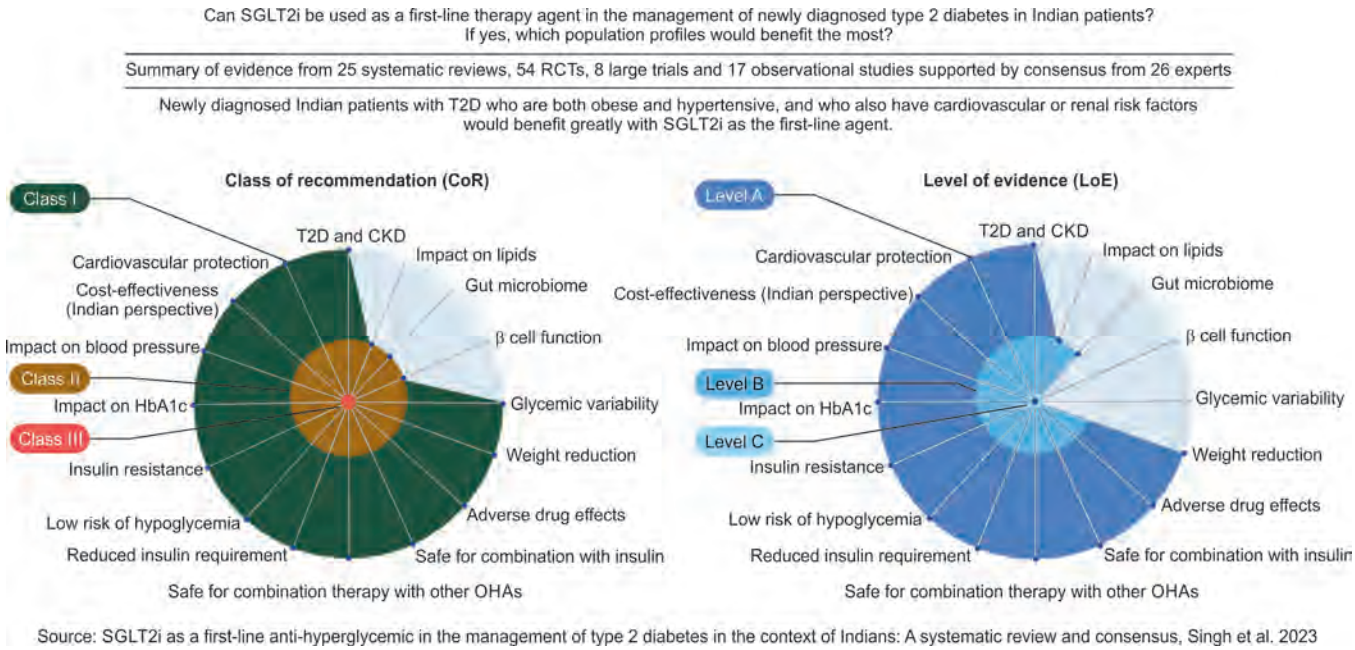
Materials and methods: First, literature was searched to identify features that are considered important when deciding on a first-line agent for managing T2D. A total of 5 broad topics were identified-glycemic control, extra glycemic effects, antihyperglycemic combination therapy, safety, and cost-effectiveness. These domains had further subheadings, and a total of 16 domains were identified. Metformin is the drug of choice as a first-line agent in such situations and has been considered the gold standard for evaluating the effects of SGLT2i across these domains. A systematic literature review on each domain was conducted to compare SGLT2i with the gold standard in Indian patients newly diagnosed with T2D. Evidence was graded (levels of evidence (LoE)—A, B, and C), and recommendations (class of recommendation (CoR)—I, II, and III) were classified by the expert group as defined in the methodology.

Results: According to the systematic reviews conducted, 11 domains had Level A evidence, 2 domains (impact on lipids and gut microbiome) had Level B, and 3 domains had Level C (β-cell function, renal protection, and glycemic variability) evidence. Based on evidence and expert opinion, the authors recommend SGLT2i as a first-line agent for managing newly diagnosed patients with T2D with a Class I recommendation for 13 domains and Class II for the remaining 3 (impact on lipids, gut microbiome, and β-cell function). Although a poorer level of evidence (Level C) was available for the glycemic variability domain, the authors still reported this as Class I recommendations according to their expert opinion and consensus.

Conclusion: This article advocates adopting SGLT2 inhibitors as the primary treatment choice for treating patients with newly diagnosed T2D in India.

Journal of the Association of Physicians of India (2023): 10.59556/japi.71.0422

Visual Abstract



Source: SGLT2i as a first-line anti-hyperglycemic in the management of type 2 diabetes in the context of Indians: A systematic review and consensus, Singh et al. 2023

[1]Consultant Endocrinologist, Department of Diabetology, GD Hospital & Diabetes Institute, Kolkata, West Bengal; [2]Consultant Endocrinologist, Department of Diabetes and Endocrinology, Fortis-C-DOC Hospital, Delhi; [3]Consultant Endocrinologist, Department of Endocrinology, Pondicherry Institute of Medical Sciences, Pondicherry; [4]Consultant Endocrinologist, Department of Endocrinology, Wellness Superspeciality Centre & Apollo BGS Hospitals, Mysuru, Karnataka; [5]Consultant Endocrinologist, Department of Endocrinology, Arogya Diabetes & Endocrine Centre, Ranchi, Jharkhand; [6]Consultant Diabetologist, Department of Diabetology, Aruna Diabetes Centre, Chennai; [7]Consultant Diabetologist, Department of Diabetology, Nithyashree Balaji Diabetes Centre, Kumbakonam, Tamil Nadu; [8]Chief Diabetologist, Department of Diabetology, Dia Care Hormone Clinic, Ahmedabad, Gujarat; [9]Consultant Endocrinologist, Department of Endocrinology, Care Hospitals, Hyderabad, Telangana; [10]Senior Diabetologist and Obesity Specialist, Department of Diabetology, Dr Makkar's Diabetes and Obesity Centre, Delhi; [11]Consultant Endocrinologist, Department of Endocrinology, St Johns Medical College, Bengaluru, Karnataka; [12]Consultant Physician, Cardio-Metabolic Specialist, Department of Internal Medicine, Bhatia Hospital (Tardeo), Breach Candy Hospital (Breach Candy), Mumbai, Maharashtra; [13]Professor and Head, Department of Internal Medicine, SCB Medical College & Hospital, Cuttack, Odisha; [14]Consultant Diabetologist, Department of Diabetology, Jothydev's Diabetes & Research Center, Trivandrum, Kerala; [15]Senior Consultant, American Board-Certified Endocrinology, Department of Diabetes and Metabolism, Diabetes and Endocrinology Clinic, Chennai, Tamil Nadu; [16]Consultant Diabetologist, Department of Diabetology, Shilpa Medical Research Centre, Mumbai, Maharashtra; [17]Consultant Endocrinologist, Department of Endocrinology, Trichy Diabetes Speciality Centre, Tiruchirappalli, Tamil Nadu; [18]Professor and HOD, Department of Endocrinology, Osmania Medical College, Hyderabad, Telengana; [19]Consultant Endocrinologist, Department of Endocrinology, HiTech Medical College and Hospitals, Bhubaneswar, Odisha; [20]Consultant Endocrinologist, Department of Diabetes Care, Aegle Clinic; Department of Medicine and Diabetes, Ruby Hall Clinic, Pune; [21]Consultant Endocrinologist, Department of Endocrinology, Saifee Hospital, Mumbai, Maharashtra; [22]Consultant Endocrinologist, Department of Endocrinology, Diabetes Thyroid and Endocrine Centre, Jaipur, Rajasthan; [23]Consultant Diabetologist, Department of Diabetology, Sunil's Diabetes Care & Research Centre, Nagpur, Maharashtra; [24]Consultant Endocrinologist, Department of Endocrinology, Apollo Clinic, Kolkata, West Bengal; [25]Chairman and Chief of Diabetology, Department of Diabetology, Dr Mohan's Diabetes Specialities Centre, Chennai, Tamil Nadu; [26]Consultant Diabetologist, Department of Diabetology, Diabetes Medicare Centre, Chennai, Tamil Nadu, India; *Corresponding Author

How to cite this article: Singh AK, Misra A, Das AK, *et al.* SGLT2i as a First-line Antihyperglycemic in the Management of Type 2 Diabetes in the Context of Indians: A Systematic Review and Consensus. J Assoc Physicians India 2023;71(12):62–74.

Introduction

Type 2 diabetes (T2D) as a disease presents the ultimate challenge for researchers, clinicians, and patients in the 21st century. Being a disorder that arises from a complex interplay between genetics, environmental, and lifestyle factors, affecting other homeostatic functions of the body synchronized by insulin activity, strategizing the aims of antidiabetic therapy itself can become an arduous task for the clinical community, let alone the therapy. It can be argued agreeably that the Indian population is already at significant risk for developing T2D, but these risk factors are not unique to T2D; instead, they contribute to a battery of other disorders that creep silently and become salient drivers of all-cause mortality in people with T2D.[1]

The high prevalence of coronary and peripheral artery disease in people with T2D has been well recognized for more than a century, yet objectives focusing on glycemic control, insulin resistance, and lifestyle interventions, which are central to the management of T2D, remain elusive in terms of their direct impact on the improvement of cardiovascular (CV) event rates.[2] The last decade has seen several clinical trials of antihyperglycemic agents (AHAs) reporting promising results for CV and renal outcomes. Not only has this led to debates on the ideal drug choice for first-line treatment in T2D in general, but it has also led to the identification of patient profiles that may benefit more from cardiac to renal protective first-line antihyperglycemic treatments—the younger Indian adults with T2D.[3]

The primary objective of this paper is to ascertain whether sodium-glucose cotransporter-2 inhibitors (SGLT2i) can be utilized as a first-line agent in patients newly diagnosed with T2D. Metformin is the gold standard in managing such patients, and thus, a direct structured, evidence-based comparison with SGLT2i is imperative for elucidating whether SGLT2i can actually be prescribed in this profile of Indian patients.

Materials and Methods

A lot has changed in managing T2D, both from a metabolic and a pharmacotherapeutic perspective. Thus, the expectations from a first-line therapy agent have also evolved. An exhaustive literature search was done to identify the most relevant factors determining an agent's suitability as a first-line therapy, in general, and in T2D. Supplementary material 1 (SM1) delineates the search strategy and methods.

Table 1 highlights a list of the topics and their respective domains that were identified as considerations before starting a patient with T2D on first-line monotherapy. Systematic literature search results and a Delphi-based discussion of the expert panel influenced this list of these factors.

A systematic literature search was conducted for each factor identified in Table 1. Cochrane, PubMed, Google Scholar, Science Direct, Clinical Trials (.gov), Clinical Trials Registry of India, medRxiv, Prospero, and Gray literature databases were searched with respective search strategies. The search criteria, strategies, methods, and selected papers are tabulated in Supplementary material 1 (SM1). For all databases, the following population (P), intervention (I), comparison (C), and outcomes (O) were used (mentioned in Supplementary material 2 (SM2).

The context-based search strategy was as follows:

- P = P1 OR P2 OR P3, P1: newly diagnosed people with T2D, P2: people with T2D who were only on diet and lifestyle interventions without any drug therapy, P3: people with T2D who may have been a previous therapy for T2D but were included in the study after a washout period of at least 4 weeks.
- I = I1 OR I2 OR I3 OR I4, I1: dapagliflozin monotherapy, I2: Canagliflozin monotherapy, I3: empagliflozin monotherapy, I4: ertugliflozin monotherapy, I5: remogliflozin monotherapy.
- C = C1 OR C2. C1: placebo, C2: metformin.
- O = based on the factors.

Appropriate search strategies were created for different databases, and relevant papers were selected as per the selection criteria. Evidence was synthesized for all domains, and the findings were presented to the expert panel.

Class of recommendation (CoR) indicates how strong a recommendation is, considering the assumed benefit vs risks and costs on a scale from I to III. Recommendation classes I and III each convey a clear message, namely a general consensus that a measure is either useful (CoR I), not useful, or even harmful (CoR III). If there is no general consensus or only doubtful evidence, an optional recommendation is conveyed with CoR II. The level of evidence (LoE) indicates how reliable the evidence underlying each recommendation is on a scale from A to C. Importantly, the CoR and LoE are independent of each other; for example, strong recommendations may build on weak evidence if the assumed benefit of an intervention or a diagnostic procedure greatly outweighs the potential risks (Table 2).

The authors framed recommendations after carefully reviewing the literature and expert consensus. Finally, all recommendations were classified into different classes. This methodology has been used elsewhere as well.[4]

Results

Glycemic Control

Glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and postprandial glucose (PPG) values are typically used to assess glycemic control. Control of postlunch glucose levels will help in maintaining the HBA1c levels. PPG and glycemic variations are risk factors for complications related to T2D. SGLT2i effectively reduces HbA1c levels, a measure of long-term blood sugar control, along with FPG and PPG.

Impact on HbA1c

Seven studies were included in which SGLT2i was directly compared with metformin. Of these seven studies, six randomized controlled trials (RCTs) and one systematic review and meta-analysis were included.

An RCT conducted by List et al.[5] in 2009 reported that adjusted mean reductions of HbA1c of dapagliflozin 10 and 50 mg (−0.85 to −0.90%) were slightly better than metformin (−0.73%). Adjusted mean PPG area under the curve (AUC) reductions in the dapagliflozin group (−7,053 to −10,149 mg/minute/dL) were superior when compared to metformin (−5,891 mg/minute/dL). In 2013, Ferrannini et al.[6] reported that both empagliflozin (−0.51–0.60%) and metformin (−0.64%) significantly reduced HbA1c levels during a 90-week trial. Ipragliflozin showed a better decrease in HbA1c (−0.49 to −0.81%) compared to metformin (−0.72%) and placebo, based on a study by Fonseca et al.[7] in 2013. RCT conducted by Aronson et al.[8] in 2018 reported that ertugliflozin at a 26-week period showed better mean HbA1c values (7.3%) when compared to placebo/metformin (7.8%). Shibuya et al.[9] in 2018 reported that Luseogliflozin (7.8 vs 6.5) had shown a better reduction in HbA1c when compared to metformin (7.4 vs 7.3). Hao et al.,[10] in 2022, reported that HbA1c was significantly lower in the canagliflozin group (−0.8 ± 0.4) compared to the metformin group (−0.2 ± 0.2). A systematic review and meta-analysis conducted by Pinto et al.[11] (39 RCTs, *n* = 25,468) in 2015 reported that SGLT2i was similar to metformin in decreasing HbA1c but was superior to placebo.

Recommendations and statements	*CoR*	*LoE*
SGLT2i can be considered a first-line in the management of T2D than metformin based on its impact on HbA1c	I	A

Glycemic Variability (GV)

Glycemic variability (GV), or glycemic fluctuation, is a clinical predictor and a key objective in managing diabetes to prevent

Table 1: List of topics and their respective domains

Glycemic control	*Extraglycemic effect*	*Antihyperglycemic combination therapy*	*Safety*	*Cost-effectiveness*
Direct impact on HbA1c	Preserve and enhance β-cell function	Safe for combination therapy with any OHAs	Low risk of hypoglycemia	Cost-effectiveness
Reduce GV	Improvement in insulin resistance	Safe for combination with insulin and reduces insulin requirement	Adverse drug effects	
	Impact gut microbiome			
	Weight reduction			
	BP regulation			
	Lipid-lowering effect			
	Renal protection			
	CV protection			

Table 2: Class of recommendation (CoR) and LoE

CoR		*LoE*		
	Definition		*Definition*	*Interpretation*
I	Evidence or general agreement that a treatment/test/procedure is beneficial, useful, or effective and that potential benefits clearly outweigh the potential risk	A	RCT or meta-analysis of RCTs with CVD outcomes; single trial enough if sufficient power and without important limitations	Strong evidence. Evidence of high certainty. It is unlikely that future studies will change the effect estimate substantially
II	Conflicting evidence or opinion about the benefit, usefulness, and effectiveness of a treatment/test/procedure or uncertainty about the benefit–risk balance	B	RCT with surrogate measures; observational studies with CVD outcomes and no major limitations; meta-analyses including the above study types	Moderate evidence. Evidence with some future studies may modify, at least the magnitude of, the effect estimate
III	Evidence or general agreement that a treatment/test/procedure is not beneficial, useful, or effective or that potential risks outweigh the potential benefit	C	Observational studies of surrogate measures; any study type may be downgraded to level C due to limitations; expert opinion	Weak evidence. Evidence of low certainty. Future studies may change the effect estimate substantially

vascular complications and enhance glycemic control.[12] Indexes representing GV include the mean amplitude of glucose excursion (MAGE), mean blood glucose (MBG) levels, standard deviation of mean blood glucose (SDMBG), and percentage of time maintaining euglycemia.[12,13]

Due to the nonavailability of literature that directly compares SGLT2i with metformin, we have included two RCTs, which compared SGLT2i with placebo in drug-naive patients or with a drug washout period. There was no literature that compared the effect of metformin monotherapy on GV. Many studies compared metformin in prediabetics or in conjunction with another oral antihyperglycemic medication or insulin. We included one study comparing metformin with post-meal exercise regarding GV.

Nishimura et al.[14] in 2015 conducted an RCT and reported that patients treated with empagliflozin showed no significant changes in MAGE, but curves of mean glucose [continuous glucose monitoring (CGM)] lowered in the empagliflozin group when compared to the placebo. It helped in improving daily glucose control. An RCT conducted by Li et al.[15] in 2016 reported that post-24 weeks, there was a significant improvement in MAGE (3.48 ± 0.98 vs placebo group 5.37 ± 2.16, $p = 0.010$) and SDMBG (2.43 ± 1.09 vs 1.51 ± 0.42, $p < 0.05$) with dapagliflozin therapy. Patients exhibited a reduction in 24-hour MBG (7.50 ± 1.49 vs 9.46 ± 1.16 mmol/L, $p = 0.026$) with lower mean plasma glucose concentrations.

In 2017, Erickson et al.[16] conducted a randomized crossover design study that revealed noteworthy findings (metformin vs postmeal exercise). The study demonstrated that metformin reduced time-averaged glucose levels (24-hour main effect: $p = 0.040$, 12-hour main effect: $p = 0.033$). Additionally, exercise was associated with a decrease in MAGE (24-hour main effect: $p < 0.001$, 12-hour main effect: $p = 0.042$) as well as metformin (12-hour main effect: $p = 0.028$). Furthermore, both exercise (24-hour main effect: $p = 0.043$, 12-hour main effect: $p < 0.001$) and metformin treatment (12-hour main effect: $p = 0.070$) contributed to a reduction in standard deviation.

Recommendations and statements	*CoR*	*LoE*
SGLT2i, as a first-line agent, may be as effective as metformin in terms of impact on GV	I	C

Extraglycemic Effect

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) improves β-cell function and insulin sensitivity and reduces insulin resistance without affecting insulin secretion. They preserve β-cell mass, improve its function, and help in better long-term glycemic control. SGLT2i has been discovered to change the makeup of gut bacteria, potentially boosting the growth of beneficial bacteria and enhancing gut health.

β-Cell Function

The fundamental pathogenic consequences of T2D include progressive β-cell dysfunction and failure. Diminished β-cell function on diagnosis and sustained decline in β-cell mass and function in T2D suggests that medical management targeting pathogenic β-cell deterioration is needed.[17] The proinsulin/insulin ratio (PI/IR)[18] *via* β-cell dysfunction and the homeostasis model assessment of β-cells (HOMA-β)[19] can be measured in diabetes. While the decrease in PI/IR generated by proinsulin shows improvement in the secretory β-cells, the increase in HOMA-β shows retention of β-cell function.[20]

Due to the nonavailability of literature directly comparing SGLT2i with metformin, we have included six studies that compared SGLT2i with a placebo. Of these six studies, four were RCTs, and two were observational studies. There was no literature that compared the effect of metformin monotherapy on β cell function. Many studies compared the use of metformin in rats or in conjunction with another oral antidiabetic medication or insulin. We have included two important studies done on metformin regarding β-cell function.

Randomized controlled trials (RCT) conducted by Inagaki et al.[21] in 2013 proved that canagliflozin improved β-cell function (HOMA-β) (2.97 ± 1.84–6.98 ± 1.94) and PI/IR (−0.0482 ± 0.0177 to −0.0500 ± 0.0186) compared to placebo. Another study by Kutoh et al.[22] in December 2018 suggested that SGLT2i preserved and enhanced β-cell function and reduced insulin sensitivity. β-cell function improvement was observed in studies conducted by Stenlöf et al.[23] in 2013 and Kutoh et al.[24] in March 2018, which reported an increase in HOMA-β and a decrease in PI/IR observed when patients were on canagliflozin (100 and 300 mg) compared with a placebo. Ferrannini et al.[25] in 2022 reported that SGLT2i-induced glucosuria improved β-cell function and insulin sensitivity compared to placebo. A study conducted by Polidori et al.[26] in 2014 [canagliflozin treatment and trial analysis–monotherapy (CANTATA-M)] revealed that SGLT2i improved insulin secretion by the β cells of the pancreas.

Within the context of the United Kingdom Prospective Diabetes Study (UKPDS),[27] individuals diagnosed with newly onset T2D and treated with metformin experienced an initial boost in β-cell function (evaluated through HOMA) during the 1st year. Nevertheless, this improvement was subsequently followed by a decline despite the persistent enhancement of insulin sensitivity due to metformin. Similarly, findings from the A Diabetes Outcome Progression Trial (ADOPT)[28] study, which concentrated on individuals recently diagnosed with T2D, indicated a minor initial advantage of metformin in terms of β-cell function [measured in response to oral glucose tolerance test (OGTT)], which was subsequently accompanied by a gradual decrease. Many studies have also shown that metformin neither preserves β-cell function[29] nor prevents progressive β-cell failure.[30,31]

Recommendations and statements	*CoR*	*LoE*
SGLT2i as a first-line agent may be as effective as metformin in terms of impact on β cell function	II	C

Insulin Resistance

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) enhances β-cell activity by reducing glucotoxicity rather than promoting insulin release. They also reduce insulin resistance and boost insulin sensitivity.[32] Homeostatic model assessment of insulin resistance by homeostasis model assessment-estimated insulin resistance (HOMA-IR) index mainly reflects liver insulin resistance, the glucose clamp method mainly reflects muscle insulin resistance, and the insulin sensitivity index reflects insulin sensitivity in both liver and muscle.[33]

A total of two studies were included in which SGLT2i was directly compared with metformin. Of these two studies, one RCT and one systematic review and meta-analysis were included.

Hao et al.,[10] in 2022, conducted an RCT that compared canagliflozin to metformin with regard to insulin resistance (HOMA), subcutaneous, and visceral adipose tissue. It was noted that patients on canagliflozin (2.5 ± 0.4 vs 1.7 ± 0.5) had a better reduction in HOMA-IR and visceral adipose tissue compared to metformin (2.4 ± 0.4 vs 2.1 ± 0.4). A systematic review and meta-analysis conducted by Fakhrolmobasheri et al.[34] (16 RCTs, $n = 1,177$) reported that SGLT2i significantly increased insulin sensitivity [standardized mean difference (SMD) 0.72 (0.32–1.12)] in T2D patients and are not inferior to metformin in reducing insulin resistance.

Recommendations and statements	CoR	LoE
SGLT2i as a first-line agent may be as effective as metformin in terms of impact on insulin sensitivity	I	A

Gut Microbiome

The gut microbiota converts nondigestible carbohydrates into short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, which are then used to control host metabolism. Therefore, changes in the microbiota (gut dysbiosis) can lead to disorders in other organs as well, such as the brain, heart, pancreas, liver, adipose tissues, muscles, and kidneys, in addition to the digestive system.[35] Certain bacterial populations (*Roseburia*, *Eubacterium*, *Escherichia–Shigella*, *Bilophila*, and *Hungatella*) that are generally found in the intestines (gut microbiota), are being considered crucial in the development of obesity, metabolic syndrome, and T2D when certain conditions cause gut dysbiosis. Alterations in the microbiota can result from exposure to various environmental factors, including diet, toxins, drugs, and pathogens.

As per inclusion criteria, only one RCT was included that compared SGLT2i with metformin in drug-naive patients.

An RCT conducted by Deng et al.[36] in 2022 reported that empagliflozin significantly reshaped the gut microbiota and increased the levels of plasma metabolites such as sphingomyelin, short-chain fatty acid-producing bacteria (*Roseburia* and *Eubacterium*) and reduced harmful bacteria (*Escherichia–Shigella*, *Bilophila*, and *Hungatella*). While metformin treatment was only associated with changes in blood glucose levels and body weight-related modifications in plasma metabolites and gut bacteria, empagliflozin modified plasma metabolites and gut bacteria related to blood glucose levels, inflammatory factors, and cardiovascular disease (CVD)—related factors.

According to current research and knowledge, metformin significantly affects the gut microbiota and microbial metabolites, while SGLT2i have slighter effects. Many human studies[37–40] have shown that metformin strongly altered the gut microbiome and its function in individuals with treatment-naive T2D.[39] There is a paucity of SGLT2i studies on humans, and animal studies have shown limited benefits on gut microbiota. Additionally, the positive influence of SGLT2i could be attributed to the possibility that participants were previously under metformin treatment, masking the potential influence of SGLT2i on the gut microbiome.[41]

Recommendations and statements	CoR	LoE
SGLT2i as a first-line agent may be as effective as metformin in terms of impact on the gut microbiome	II	B

Impact on Weight

Type 2 diabetes (T2D) is associated with obesity and physical inactivity. The lack of weight management in T2D patients and the urgent need to identify effective ways to address diabetes and obesity have given rise to a new term: diabesity.[42] A biphasic weight loss pattern has been observed in clinical studies with SGLT2i: a substantial early impact, perhaps due to improved fluid excretion, was followed by a steady rise, with mean weights lower than baseline at any assessment.[43,44] The initial weight loss is due to caloric loss owing to glucose excretion (calorie restriction mimicry) and water loss due to osmotic diuresis.[45]

Seven studies were included in which SGLT2i was directly compared with metformin. Of these seven studies, one systematic review and meta-analysis, six RCTs were included.

An RCT conducted by List et al.[5] in 2009 reported a greater reduction in body weight by different doses of dapagliflozin (–2.5 to –3.4) compared to metformin (–1.7). In 2013, Ferrannini et al.[6] reported that empagliflozin (–1.87 to –2.08) showed a better reduction in body weight when compared to metformin (–0.89) during a 90-week trial. In a study conducted by Fonseca et al.[7] in 2013, dose-dependent weight loss was higher in the ipragliflozin group (–0.50 to –1.67) when compared to metformin (–0.12). The mean change from baseline to 52 weeks in empagliflozin and metformin groups was –3.6 and –3.7, respectively, as Aronson et al.[8] reported in 2018. An RCT conducted by Shibuya et al.[9] in 2018 has shown that luseogliflozin (27.9 vs 27 kg/m^2) was superior to metformin (27.2 vs 27.3 kg/m^2) in reducing body mass index (BMI). Hao et al.[10] in 2022 reported a reduction in BMI (–0.5 vs –0.2), waist–hip ratio (–0.03 vs –0.01), subcutaneous adipose tissue (–3.5 vs –2.4) from baseline to 12 weeks in canagliflozin group when compared to metformin. Systematic review and meta-analysis conducted by Pinto et al.[11] in 2015 have shown that SGLT2i (–2.66 kg (canagliflozin); –1.81 kg (empagliflozin); –1.80 kg (dapagliflozin) are better than metformin (–1.04 kg) in reducing weight.

Recommendations and statements	CoR	LoE
SGLT2i as a first-line agent may be as effective as metformin in terms of impact on weight	I	A

Impact on Blood Pressure (BP)

Reduction of arterial BP is associated with a reduction of CV morbidity and mortality in patients with T2D.[46] Benefits of SGLT2i include its effect on arterial stiffness, increased glucose excretion alone results in an extra osmotic diuretic impact, and blockage of the cotransporters in the proximal tubule induces a slight rise in sodium urine output (natriuretic effect). Secondly, it has also been suggested that losing weight and reducing sympathetic nervous system activity might lower BP.[47]

Five studies were included in which SGLT2i was directly compared with metformin. Of these five studies, one systematic review and meta-analysis, four RCTs were included.

An RCT conducted by List et al.[5] in 2009 has reported a greater reduction in systolic (–2.6 to –6.4 vs –0.4) and diastolic (–2.6–0.8 vs –0.6) BP in dapagliflozin group when compared to metformin group. In 2013, Ferrannini et al.[6] reported that empagliflozin showed a better reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline. The change from baseline [95% confidence interval (CI)] in SBP for empagliflozin was 0.1 to –1.7 and 2.0 for metformin. The change from baseline (95% CI) in DBP for empagliflozin was –1.6 to –2.2 and –0.6 for metformin. There was a slight increase in the systolic (–3.0–0.5 vs 3.1) and diastolic (–0.1–0.4 vs 1.5) BP in the metformin group when compared to ipragliflozin, based on a study by Fonseca et al.[7] in 2013. The mean change from baseline to 52 weeks was more in both systolic (–3.7 vs –2.4) and diastolic (–0.8 vs –0.2) BP in the ertugliflozin group when compared to metformin as reported by Aronson et al.[8] in 2018. A systematic review and meta-analysis conducted by Pinto et al.[11] in 2015 has shown that SGLT2i is better than metformin in reducing SBP.

Recommendations and statements	CoR	LoE
SGLT2i, as a first-line agent, may be as effective as metformin in terms of impact on BP	I	A

Impact on Lipids

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) has a significant impact on adipose tissue with an increase in lipid mobilization and lipolysis.[48] They reduce insulin concentration, a potent inhibitor of lipolysis, and therefore cause increased lipolysis.[49]

A total of one RCT was included in which SGLT2i was directly compared with metformin.

VERTIS-MONO extension study by Aronson et al.[8] in 2018 reported an increase

in low-density lipoprotein cholesterol (LDL-C) (98.6–101.7 vs 99.7–103.3) and high-density lipoprotein cholesterol (HDL-C) (45.3–46.3 vs 47.4–51.3) levels in the ertugliflozin groups compared with decreased LDL-C (99.2 vs 89.8) and increased HDL-C (45.9 vs 48.2) in the placebo/metformin group, although there was no increase in the LDL-C:HDL-C ratio. SGLT2i causes a modest increase in LDL-cholesterol and HDL-cholesterol, while metformin decreases LDL-C and increases HDL-C.[50,51]

Recommendations and statements	*CoR*	*LoE*
SGLT2i as a first-line agent may be as effective as metformin in decreasing LDL-C and increasing HDL-C	II	B

Cardiovascular (CV) Protection

The leading cause of mortality worldwide is CVD,[52] and patients with T2D have a two- to threefold higher risk of developing CVD.[53,54] The cause of mortality in T2D patients is ascribed to CVD in about 40% of cases. Additionally, patients with T2D have a high incidence of nonfatal CV events, with heart failure (HF) hospitalizations making up as much as 33% of these events.[55,56] A recent observational study conducted by Unnikrishnan et al.[57] in 2022 suggested that Indian patients with diabetes had a CVD risk of 15.3 ± 12.3%. Early diagnosis and prevention of CV complications are very important in managing patients with T2D.

Four RCTs were included in which SGLT2i was directly compared with metformin. Eleven important trials conducted on the cardiac protection of SGLT2i are included.

Chen et al.[58] in 2020 suggested that use of SGLT2i has reduced events of HF hospitalization [hazard ratio (HR) 0.47 (95% CI 0.41–0.54, $p < 0.0001$)], acute coronary syndrome (HR 0.50 (95% CI 0.41–0.61, $p < 0.0001$)), and all-cause mortality [HR 0.49 (95% CI 0.44–0.55, $p < 0.0001$)], but increased events of ischemic stroke [HR 1.21 (95% CI 1.10–1.32, $p < 0.0001$)] compared with metformin as first-line treatment. An RCT conducted by Hao et al.[10] in 2022 reported that, when compared to the metformin group, the volume of visceral adipose tissue (associated with cardiometabolic disorders) was also lower in the SGLT2i group. RCT conducted by Deng et al.[36] in 2022 reported that empagliflozin showed HbA1c reduction and improved CVD risk factors. Only individuals receiving empagliflozin showed a drop in BP and uric acid levels and increased hematocrit and adipokine. The considerable improvement in clinical indicators of CVD risk factors in this research indicates that empagliflozin is more helpful to the CV system. Shin et al.,[59] in 2022, conducted an observational study that compared SGLT2i to metformin and reported that patients on SGLT2i had a lower risk for myocardial infarction (HR, 0.70; CI, 0.48–1.00), all-cause mortality (HHF/mortality) (HR, 0.80; CI, 0.66–0.97) and HF hospitalizations (HR, 0.78; CI, 0.63–0.97). A mini-review by Koufakis et al.[60] in 2023 suggested that T2D patients with cardiorenal issues benefit more from SGLT2i.

International Guidelines

American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) Guideline for the Management of Heart Failure, 2022 recommends SGLT2i in patients with T2D as primary prevention for HF, patients with heart failure and reduced ejection fraction (HFrEF), and for patients with heart failure and preserved ejection fraction (HFpEF).[61] The American Diabetes Association (ADA), 2022 standards of care[62] and Expert Consensus Statement, 2020[63] by the ACC suggest using SGLT2i as the first line of treatment for glucose control and high-risk for established heart disease. The Korean Diabetes Association (KDA)[64] in 2021 and the consensus statement by the American Association of Clinical Endocrinologists (AACE)[65] and the American College of Endocrinology in 2020 recommend SGLT2i as initial therapy for individuals with T2D with or at high-risk atherosclerotic cardiovascular disease (ASCVD), HF, and/or chronic kidney disease (CKD).

Important Trials: SGLT2i

DELIVER trial ($n = 6,263$) conducted by Peikert et al.[66] in 2022, SOLOIST-WHF study ($n = 1222$) by Bhatt et al.[67] in 2021, EMPEROR-Reduced study ($n = 1,863$) by Packer et al.[68] in 2020, VERTIS CV study ($n = 8,246$) by Cannon et al.[69] in 2020, DECLARE-TIMI ($n = 17,160$) by Wiviott et al.[70] in 2019 and Cahn et al.[71] in 2021, CREDENCE Trial ($n = 4,401$) by Mahaffey et al.[72] in 2019 and EMPA-REG OUTCOME ($n = 7,020$) trial by Zinman et al.[55] in 2015 have shown that treatment with SGLT2i resulted in a significantly lower rate of CV death or hospitalization for HF when compared to placebo. A *post hoc* analysis was performed on EMPA-REG data by Levin et al.[73] in 2020, and it was found that the reduction in risk of CV outcomes with empagliflozin and placebo showed consistent results. Packer et al.,[74] in an EMPEROR-preserved study, suggested that empagliflozin reduced inpatient and outpatient HF events. DAPA HF[75] trial ($n = 4,744$) has reported among patients with HF and a reduced ejection fraction, the risk of worsening HF or death from CV causes was lower among the dapagliflozin group when compared to the placebo.

Recommendations and statements	*CoR*	*LoE*
SGLT2i, as a first-line agent, may be superior to metformin in providing CV protection in people with CVD and/or HF	I	A

Renal Protection

Renal abnormalities are widespread in T2D, with roughly 50% of patients acquiring some level of renal impairment over time.[76] Many individuals with diabetes already have some degree of renal impairment or abnormalities at diagnosis. As a result, end-stage kidney disease (ESKD), CKD, or both develop over time. SGLT2i work on the extracellular surface of the brush border cell membrane (proximal convoluted tubule—90% of the kidney's reabsorption of glucose), which they reach *via* glomerular filtration and tubular secretion.[77,78] They reduce blood glucose levels and enhance urinary glucose excretion by inhibiting renal glucose reabsorption.

Due to the nonavailability of literature directly comparing SGLT2i with metformin, we have included three systematic review and meta-analysis studies that compared SGLT2i with placebo and seven large trials. RCTs are scarce to evaluate the renoprotective function of metformin monotherapy in patients with T2D. We have included five observational studies and one systematic review.

A systematic review and meta-analysis (27 studies, $n = 7,363$) conducted by Toyama et al.[79] in 2019 has concluded that SGLT2i reduced the annual decline in estimated glomerular filtration rate (eGFR) slope (annual mean difference in kidney function between treatment and control: 1.35 mL/1.73 m^2/year; 95% CI, 0.78–1.93) risk of composite renal outcomes [doubling of serum creatinine (Scr), ESKD, or renal death: HR, 0.71; 95% CI, 0.53–0.95] in patients with T2D and CKD. SGLT2i substantially reduced the risk of dialysis, transplantation, or death due to kidney disease [relative risk (RR) 0.67, 95% CI 0.52–0.86, $p = 0.0019$], reduced ESKD (0.65, 0.53–0·81, $p < 0.0001$), and acute kidney injury (AKI) (0.75, 0.66–0.85, $p < 0.0001$) based on a meta-analysis conducted on important trials.[80] SGLT2i are linked to a notable reduction in adverse renal events, and these benefits are evident even in individuals with an eGFR of <60 mL/minute/1.73 m^2.[81] Zelniker et al.[82] in 2019 conducted a systematic review and meta-analysis and reported that SGLT2i reduced the progression of renal disease by 45% [0.55 (0.48–0.64), $p < 0.0001$] with or without CVD.

In 2016, the United States Food and Drug Administration affirmed the safety of metformin for individuals with mild to moderate kidney impairment (eGFR: 30–60 mL/minute/1.73 m^2), but metformin use is contraindicated in patients with eGFR values <30 mL/minute/1.73 m^2.[83] Notably, research has highlighted the potential protective qualities of metformin in various conditions, including AKI, CKD, diabetic kidney disease (DKD), autosomal dominant (adult) polycystic kidney disease (ADPKD), lupus nephritis (LN), renal neoplasms, and kidney transplantation.[84–89]

In 2012, Ekström et al.[90] conducted a cohort study involving 51,675 participants from the Swedish National Diabetes Register. The study revealed that among patients with an eGFR ranging from 45 to 60 mL/minute/1.73 m^2, metformin was associated with reduced risks of acidosis/serious infection (adjusted HR 0.85, 95% CI 0.74–0.97) and all-cause mortality (HR 0.87, 95% CI 0.77–0.99). Notably, no heightened risks of all-cause mortality, acidosis/serious infection, or CVD were observed in patients with an eGFR of 30–45 mL/minute/1.73 m^2. Hsu et al.,[91] in their study, concluded that continuous treatment with metformin in patients with moderate CKD and T2D caused a decrease in renal function. Bell et al.[84] in 2017 conducted a large cohort study (n = 25,148) and reported that metformin was associated with a higher rate of survival at 28 days (HR 0.81, 95% CI 0.69, 0.94, p = 0.006) in AKI patients. Metformin was associated with a decreased risk of severe kidney failure based on a cohort study (n = 469,688) by Hippisley-Cox et al.[92] Zhang et al.[93] in 2022 reported that kidney function markers [Scr and blood urea nitrogen (BUN)] were reduced in the metformin group when compared to the control group. A systematic review (17 observational studies) conducted by Crowley et al.[94] in 2017 reported that metformin was associated with reduced all-cause mortality in patients with CKD (eGFR = 30–60 mL/minute/1.73 m^2).

Important Trials: SGLT2i

EMPA-KIDNEY[95] study (n = 6,609) has reported that patients in the empagliflozin group had fewer hospitalizations and reduced composite risk outcomes of kidney disease progression. Heerspink et al.[96] in 2020 conducted a study (DAPA-CKD; n = 4,304) that reported patients on dapagliflozin showed significant reductions in the primary renal composite endpoint (eGFR <50%, ESKD, or renal or CV death) when compared to placebo. CREDENCE trial (n = 4,401) conducted by Perkovic et al.[97] in 2019 in patients with CKD and T2D has shown results similar to DAPA-CKD with a doubling of Scr as an added primary composite endpoint. EMPA-REG OUTCOME (n = 7,020) study by Zinman et al.[55] in 2015 suggested that fewer patients in the empagliflozin group experienced worsening nephropathy due to slower progression to macroalbuminuria. The CANVAS[56] study (n = 10,142) showed similar results, with the progression of albuminuria occurring less frequently with canagliflozin. DECLARE-TIMI 58 study (n = 17,160) by Cahn et al.[71] in 2021 included patients with T2D and multiple CV risk factors. Dapagliflozin was associated with significant decreases in renal composite endpoints and urinary albumin-to-creatinine ratio. According to the EMPEROR-REDUCED trial by Packer et al.[68] in 2020, the annual rate of decline in the eGFR was slower in the empagliflozin group than in the placebo group with less serious renal outcomes. Multiple studies have shown greater declines in eGFR while using SGLT2i,[98,99] and few studies reported no significant changes in eGFR during longer-term treatments.[100]

Recommendations and statements	*CoR*	*LoE*
SGLT2i as a first-line agent may be more effective than metformin in people with T2D and CKD	I	A
SGLT2i as a first-line agent may be as effective as metformin in terms of its impact on renal protection	I	C

Antihyperglycemic Combination Therapy

Combination treatment is required to address all pathophysiological routes of T2D and euglycemia since monotherapy alone cannot treat many pathophysiological abnormalities.[101] Additionally, the drug combination should work to restore overall metabolic health rather than just reducing levels of HbA1c. Combination therapy helps target multiple pathways involved in glucose regulation, leading to better glycemic control.

Safe for Combination Therapy with Other Oral Hypoglycemic Agents (OHAS)

The only OHA that specifically targets impaired glucose reabsorption in the kidney, a crucial part of the ominous octet (impaired function of eight organ sets), is SGLT2i.[102] If HbA1c targets are not met after 3 months of monotherapy, the ADA and the European Association for the Study of Diabetes (EASD) advise starting "dual combination therapy" and moving on to "triple combination therapy" if those targets are still not met after 3 months of dual therapy. Furthermore, if the goal HbA1c levels are not reached after 3 months of triple combination treatment, it is advised that insulin (basal or prandial) be administered in addition to the oral glycemic agent.[103]

A total of 23 studies were included: six were RCTs, 12 were systematic reviews and meta-analyses, four were observational studies, and one was a large trial.

Clar et al.[104] (seven RCTs, n = 3,849) in 2012 has shown that combination therapy of dapagliflozin and other OHAs has a better reduction in HbA1c (−0.21 to −0.54%), weight loss (−1.81 to −2.3 kg), than a combination with placebo. When used as a combination therapy, empagliflozin reduced glycemic parameters along with a reduction in CV risk mortality.[105,106] Subgroup analysis of a systematic review conducted by Xu et al.[107] (15 studies) in 2022 reported that compared with placebo, dapagliflozin combined with metformin [mean difference (MD) = −0.45, 95% CI: −0.61 to 0.29, p < 0.00001], insulin (MD = −0.59, 95% CI: −0.83 to −0.36, p < 0.00001), or exenatide (MD = −0.26, 95% CI: −0.53 to 0.01, p < 0.00001) showed a significant reduction in HbA1c levels. With the advent of newer sulfonylureas (SUs), the incidence of hypoglycemic events has reduced. SGLT2i, in combination with SUs, has been shown to lower HBA1c (−0.74 to −0.83%) and other parameters [body weight (−1.8%)], but caution was advised regarding the side effects.[108] The combination of SGLT2i with dipeptidyl peptidase-4 inhibitors (DPP-4i) has better glycemic control with fewer side effects, and a triple therapy along with metformin is preferred.[109,110] This is supported by a systematic review and meta-analysis by Min et al.[111] (seven RCTs, n = 2082) in 2018 and expert opinion by Chadha et al.[112] in 2022. A systematic review and meta-analysis conducted by Li et al.[113] (eight RCTs, n = 1895) in 2022 have concluded that combination therapy of SGLT2i and glucagon-like peptide-1 receptor agonists (GLP-1RA) has a superior effect in reducing HbA1c (0.77–1.75%), BP (SBP: −0.33 mm Hg), lipid values (LDL-C: −23.41 mmol/L). Metformin and SGLT2i complement each other's action, help decrease glycemic parameters and BP, and are well tolerated. This is proved in a systematic review by Kuecker et al.[114] (seven RCTs) in 2016, Jingfan et al.[115] (nine RCTs, n = 2,509) in 2019, Chen et al.[116] (five RCTs, n = 847) in 2019 Gebrie et al.[117] (nine RCTs, n = 10,974) in 2020 and an RCT by Häring et al.[118] in 2014. A systematic review (four RCTs, n = 3749) has shown that the initial dose combination of metformin with SGLT2i has better glycemic reduction benefits than a high dose[119] but with a risk of lactic acidosis and ketoacidosis.[51]

Triple combination therapy of SGLT2i, SU, and metformin has shown favorable

results in achieving the glycemic targets.[120,121] SGLT2i, DPP-4i, and metformin have also shown promising results in reducing blood glucose values.[122–124] Combination with thiazolidinediones has improved glucose levels, but genital mycotic infections (GMIs) were more common.[125]

Recommendations and statements	*CoR*	*LoE*
SGLT2i, as a first-line agent, may be as safe as metformin for combination therapy with other OHAs	I	A

Safe for Combination with Insulin and Decreased Insulin Requirement

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) is a potential class of drugs for use in conjunction with exogenous insulin. They lower insulin dosage needs, mitigate insulin-induced weight gain, and improve glucose control,[126] but the side effects of SGLT2i should be considered.

A total of 11 studies were included: six were RCTs, one was a systematic review and meta-analysis, two were large trials, and two observational studies were included.

Wilding et al.[127] in 2014 conducted a study for 2 years and reported that dapagliflozin when administered with insulin, reduced the glycemic variables (−0.4%) and weight (0.9–1.4 kg) and stabilized the insulin dose. Inagaki et al., in two studies conducted in 2016[128] and 2018,[129] reported similar results with a decrease in insulin dose and glycemic parameters when compared to a placebo. Neal et al.[130] in 2017 (CANVAS trial) suggested a reduction in HbA1c (−0.58 to −0.73%) along with insulin dose and body weight, supported by other studies.[127,131] An RCT conducted by Sone et al.[132] in 2020 suggested that empagliflozin, when given along with insulin, reduced HbA1c (0.92–1.00%), FBS (–27.62 mg/dL to –21.99 mg/dL), body weight (–1.78 to –1.92 kg), and insulin dose compared to placebo. Similar results were also seen in studies conducted by Rosenstock et al.[133] in 2014 (EMPA-REG MDI trial) and Rosenstock et al.[131] in 2015 (EMPA-REG BASALTM trial). Kanazawa et al.[134] in 2019 conducted an RCT in which patients were divided into the insulin and the insulin+dapagliflozin groups. It was observed that patients on both insulin and dapagliflozin had a higher rate of euglycemia; the total daily dose of insulin was 19% lower. Wehrman et al.[135] in 2022 reported that patients who received multiple daily insulin injections when added with SGLT2i showed a 2.45-unit reduction in basal insulin and a 7.12-unit reduction in short-acting insulin along with a significant reduction in HbA1c and weight. A study conducted by Jiang et al.[136] in 2022 included 62 patients who were given dapagliflozin as an adjunct to insulin. Patients on dapagliflozin and insulin demonstrated a significant decrease in the MAGE (6.25 ± 2.55 vs 2.34 ± 1.10) and improved insulin sensitivity (reduction in HOMA-IR and increase in HOMA-B) compared to insulin alone. A systematic review and meta-analysis of RCTs (n = 3,069) conducted by Yang et al.[137] in 2017 reported that when SGLT2i was given along with insulin, it helped reduce HbA1c (MD: 1.35%, 95% CI [–2.36 to –0.34], p=0.009)], weight [MD –2.30kg, 95%CI (–3.09 to –1.50), p< 0.00001], BP, the total dosage of insulin [MD –4.85U/24hours, 95%CI (–7.42 to –2.29), p= 0.002], and FPG [MD –1.01mmol/L, 95%CI (–1.98 to 0.04), p= 0.04], with an increase in hypoglycemia and urinary tract infections, compared to the control group.

Recommendations and statements	*CoR*	*LoE*
SGLT2i, as a first-line agent, may be as safe as metformin in combination with insulin	I	A
SGLT2i as a first-line agent may be as effective as metformin in decreasing insulin requirement	I	A

Safety

Identification of predisposing or precipitating risk factors that might assist in preventing the most severe problems is a crucial component while assessing the patient. The overall CV and renal advantages are unaffected by adverse events. The safety profile of SGLT2i is good, and the risk of adverse events is rare.

Low Risk of Hypoglycemia

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) only lowers plasma glucose levels by preventing the reabsorption of filtered glucose, which decreases as plasma glucose levels fall. As a result, in the absence of hypoglycemia-causing therapies, they seldom induce hypoglycemia.[138] In T2D patients, SGLT2i enhances plasma glucagon concentrations and gluconeogenesis. As a result, the risk of hypoglycemia with SGLT2i is minimal.[25,139] The risk of hypoglycemia with SGLT2i is low unless coadministered with insulin and other anti-diabetic drugs (sulphonylurea, α-glucosidase, etc.).[140–143] As a result, when taken with an SGLT2i, the dose of insulin and/or insulin secretagogues may need to be lowered to avoid hypoglycemia.

A total of six studies were included in which SGLT2i was directly compared with metformin. Of these six studies, one systematic review and meta-analysis, five RCTs were included.

In a study by List et al.[5] in 2009, hypoglycemia was reported in 6–10% of patients on dapagliflozin (dose independent), 4% of placebo-treated patients, and 9% of metformin-treated patients. In a study conducted by Fonseca et al.[7] in 2013, hypoglycemia events were observed in two out of 135 patients on Ipragliflozin, while zero events were reported in the metformin and placebo groups. Ferrannini et al.,[6] in 2013, also conducted a study that reported empagliflozin (three events) showing slightly higher episodes of hypoglycemia when compared to metformin (two events). Hypoglycemic events were slightly low in the ertugliflozin group (1.3–2.6%) compared to the placebo/metformin group (4.6%) in a study conducted by Aronson et al.[8] in 2018. Hao et al.[10] in 2022 reported that hypoglycemia was low both in the canagliflozin and metformin groups. A systematic review and meta-analysis conducted by Storgaard et al.[144] (34 RCTs, n = 9,154) in 2016 reported that SGLT2i was associated with an increased risk of nonsevere hypoglycemia compared to metformin.

Recommendations and statements	*CoR*	*LoE*
SGLT2i as a first-line agent may be as effective as metformin in lowering the risk of hypoglycemia	I	A

Adverse Drug and Side Effects

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) has many beneficial effects, though there are some risks as well. Clinicians should verify the patient's bone density, review their cardiac profile, and evaluate their hepatic and renal function before beginning them on SGLT2i medication.[145]

A total of six studies were included in which SGLT2i was directly compared with metformin. Of these six studies, five RCTs and one cohort study were included.

Reported urinary tract infections in the dapagliflozin, placebo, and metformin groups are 5–12, 6, and 9%, respectively, as reported by List et al.[5] Genital infections also were slightly more in the dapagliflozin (2–7%) compared to metformin (2%) while hypotensive events were more in the metformin group (4 vs 0–2%). In a study carried out by Fonseca et al.[7] in 2013, it was found that drug-related adverse events were similar in ipragliflozin (11.4–25.4%), placebo (24.6%), and metformin (18.8%) groups. Ferrannini et al.,[6] in their study, concluded that, in the empagliflozin groups, the incidence of investigator-defined drug-related adverse effects (11.9–13.2%) was higher compared to the metformin group (7.1%). Adverse events resulted in discontinuation for 0.9–4.7%

of patients in the empagliflozin groups and 1.8% of patients receiving metformin. Hypoglycemic events were documented in 0.9–2.4% of patients using empagliflozin and 3.6% of those on metformin monotherapy. Incidents consistent with urinary tract infections were reported in 3.8–6.4% of patients on empagliflozin monotherapy and 3.6% on metformin monotherapy. Genital infections occurred more frequently with empagliflozin (3.0–5.5%) than with metformin monotherapy (1.8%). GMIs were slightly more common in females than males; in a study conducted by Aronson et al.,[8] the ertugliflozin group had a slightly higher incidence of GMI than metformin. Hypovolemia was more in the placebo/metformin (4.6%) group than ertugliflozin (1.9–2%). Genital infections were also reported more in SGLT2i (HR, 2.19; CI, 1.91–2.51) compared to metformin in a study by Shin et al.[59] Hao et al.[10] in 2022 reported that patients on canagliflozin had a higher rate of GMI (three cases) than metformin (one case). The overall adverse events rate was slightly higher in the canagliflozin group (8.7 vs 6.8%).

Recommendations and statements	*CoR*	*LoE*
SGLT2i, as a first-line agent, may have greater chances of genital infections compared to metformin and should be used cautiously	I	A

Cost-effectiveness

Patients with diabetes are more likely to develop macrovascular or microvascular complications. As a result, individuals are frequently and exhaustively confronted with healthcare systems. Diabetes treatment and its related consequences impose a massive economic burden on both the family and national levels. In a developing country like India, most diabetes patients face substantial out-of-pocket costs.[146] The most generally reported costing elements were direct cost items[147] (expenditure on medications, diagnostic expenditures, transportation cost, hospitalization, and consultation fee) and indirect cost items (wage loss, health class spending, and trip expenditure).[148] The majority of the research on the cost of diabetes identified "drugs" as the most significant cost component.[146] The International Diabetes Federation (IDF) reported that the total diabetes-related health cost (United States dollar) in India for individuals (20–79 years) with diabetes in 2021 is up to 10 billion.[149]

Four studies were included in which SGLT2i was directly compared with metformin. Of these four studies, one was a systematic review, one was a meta-analysis, and two observational studies were included.

To compare the cost-effectiveness of empagliflozin to conventional care in preventing CV morbidity and death in T2D patients, a Markov model was developed by Nguyen et al.[150] in 2018. A study conducted in China by Cai et al.[151] in 2019, based on the Cardiff diabetes model and meta-analysis from the 71 clinical trials, reported that treatment with dapagliflozin (8,626 Chinese Yuan) was more cost-effective than metformin. Therapy with dapagliflozin resulted in 0.8 more quality-adjusted life years (QALYs) than metformin. A study conducted by Nian et al.[152] in 2020 reported that dapagliflozin was more costly and produced fewer health benefits when compared to metformin. A systematic review of 24 studies conducted by Yoshida et al.[153] in 2020 suggested that SGLTi are cost-effective compared to metformin/standard care. Based on total lifetime treatment costs, QALYs, and incremental cost-effectiveness ratios (ICERs), empagliflozin might be cost-effective compared to standard treatment in T2D patients at high CV risk.

Recommendations and statements	*CoR*	*LoE*
SGLT2i as a first-line agent may be as cost-effective as metformin for treating patients with T2D in India	I	A

Discussion

While the clinical and scientific communities progress to map the boundaries of the pathophysiology and complications of T2D, more and more people across the globe are constantly adding themselves to this group. A lot of progress may have occurred in our understanding of the disease, but its direct impact on the reduction of morbidity and mortality is yet to be realized. Prevention, reversal, management, and prevention of diabetes-specific complications are definite priorities in managing diabetes, but the growing burden of obesity, CV, and renal events, especially in populations at risk, such as Indians, is still a significant concern that needs a serious address.

The choice of first-line therapy may be a clinical decision based on the segmented pathophysiology of the disease, but it must consider the patient as a whole and provide the best possible management that mitigates the disease while promoting the overall health and general well-being of the patient. By undertaking a methodical, systematic literature search and review, the authors have discussed the suitability of SGLT2i on various aspects of the first-line of therapy of T2D based on glycemic control, management of diabetes, management of diabetes-related complications, combination therapy, safety, and cost-effectiveness. This analysis summarizes that SGLT2i may be considered to be noninferior to metformin on parameters related to the pathophysiology of diabetes, but additionally, they bring with them superior qualities pertaining especially to CV and renal protection. The methods of this paper are purely qualitative. Quantitative analysis will have to be summarized to claim the noninferiority. However, this qualitative evidence synthesis comprehensively summarizes available literature and irrevocably advocates the noninferiority of SGLT2i against metformin.

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) had a significant impact on glycemic control with a reduction in HbA1c and postlunch glucose levels and by reducing GV. They do not have a role in insulin secretion, but they preserve β-cell function, increase insulin sensitivity, and reduce insulin resistance. Apart from glycemic control, SGLT2i helps reduce weight, BP, and lipid levels. SGLT2i is far superior when compared to metformin due to its cardiorenal protection. In India, these are extremely important aspects of first-line therapy (patients with T2D), as the risk factors for T2D impact cardiac and renal disorders (Table 3).

The cardiorenal protection potential of SGLT2i in the general population also shifts the paradigm in the concept of first-line therapy by SGLT2i. The ADA, KDA, and AACE associations strongly suggest using SGLT2i as initial therapy for T2D patients with high-risk cardiac and renal disorders. The authors strongly recommend using SGLT2i for this cohort of patients in India as the risk of cardiac and renal disorders in patients with diabetes occurs more prematurely. Our analysis also shows that they are safe to use in combination therapy with other oral antihyperglycemic drugs and insulin, but care must be taken to adjust the dosage of other drugs to prevent hypoglycemia complications.

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) has a good safety profile that is noninferior to metformin and has rare side effects (genitourinary tract infection, ketoacidosis, amputations, fractures). The balance between risk and benefits should be considered before the initiation of SGLT2i on a case-to-case basis. SGLT2i is as cost-effective as metformin, even more so with the availability of generic drugs in India.

Delayed achievement of HbA1c goals in newly diagnosed patients with T2D is related to an increased long-term risk of acquiring CVD, a phenomenon known as the legacy

Table 3: Recommendations, CoR, and LoE for each domain

Topic	*Domain*		*Recommendations and statements*	*CoR*	*LoE*
Glycemic control	1.1	Impact on HbA1c	SGLT2i can be considered a first-line in the management of T2D than metformin based on its impact on HbA1c	I	A
	1.2	GV	SGLT2i as a first-line agent may be as effective as metformin in terms of impact on GV	I	C
Extraglycemic effect	2.1	β-cell function	SGLT2i as a first-line agent may be as effective as metformin in terms of impact on β cell function	I	C
	2.2	Insulin resistance	SGLT2i as a first-line agent may be as effective as metformin in terms of impact on insulin sensitivity	I	A
	2.3	Gut microbiome	SGLT2i as a first-line agent may be as effective as metformin in terms of impact on gut microbiome	II	B
	2.4	Impact on weight	SGLT2i as a first-line agent may be as effective as metformin in terms of impact on weight	I	A
	2.5	Impact on BP	SGLT2i as a first-line agent may be as effective as metformin in terms of impact on BP	I	A
	2.6	Impact on lipids	SGLT2i as a first-line agent may be as effective as metformin in decreasing LDL-C and increasing HDL-C	II	B
	2.7	CV protection	SGLT2i as a first-line agent may be superior to metformin in providing CV protection in people with CVD and/or HF	I	A
	2.8	Renal protection	SGLT2i as a first-line agent may be more effective than metformin in people with T2D and CKD	I	A
			SGLT2i as a first-line agent may be as effective as metformin in terms of its impact on renal protection	I	C
Antihyperglycemic combination therapy	3.1	Safe for combination therapy with other OHAs	SGLT2i as a first-line agent may be as safe as metformin for combination therapy with other OHAs	I	A
	3.2	Safe for combination with insulin and decreases insulin requirement	SGLT2i, as a first-line agent, may be as safe as metformin in combination with insulin	I	A
			SGLT2i as a first-line agent may be as effective as metformin in decreasing insulin requirement	I	A
Safety	4.1	Low risk of hypoglycemia	SGLT2i as a first-line agent may be as effective as metformin in lowering the risk of hypoglycemia	I	A
	4.2	Adverse drug and side effects	SGLT2i, as a first-line agent, may have greater chances of genital infections as compared to metformin and should be used cautiously	I	A
Cost-effectiveness	5	Cost-effectiveness	SGLT2i as a first-line agent may be as cost-effective as metformin for treating patients with T2D in India	I	A

effect. When SGLT-2i was introduced in the first 2 years, this association was no longer evident, indicating that these medications minimize the occurrence of the legacy effect. Early therapy with these medications may potentially have a long-term advantage in people who do not achieve optimal glycemic control following T2D diagnosis.[154]

Conclusion

Given the growing emphasis on preventing risks in individuals diagnosed with diabetes, renewed attention is focused on finding an initial treatment option to complement the current preferred first-line agent, metformin. SGLT2i have been extensively studied and can potentially serve as the primary choice for people recently diagnosed with diabetes, even when other associated health issues are not yet evident during the early stages of the condition. This article identifies various scientific aspects that should be considered when considering a primary treatment for T2D. It also provides an unbiased summary of the available research findings in these areas, directly comparing SGLT2i with metformin in relation to specific outcomes relevant to these different aspects. In cases where no direct studies were comparing SGLT2i with metformin, studies comparing SGLT2i with placebo were taken into consideration. The recommendations provided in this article are rooted in evidence-based practices and are further supported by a consensus-based recommendation system. In conclusion, this article recommends using SGLT2i as the first-line treatment option for managing newly diagnosed T2D patients in India.

Acknowledgments

We acknowledge Dr Ashish Birla, Dr Ashish Prasad, and Dr Smriti Gadia from USV Pvt Ltd for their assistance in the conduct of the project. Dr Raghunath Dantu and Dr Uday Pratap Singh from MEDEVA provided literature search support, evidence synthesis, and medical writing support.

Authors Declaration

Supplementary tables are available with corresponding author and can be provided whenever required.

References

1. Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. Indian J Ophthalmol 2021;69(11):2932–2938.
2. Martín-Timón I, Sevillano-Collantes C, Segura-Galindo A, et al. Type 2 diabetes and cardiovascular disease: have all risk factors the same strength? World J Diabetes 2014;5(4):444–470.
3. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41(12):2669–2701.
4. Mancia G, Kreutz R, Brunström M, et al. 2023 ESH guidelines for the management of arterial hypertension the task force for the management

of arterial hypertension of the European Society of Hypertension endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH). J Hypertens 2023;41(12):1874–2071.
5. List JF, Woo V, Morales E, et al. Sodium-glucose cotransport inhibition with dapagliflozin in Type 2 diabetes. Diabetes Care 2009;32(4):650–657.
6. Ferrannini E, Berk A, Hantel S, et al. Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: an active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. Diabetes Care 2013;36(12):4015–4021.
7. Fonseca VA, Ferrannini E, Wilding JP, et al. Active- and placebo-controlled dose-finding study to assess the efficacy, safety, and tolerability of multiple doses of ipragliflozin in patients with type 2 diabetes mellitus. J Diabetes Complications 2013;27(3):268–273.
8. Aronson R, Frias J, Goldman A, et al. Long-term efficacy and safety of ertugliflozin monotherapy in patients with inadequately controlled T2DM despite diet and exercise: VERTIS MONO extension study. Diabetes Obes Metab 2018;20(6):1453–1460.
9. Shibuya T, Fushimi N, Kawai M, et al. Luseogliflozin improves liver fat deposition compared to metformin in type 2 diabetes patients with non-alcoholic fatty liver disease: a prospective randomized controlled pilot study. Diabetes Obes Metab 2018;20(2):438–442.
10. Hao Z, Sun Y, Li G, et al. Effects of canagliflozin and metformin on insulin resistance and visceral adipose tissue in people with newly-diagnosed type 2 diabetes. BMC Endocr Disord 2022;22(1):37.
11. Pinto LC, Rados DV, Remonti LR, et al. Efficacy of SGLT2 inhibitors in glycemic control, weight loss and blood pressure reduction: a systematic review and meta-analysis. Diabetol Metab Syndr 2015;7(Suppl 1):A58.
12. Suh S, Kim JH. Glycemic variability: how do we measure it and why is it important? Diabetes Metab J 2015;39(4):273–282.
13. Makris K, Spanou L. Is there a relationship between mean blood glucose and glycated hemoglobin? J Diabetes Sci Technol 2011;5(6):1572–1583.
14. Nishimura R, Tanaka Y, Koiwai K, et al. Effect of empagliflozin monotherapy on postprandial glucose and 24-hour glucose variability in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, 4-week study. Cardiovasc Diabetol 2015;14(1):11.
15. Li FF, Gao G, Li Q, et al. Influence of dapagliflozin on glycemic variations in patients with newly diagnosed type 2 diabetes mellitus. J Diabetes Res 2016;2016:5347262.
16. Erickson ML, Little JP, Gay JL, et al. Postmeal exercise blunts postprandial glucose excursions in people on metformin monotherapy. J Appl Physiol 2017;123(2):444–450.
17. Lu J, Zang J, Li H. Impact of three oral antidiabetic drugs on markers of β-cell function in patients with type 2 diabetes: a meta-analysis. PLOS ONE 2013;8(10):e76713.
18. Tura A, Pacini G, Kautzky-Willer A, et al. Basal and dynamic proinsulin-insulin relationship to assess beta-cell function during OGTT in metabolic disorders. Am J Physiol Endocrinol Metab 2003;285(1):E155–E162.
19. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27(6): 1487–1495.
20. Standl E. The importance of beta-cell management in type 2 diabetes. Int J Clin Pract Suppl 2007;153:10–19.
21. Inagaki N, Kondo K, Yoshinari T, et al. Efficacy and safety of canagliflozin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, 12-week study. Diabetes Obes Metab 2013;15(12):1136–1145.
22. Kutoh E, Wada A, Murayama T, et al. Two glucose-lowering mechanisms of canagliflozin depending on body weight changes in drug-naïve subjects with type 2 diabetes. Drugs R D 2018;18(4):309–315.
23. Stenlöf K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab 2013;15(4): 372–382.
24. Kutoh E, Wada A, Murayama T, et al. Characterization of metabolic parameters in responders and nonresponders treated with canagliflozin monotherapy in drug-naive subjects with type 2 diabetes. Indian J Endocrinol Metab 2018;22(2):185–190.
25. Ferrannini E, Muscelli E, Frascerra S, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J Clin Invest 2014;124(2):499–508.
26. Polidori D, Mari A, Ferrannini E. Canagliflozin, a sodium glucose co-transporter 2 inhibitor, improves model-based indices of beta cell function in patients with type 2 diabetes. Diabetologia 2014;57(5):891–901.
27. U.K. Prospective Diabetes Study Group 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. Diabetes 1995;44(11):1249–1258.
28. Kahn SE, Lachin JM, Zinman B, et al. Effects of rosiglitazone, glyburide, and metformin on β-cell function and insulin sensitivity in adopt. Diabetes 2011;60(5):1552–1560.
29. Turner RC, Cull CA, Frighi V, et al. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) group. JAMA 1999;281(21):2005–2012.
30. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329(14):977–986.
31. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352(9131):854–865.
32. Xu B, Li S, Kang B, et al. The current role of sodium-glucose cotransporter 2 inhibitors in type 2 diabetes mellitus management. Cardiovasc Diabetol 2022;21(1):83.
33. Muniyappa R, Lee S, Chen H, et al. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. Am J Physiol Endocrinol Metab 2008;294(1):E15–E26.
34. Fakhrolmobasheri M, Abhari AP, Manshaee B, et al. Effect of sodium–glucose cotransporter 2 inhibitors on insulin resistance; a systematic review and meta-analysis. Acta Diabetol 2023;60(2):191–202.
35. Carding S, Verbeke K, Vipond DT, et al. Dysbiosis of the gut microbiota in disease. Microb Ecol Health Dis 2015;26:26191.
36. Deng X, Zhang C, Wang P, et al. Cardiovascular benefits of empagliflozin are associated with gut microbiota and plasma metabolites in type 2 diabetes. J Clin Endocrinol Metab 2022;107(7):1888–1896.
37. Forslund K, Hildebrand F, Nielsen T, et al. Disentangling the effects of type 2 diabetes and metformin on the human gut microbiota. Nature 2015;528(7581):262–266.
38. Tong X, Xu J, Lian F, et al. Structural alteration of gut microbiota during the amelioration of human type 2 diabetes with hyperlipidemia by metformin and a traditional Chinese herbal formula: a multicenter, randomized, open label clinical trial. mBio 2018;9(3):e02392–e02317.
39. Wu H, Esteve E, Tremaroli V, et al. Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug. Nat Med 2017;23(7):850–858.
40. Mueller NT, Differding MK, Zhang M, et al. Metformin affects gut microbiome composition and function and circulating short-chain fatty acids: a randomized trial. Diabetes Care 2021;44(7):1462–1471.
41. van Bommel EJM, Herrema H, Davids M, et al. Effects of 12-week treatment with dapagliflozin and gliclazide on faecal microbiome: results of a double-blind randomized trial in patients with type 2 diabetes. Diabetes Metab 2020;46(2):164–168
42. Leitner DR, Frühbeck G, Yumuk V, et al. Obesity and type 2 diabetes: two diseases with a need for combined treatment strategies - EASO can lead the way. Obes Facts 2017;10(5):483–492.
43. Scheen AJ. Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2(SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. Drugs 2015;75(1):33–59.
44. Fioretto P, Giaccari A, Sesti G. Efficacy and safety of dapagliflozin, a sodium glucose cotransporter 2(SGLT2) inhibitor, in diabetes mellitus. Cardiovasc Diabetol 2015;14:142.
45. Janež A, Fioretto P. SGLT2 inhibitors and the clinical implications of associated weight loss in type 2 diabetes: a narrative review. Diabetes Ther 2021;12(8):2249–2261.
46. Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000;321(7258):412–419.
47. van Baar MJB, van Ruiten CC, Muskiet MHA, et al. SGLT2 inhibitors in combination therapy: from mechanisms to clinical considerations in type 2 diabetes management. Diabetes Care 2018;41(8):1543–1556.
48. Zaccardi F, Webb DR, Htike ZZ, et al. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. Diabetes Obes Metab 2016;18(8): 783–794.
49. Søndergaard E, Espinosa De Ycaza AE, Morgan-Bathke M, et al. How to measure adipose tissue insulin sensitivity. J Clin Endocrinol Metab 2017;102(4): 1193–1199.
50. Sánchez-García A, Simental-Mendía M, Millán-Alanís JM, et al. Effect of sodium-glucose co-transporter 2 inhibitors on lipid profile: a systematic review and meta-analysis of 48 randomized controlled trials. Pharmacol Res 2020;160:105068.
51. Donnan K, Segar L. SGLT2 inhibitors and metformin: dual antihyperglycemic therapy and the risk of metabolic acidosis in type 2 diabetes. Eur J Pharmacol 2019;846:23–29.
52. Ritchie H, Spooner F, Roser M. Causes of death. Our World in Data [Internet]. 2018 Feb 14 [cited 2023 May 2]; Available from: https://ourworldindata.org/causes-of-death
53. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 2006;332(7533):73–78.
54. Emerging Risk Factors Collaboration,Sarwar N, Gao P, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375(9733):2215–2222.
55. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373(22):2117–2128.
56. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377(7):644–657.
57. Unnikrishnan AG, Sahay RK, Phadke U, et al. Cardiovascular risk in newly diagnosed type 2 diabetes patients in India. PLOS ONE 2022;17(3):e0263619.
58. Chen TH, Li YR, Chen SW, et al. Sodium-glucose cotransporter 2 inhibitor versus metformin as first-line therapy in patients with type 2 diabetes mellitus: a multi-institution database study. Cardiovasc Diabetol 2020;19(1):189.
59. Shin H, Schneeweiss S, Glynn RJ, et al. Cardiovascular outcomes in patients initiating first-line treatment of type 2 diabetes with sodium–glucose cotransporter-2 inhibitors versus metformin. Ann Intern Med 2022;175(7):927–937.
60. Koufakis T, Papazafiropoulou A, Makrilakis K, et al. Sodium-glucose co-transporter 2 inhibitors versus metformin as the first-line treatment for type 2 diabetes: is it time for a revolution? Cardiovasc Drugs Ther 2023;37(2):315–321.

61. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. Circulation 2022;145(18):e895–e1032.
62. American Diabetes Association. Standards of medical care in diabetes—2022 abridged for primary care providers. Clinical Diabetes 2022;40(1):10–38.
63. Das SR, Everett BM, Birtcher KK, et al. 2020 expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes; a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2020;76(9):1117–1145.
64. Hur KY, Moon MK, Park JS, et al. 2021 clinical practice guidelines for diabetes mellitus in Korea. Diabetes Metab J 2021;45(4):461–481.
65. Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American association of clinical endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2020 executive summary. Endocr Pract 2020;26(1):107–139.
66. Peikert A, Martinez FA, Vaduganathan M, et al. Efficacy and safety of dapagliflozin in heart failure with mildly reduced or preserved ejection fraction according to age: The DELIVER trial. Circ Heart Fail 2022;15(10):e010080.
67. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med 2021;384(2):117–128.
68. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383(15):1413–1424.
69. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med 2020;383(15):1425–1435.
70. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380(4):347–357.
71. Cahn A, Raz I, Leiter LA, et al. Cardiovascular, renal, and metabolic outcomes of dapagliflozin versus placebo in a primary cardiovascular prevention cohort: analyses from DECLARE-TIMI 58. Diabetes Care 2021;44(5):1159–1167.
72. Mahaffey KW, Jardine MJ, Bompoint S, et al. Canagliflozin and cardiovascular and renal outcomes in type 2 diabetes mellitus and chronic kidney disease in primary and secondary cardiovascular prevention groups. Circulation 2019;140(9):739–750.
73. Levin A, Perkovic V, Wheeler DC, et al. Empagliflozin and cardiovascular and kidney outcomes across KDIGO risk categories: post hoc: analysis of a randomized, double-blind, placebo-controlled, multinational trial. Clinical J Am Soc Nephrol 2020;15(10):1433–1444.
74. Packer M, Butler J, Zannad F, et al. Effect of empagliflozin on worsening heart failure events in patients with heart failure and preserved ejection fraction: EMPEROR-preserved trial. Circulation 2021;144(16):1284–1294.
75. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381(21):1995–2008.
76. Thomas MC, Cooper ME, Zimmet P. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. Nat Rev Nephrol 2016;12(2):73–81.
77. Fu Y, Breljak D, Onishi A, et al. Organic anion transporter OAT3 enhances the glucosuric effect of the SGLT2 inhibitor empagliflozin. Am J Physiol Renal Physiol 2018;315(2):F386–F394.
78. Ghezzi C, Hirayama BA, Gorraitz E, et al. SGLT2 inhibitors act from the extracellular surface of the cell membrane. Physiol Rep 2014;2(6):e12058.
79. Toyama T, Neuen BL, Jun M, et al. Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: a systematic review and meta-analysis. Diabetes Obes Metab 2019;21(5):1237–1250.
80. Neuen BL, Young T, Heerspink HJL, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2019;7(11):845–854.
81. Lo KB, Gul F, Ram P, et al. The effects of SGLT2 inhibitors on cardiovascular and renal outcomes in diabetic patients: a systematic review and meta-analysis. Cardiorenal Med 2020;10(1):1–10.
82. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393(10166):31–39.
83. Lipska KJ, Flory J, Hennessy S, et al. Modifying prescribing guidelines by petitioning the FDA: the metformin experience. Circulation 2016;134(18): 1405–1408.
84. Bell S, Farran B, McGurnaghan S, et al. Risk of acute kidney injury and survival in patients treated with metformin: an observational cohort study. BMC Nephrol 2017;18(1):163.
85. Neven E, Vervaet B, Brand K, et al. Metformin prevents the development of severe chronic kidney disease and its associated mineral and bone disorder. Kidney Int 2018;94(1):102–113.
86. Ravindran S, Kuruvilla V, Wilbur K, et al. Nephroprotective effects of metformin in diabetic nephropathy. J Cell Physiol 2017;232(4):731–742.
87. Tan MKX, Heng TYJ, Mak A. The potential use of metformin, dipyridamole, n-acetylcysteine and statins as adjunctive therapy for systemic lupus erythematosus. Cells 2019;8(4):323.
88. Tseng CH. Use of metformin and risk of kidney cancer in patients with type 2 diabetes. Eur J Cancer 2016;52:19–25.
89. Stephen J, Anderson-Haag TL, Gustafson S, et al. Metformin use in kidney transplant recipients in the United States: an observational study. Am J Nephrol 2014;40(6):546–553.
90. Ekström N, Schiöler L, Svensson AM, et al. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ Open 2012;2(4):e001076.
91. Hsu WH, Hsiao PJ, Lin PC, et al. Effect of metformin on kidney function in patients with type 2 diabetes mellitus and moderate chronic kidney disease. Oncotarget 2017;9(4):5416–5423.
92. Hippisley-Cox J, Coupland C. Diabetes treatments and risk of amputation, blindness, severe kidney failure, hyperglycaemia, and hypoglycaemia: open cohort study in primary care. BMJ 2016;352:i1450.
93. Zhang Z, Dong H, Chen J, et al. Effects of metformin on renal function, cardiac function, and inflammatory response in diabetic nephropathy and its protective mechanism. Dis Markers 2022;2022:e8326767.
94. Crowley MJ, Diamantidis CJ, McDuffie JR, et al. Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: a systematic review. Ann Intern Med 2017;166(3):191–200.
95. The EMPA-KIDNEY Collaborative Group, Herrington WG, Staplin N, et al. Empagliflozin in patients with chronic kidney disease. N Engl J Med 2023;388(2):117–127.
96. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383(15):1436–1446.
97. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380(24):2295–2306.
98. Kashiwagi A, Takahashi H, Ishikawa H, et al. A randomized, double-blind, placebo-controlled study on long-term efficacy and safety of ipragliflozin treatment in patients with type 2 diabetes mellitus and renal impairment: results of the long-term ASP1941 safety evaluation in patients with type 2 diabetes with renal impairment (LANTERN) study. Diabetes Obes Metab 2015;17(2):152–160.
99. Kohan DE, Fioretto P, Johnsson K, et al. The effect of dapagliflozin on renal function in patients with type 2 diabetes. J Nephrol 2016;29(3):391–400.
100. Ji L, Ma J, Li H, et al. Dapagliflozin as monotherapy in drug-naive Asian patients with type 2 diabetes mellitus: a randomized, blinded, prospective phase III study. Clin Ther 2014;36(1):84–100.e9.
101. DeFronzo RA, Eldor R, Abdul-Ghani M. Pathophysiologic approach to therapy in patients with newly diagnosed type 2 diabetes. Diabetes Care 2013;36(Suppl 2):S127–S138.
102. Vivian EM. Sodium-glucose co-transporter 2(SGLT2) inhibitors: a growing class of antidiabetic agents. Drugs Context 2014;3:212264.
103. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38(1):140–149.
104. Clar C, Gill JA, Court R, Waugh N. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. BMJ Open 2012;2(5):e001007.
105. Hershon KS. Options for empagliflozin in combination therapy in type 2 diabetes mellitus. Int J Gen Med 2016;9:155–712.
106. Romera I, Gomis R, Crowe S, et al. Empagliflozin in combination with oral agents in young and overweight/obese Type 2 diabetes mellitus patients: A pooled analysis of three randomized trials. J Diabetes Complications 2016;30(8):1571–1576.
107. Xu X, Xu W, Zhuo Q, et al. The efficacy and safety of dapagliflozin combined with oral hypoglycemic agents in patients with type 2 diabetes: a systematic review and meta-analysis. Ann Palliat Med 2022;11(3):1028–1037.
108. Fulcher G, Matthews DR, Perkovic V, et al. Efficacy and safety of canagliflozin used in conjunction with sulfonylurea in patients with type 2 diabetes mellitus: a randomized, controlled trial. Diabetes Ther 2015;6(3):289–302.
109. Scheen AJ. DPP-4 inhibitor plus SGLT-2 inhibitor as combination therapy for type 2 diabetes: from rationale to clinical aspects. Expert Opin Drug Metab Toxicol 2016;12(12):1407–1417.
110. Rosenstock J, Hansen L, Zee P, et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. Diabetes Care 2015;38(3):376–383.
111. Min SH, Yoon JH, Moon SJ, et al. Combination of sodium-glucose cotransporter 2 inhibitor and dipeptidyl peptidase-4 inhibitor in type 2 diabetes: a systematic review with meta-analysis. Sci Rep 2018;8(1):4466.
112. Chadha M, Das AK, Deb P, et al. Expert opinion: optimum clinical approach to combination-use of SGLT2i + DPP4i in the Indian Diabetes Setting. Diabetes Ther 2022;13(5):1097–1114.
113. Li C, Luo J, Jiang M, et al. The efficacy and safety of the combination therapy with GLP-1 receptor agonists and SGLT-2 Inhibitors in type 2 diabetes mellitus: a systematic review and meta-analysis. Front Pharmacol 2022:13:838277.
114. Kuecker CM, Vivian EM. Patient considerations in type 2 diabetes – role of combination dapagliflozin–metformin XR. Diabetes Metab Syndr Obes 2016;9: 25–35.
115. Jingfan Z, Ling L, Cong L, et al. Efficacy and safety of sodium-glucose cotransporter-2 inhibitors in type 2 diabetes mellitus with inadequate glycemic control on metformin: a meta-analysis. Arch Endocrinol Metab 2019;63(5):478–486.
116. Chen W, Li P, Wang G, et al. Efficacy and safety of ipragliflozin as add-on to metformin for type 2 diabetes: a meta-analysis of double-blind randomized controlled trials. Postgrad Med 2019;131(8):578–588.
117. Gebrie D, Getnet D, Manyazewal T. Cardiovascular safety and efficacy of metformin-SGLT2i versus metformin-sulfonylureas in type 2 diabetes:

systematic review and meta-analysis of randomized controlled trials. Sci Rep 2021;11(1):137.
118. Häring HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care 2014;37(6):1650–1659.
119. Milder TY, Stocker SL, Abdel Shaheed C, et al. Combination therapy with an SGLT2 Inhibitor as initial treatment for type 2 diabetes: a systematic review and meta-analysis. J Clin Med 2019;8(1):45.
120. Rosenstock J, Seman LJ, Jelaska A, et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2(SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. Diabetes Obes Metab 2013;15(12):1154–1160.
121. Matthaei S, Bowering K, Rohwedder K, et al. Dapagliflozin improves glycemic control and reduces body weight as add-on therapy to metformin plus sulfonylurea: a 24-week randomized, double-blind clinical trial. Diabetes Care 2015;38(3):365–372.
122. Jabbour SA, Hardy E, Sugg J, et al. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes Care 2014;37(3):740–750.
123. Tinahones FJ, Gallwitz B, Nordaby M, et al. Linagliptin as add-on to empagliflozin and metformin in patients with type 2 diabetes: two 24-week randomized, double-blind, double-dummy, parallel-group trials. Diabetes Obes Metab 2017;19(2):266–274.
124. Mathieu C, Catrinoiu D, Ranetti AE, et al. Characterization of the open-label lead-in period of two randomized controlled phase 3 trials evaluating dapagliflozin, saxagliptin, and metformin in type 2 diabetes. Diabetes Ther 2018;9(4):1703–1711.
125. Kovacs CS, Seshiah V, Swallow R, et al. Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-C trial. Diabetes Obes Metab 2014;16(2):147–158.
126. DeFronzo RA, Davidson JA, Del Prato S. The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. Diabetes Obes Metab 2012;14(1):5–14.
127. Wilding JP, Woo V, Rohwedder K, et al. Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years. Diabetes Obes Metab 2014;16(2):124–136.
128. Inagaki N, Harashima S, Maruyama N, et al. Efficacy and safety of canagliflozin in combination with insulin: a double-blind, randomized, placebo-controlled study in Japanese patients with type 2 diabetes mellitus. Cardiovasc Diabetol 2016;15:89.
129. Inagaki N, Harashima SI, Kaku K, et al. Long-term efficacy and safety of canagliflozin in combination with insulin in Japanese patients with type 2 diabetes mellitus. Diabetes Obes Metab 2018;20(4):812–820.
130. Neal B, Perkovic V, de Zeeuw D, et al. Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. Diabetes Care 2015;38(3):403–411.
131. Rosenstock J, Jelaska A, Zeller C, et al. Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: a 78-week randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab 2015;17(10):936–948.
132. Sone H, Kaneko T, Shiki K, et al. Efficacy and safety of empagliflozin as add-on to insulin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab 2020;22(3):417–426.
133. Rosenstock J, Jelaska A, Frappin G, et al. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. Diabetes Care 2014;37(7):1815–1823.
134. Kanazawa K, Uchino H, Shigiyama F, et al. Sustained fasting glucose oxidation and postprandial lipid oxidation associated with reduced insulin dose in type 2 diabetes with sodium–glucose cotransporter 2 inhibitor: a randomized, open-label, prospective study. J Diabetes Investig 2019;10(4):1022–1031.
135. Wehrman G, Halton M, Riveland B, et al. Comparison of A1c reduction, weight loss, and changes in insulin requirements with addition of GLP-1 agonists vs SGLT-2 inhibitors in patients using multiple daily insulin injections. J Pharm Pract 2022:8971900221134174.
136. Jiang LL, Zhang P, Liu BL, et al. Effects of dapagliflozin adjunct to insulin on glycemic variations in patients with newly diagnosed type 2 diabetes: a randomized, controlled, open-labeled trial. Biomed Res Int 2021;2021:6618257.
137. Yang Y, Chen S, Pan H, et al. Safety and efficiency of sglt2 inhibitor combining with insulin in subjects with diabetes: systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2017;96(21):e6944.
138. DeSantis A, Nathan DM, Mulder JE. Sodium-glucose co-transporter 2 inhibitors for the treatment of hyperglycemia in type 2 diabetes mellitus. 2021;2.
139. Merovci A, Solis-Herrera C, Daniele G, et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. J Clin Invest 2014;124(2):509–514.
140. Li J, Shao YH, Wang XG, et al. Efficacy and safety of sodium-glucose cotransporter 2 inhibitors as add-on to metformin and sulfonylurea treatment for the management of type 2 diabetes: a meta-analysis. Endocr J 2018;65(3):335–344.
141. Yabe D, Yasui A, Ji L, et al. Safety and tolerability of empagliflozin in East Asian patients with type 2 diabetes: Pooled analysis of phase I–III clinical trials. J Diabetes Investig 2019;10(2):418–428.
142. Committee on the Proper Use of SGLT2 Inhibitors. Recommendations on the proper use of SGLT2 inhibitors. J Diabetes Investig 2020;11(1):257–261.
143. Cai X, Gao X, Yang W, et al. No disparity of the efficacy and all-cause mortality between Asian and non-Asian type 2 diabetes patients with sodium–glucose cotransporter 2 inhibitors treatment: a meta-analysis. J Diabetes Investig 2018;9(4):850–861.
144. Storgaard H, Gluud LL, Bennett C, et al. Benefits and harms of sodium-glucose co-transporter 2 inhibitors in patients with type 2 diabetes: a systematic review and meta-analysis. PLoS One 2016;11(11):e0166125.
145. Pittampalli S, Upadyayula S, Mekala HM, et al. Risks vs benefits for SGLT2 inhibitor medications. Fed Pract 2018;35(7):45–48.
146. Oberoi S, Kansra P. Economic menace of diabetes in India: a systematic review. Int J Diabetes Dev Ctries 2020;40(4):464–475.
147. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2013;36 (Suppl 1):S67–S74.
148. Bansode B, Jungari DS. Economic burden of diabetic patients in India: a review. Diabetes Metab Syndr 2019;13(4):2469–2472.
149. Federation ID. IDF Diabetes Atlas, tenth International Diabetes. 2021;
150. Nguyen E, Coleman CI, Nair S, et al. Cost-utility of empagliflozin in patients with type 2 diabetes at high cardiovascular risk. J Diabetes Complications 2018;32(2):210–215.
151. Cai X, Shi L, Yang W, et al. Cost-effectiveness analysis of dapagliflozin treatment versus metformin treatment in Chinese population with type 2 diabetes. J Med Econ 2019;22(4):336–343.
152. Nian H, Wan X, Ma J, et al. Economic evaluation of dapagliflozin versus metformin in Chinese patients whose diabetes is inadequately controlled with diet and exercise. Cost Eff Resour Alloc 2020;18:12.
153. Yoshida Y, Cheng X, Shao H, et al. A systematic review of cost-effectiveness of sodium-glucose cotransporter inhibitors for type 2 diabetes. Curr Diab Rep 2020;20(4):12.
154. Ceriello A, Lucisano G, Prattichizzo F, et al. The legacy effect of hyperglycemia and early use of SGLT-2 inhibitors: a cohort study with newly-diagnosed people with type 2 diabetes. Lancet Reg Health Eur 2023;31:100666.

REVIEW ARTICLE

Role of Bisoprolol in Heart Failure Management: A Consensus Statement from India

H K Chopra[1], Tiny Nair[2], G S Wander[3*], C K Ponde[4], Saumitra Ray[5], Dinesh Khullar[6], Navin C Nanda[7], Ravi R Kasliwal[8], D S Rana[9], Ashok Kirpalani[10], J P S Sawhney[11], Praveen Chandra[12], Yatin Mehta[13], Viveka Kumar[14], S Tewari[15], A K Pancholia[16], Vijay Kher[17], Sandeep Bansal[18], Sanjay Mittal[19], Praful Kerkar[20], P K Sahoo[21], Ramesh Hotchandani[22], Sunil Prakash[23], Nagendra Chauhan[24], Vishal Rastogi[25], A Jabir[26], S Shanmugasundaram[27], Mangesh Tiwaskar[28], Ajay Sinha[29], Vittul Gupta[30], S S Mishra[31], S N Routray[32], A K Omar[33], Onkar C Swami[34], Aparna Jaswal[35], Shamsad Alam[36], Rajeev Passey[37], Rajeeve Rajput[38], Justin Paul[39], Aditya Kapoor[40], D Prabhakar[41], Subhash Chandra[42], Poonam Malhotra[43], Vivudh Pratap Singh[44], Manish Bansal[45], Priyank Shah[46], Sanjay Jain[47], Mohan Bhargava[48], I B Vijayalakshmi[49], Kiron Varghaese[50], Dharmender Jain[51], Anupam Goel[52], Namrata Gaur[53], Rohit Tandon[54], Asha Moorthy[55], Sheeba George[56], V K Katyal[57], R R Mantri[58], Rahul Mehrotra[59], Dilip Bhalla[60], Vinod Mittal[61], Sarita Rao[62], Manish Jagia[63], Harmeet Singh[64], Surabhi Awasthi[65], Ameet Sattur[66], Rekha Mishra[67], Anand Pandey[68], Rajeev Chawla[69], Shalini Jaggi[70], Blessy Sehgal[71], Alok Sehgal[72], Naresh Goel[73], Ripen Gupta[74], Samir Kubba[75], Abhinav Chhabra[76], Saurabh Bagga[77], N R Shastry[78]

Received: 27 September 2023; *Accepted:* 04 October 2023

Abstract

In India, heart failure (HF) is an important health concern affecting younger age groups than the western population. A limited number of Indian patients receive guideline-directed medical therapy (GDMT). Selective β-1 blockers (BB) are one of the GDMTs in HF and play an important role by decreasing the sympathetic overdrive. The BB reduces heart rate (HR) reverse the adverse cardiac (both ventricular and atrial), vascular, and renovascular remodeling seen in HF. Bisoprolol, a β-1 blocker, has several advantages and can be used across a wide spectrum of HF presentations and in patients with HF and comorbid conditions such as coronary artery disease (CAD), atrial fibrillation (AF), post-myocardial infarction (MI), uncontrolled diabetes, uncontrolled hypertension, and renal impairment. Despite its advantages, bisoprolol is not optimally utilized for managing HF in India. This consensus builds on updated evidence on the efficacy and safety of bisoprolol in HF and recommends its place in therapy with a focus on Indian patients with HF.

Journal of the Association of Physicians of India (2023): 10.59556/japi.71.0426

[1]Senior Consultant, Department of Cardiology, Medanta Moolchand Heart Center, Delhi; [2]Head, Department of Cardiology, PRS Hospital, Trivandrum, Kerala; [3]Professor, Department of Cardiology, Dayanand Medical College and Hospital, Ludhiana, Punjab; [4]Consultant Cardiologist and Head, Department of Cardiology, PD Hinduja National Hospital and Medical Research Centre, Mumbai, Maharashtra; [5]Director, Department of Invasive Cardiology, AMRI Hospital, Kolkata, West Bengal; [6]Chairman, Nephrology and Renal transplant Medicine, Dept. of Nephrology and Renal transplant medicine, Max Super-speciality Hospital, Delhi; [7]Distinguished Professor of Medicine and Cardiovascular Disease, Division of Cardiology, University of Alabama at Birmingham, Birmingham, Alabama, USA; [8]Chairman, Department of Clinical and Preventive Cardiology, Medanta-The Medicity, Gurgaon, Haryana; [9]Chairman, Department of Nephrology, Sir Ganga Ram Hospital, Delhi; [10]Consultant Nephrologist, Bombay Hospital, Mumbai, Maharashtra; [11]Chief of Clinical and Preventive Cardiology, Chairman, Department of Cardiology, Sir Gangaram Hospital, Delhi; [12]Chairman, Department of Interventional and Structural Heart Cardiology, Medanta - The Medicity, Gurgaon, Haryana; [13]Director, Dept of Critical care medicine, Medanta Institute of Critical care Anaesthesiology, Medanta, The Medicity, Gurgaon, Haryana; [14]Principal Director and Chief of Cath Labs (Pan Max), Department of Cardiac Sciences, Max Hospital, Delhi; [15]Professor of Cardiology at SGPGIMS, Lucknow, Uttar Pradesh; [16]Head of Department, Department of Clinical and Preventive Cardiology, Arihant Hospital and Research Centre, Indore, Madhya Pradesh; [17]Chairman, Department of Nephrology, Department of Kidney Transplant, Epitome Kidney Urology Institute and Lions Hospital, Delhi; [18]Consultant in Cardiology, Professor and Head, Department of Cardiology, Vardhaman Mahavir Medical College and Safdarjung Hospital, Delhi; [19,24,45,77]Senior Cardiologist, Medanta-The Medicity ,Gurgaon, Haryana; [20]Senior Consultant Interventional Cardiologist, Asian Heart Institute, Mumbai, Maharashtra; [21]Interventional Cardiology, Department of Cardiology, Apollo Hospital, Bhubaneshwar, Odisha; [22]Consultant, Head, Department of Nephrology, Moolchand Centre for Renal Care and Dialysis, Moolchand Hospital, Delhi; [23]Senior Director and Head, Department of Nephrology and Renal Transplantation, BLK-Max Super Speciality Hospital, Delhi; [25]Director, Department of Interventional Cardiology, Head of Advanced Heart Failure Program, Fortis Escort Heart Institute, Delhi; [26]Senior Cardiologist and Assistant Professor, Lisie Hospital, Cochin, Kerala; [27]Senior Cardiologist, Billroth Hospitals, Chennai, Tamil Nadu; [28]Consultant Physician and Diabetologist, Shilpa Medical Research Centre, Mumbai, Maharashtra; [29]Senior Consultant, Department of Cardiology, Medanta Heart Institute, Patna, Bihar; [30]Consulting Physician, Department of Internal Medicine, Kishori Ram Hospital and Diabetes Care Centre, Bhatinda, Punjab; [31]Director and Senior Consultant Cardiologist, Med N Heart Clinic, Cuttack, Odisha; [32]Professor and Head, Department of Cardiology, SCB Medical College, Cuttack, Odisha; [33]Director, Fortis Escorts Heart Institute, Department of Non-invasive Cardiology, Delhi; [34]Sr. Vice President, Medical Services, Alembic Pharmaceuticals Ltd, Mumbai, Maharashtra; [35]Director, Department of Cardiac Pacing and Electrophysiology, Fortis Escorts Heart Institute, Delhi; [36]Consultant Interventional Cardiologist, Jayprabha Medanta Super Speciality Hospital, Patna, Bihar; [37]Consultant Cardiologist, Sir Ganga Ram Hospital, Delhi; [38]Senior Consultant Cardiologist, Apollo Hospitals, Delhi; [39]Professor of Cardiology, Madras Medical College, Chennai, Tamil Nadu; [40]Head, Department of Cardiology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh; [41]Consultant Interventional Cardiologist, Ashwin Clinic, Chennai, Tamil Nadu; [42]Chairman and Head, Dept. of Cardiology and Structural Heart Disease, BLK Max Superspeciality Hospital, Delhi; [43]Senior Professor, Cardiac Anaesthesia, All India Institute of Medical Sciences, Delhi; [44] Sr. Consultant, Interventional Cardiologist, Fortis Escort Heart Institute, Delhi; [46]Assistant General Manager, Medical Services, Alembic Pharmaceuticals Ltd., Mumbai, Maharashtra; [47]Associate Vice President, Medical Services, Alembic Pharmaceuticals Ltd., Mumbai, Maharashtra; [48]Director of Cardiology and Interventional Cardiologist, Max Hospital, Delhi; [49]Professor Emeritus, Former Head Pediatric Cardiology,

Shri Jayadeva Institute of Cardiovascular sciences and Research, Bengaluru, Karnataka; [50]Professor and Former Head, Department of Cardiology, St. John's Medical College, Bangalore; [51]Professor and Former head, Department of Cardiology, IMS, BHU, Varanasi, Uttar Pradesh; [52]Director, Interventional Cardiology, Max Super-speciality hospital, Delhi; [53]CVTS, AIIMS Rishikesh, Rishikesh, Uttarakhand; [54]Consultant, Department of Cardiology, Dayanand Medical College and Hospital, Ludhiana, Punjab; [55]Senior Consultant Cardiologist, SIMS Hospital, Chennai, Tamil Nadu; [56]Sree Mookambika Institute of Medical Sciences, Thiruvananthapuram, Kerala; [57]Head of Dept. Department of General Medicine, Positron Hospital; Formerly Senior Professor, Department of Medicine, Pt. B.D.Sharma, Post Graduate Institute of Medical Sciences, Rohtak, Haryana; [58]Director, Department of Cardiology, Sir Ganga Ram Hospital, Delhi; [59]Director and Head, Department of Non-Invasive Cardiology, Max Super Speciality Hospital, Delhi; [60]Senior Director, Department of Nephrology and Renal Transplant, Max Super Speciality Hospital, Delhi; [61]Senior Consultant Diabetologist and Head, Centre for Diabetes and Metabolic Diseases, Heart and Lung Institute, Delhi; [62]Sr. Interventional Cardiologist, Director Cath Lab, Apollo Hospital, Indore, Madhya Pradesh; [63]Director, Department of Anaesthesia and Critical care, Moolchand Hospital, Delhi; [64]Consultant, Critical Care Specialist, Max Super-speciality hospital, Ghaziabad, Uttar Pradesh; [65]Consultant, Critical Care Specialist, Moolchand Hospital, Delhi; [66]Director of Cath Lab HCG, Suchiraya Hospital, Hubli, Karnataka; [67]Consultant Cardiologist, Indraprastha, Apollo Hospital, Delhi; [68]Sr. Consultant Cardiologist, Delhi; [69]Sr. Consultant Diabetologist and Director of North Delhi Diabetes and Cardiac Centre, Delhi; [70]Consultant Diabetologist and Head at Dr. Mohans Diabetes Specialities Centre, Delhi; [71]Sr. Consultant Nephrology, Shree Balaji Action Medical Institute, Delhi; [72]Head of Dept. and Chief Interventional Cardiologist, Yeshoda Superspeciality Hospital, Ghaziabad, Uttar Pradesh; [73]Sr. cardiologist, Department of Cardiology BLK Super-speciality Hospital, Delhi; [74]Interventional Cardiologist, Max Super Speciality hospital, Delhi; [75]Director and Unit Head, Cardiology Department Dharmshila Narayana Superspeciality Hospital, Delhi; [76]Interventional Cardiologist, Fortis Hospital, Delhi; [78]Consultant Cardiologist, Medanta Moolchand Heart Center, Delhi; *Corresponding Author

How to cite this article: Chopra HK, Nair T, Wander G, *et al.* Role of Bisoprolol in Heart Failure Management: A Consensus Statement from India. J Assoc Physicians India 2023;71(12):77–88.

Introduction

Heart failure (HF) is a global health issue and an important public health concern in India due to its impact on the economic and mortality burden.[1–3] HF is seen in 1% of the Indian population, and its annual incidence is expected to increase by 18% by 2025.[1,2]

Heart failure (HF) encompasses a wide spectrum of presentations (Fig. 1).[3] The recent study from the Cardiology Society of India-Kerala Acute Heart Failure Registry (CSI-KHFR) with the participation of 7,507 patients with acute HF (AHF) reported that more than two-thirds of patients (67.5%) had reduced ejection fraction [heart failure with reduced ejection fraction (HFrEF)]; unfortunately, the disease affected younger population in their sixties.[4] HF with mildly reduced ejection fraction (HFmrEF) and preserved ejection fraction (HFpEF) were noted in 17.6% and 14.9% of patients, respectively.[4]

In HF, the cardiac output (CO) decreases and subsequently activates the sympathetic nervous system (SNS), the renin–angiotensin–aldosterone system (RAAS), and the natriuretic peptide system (NPS) (Figs 2 and 3).[5–8] Though initially beneficial, continued SNS, RAAS, and NPS activation develops reverse cardiac remodeling over a period of time.[5,8,9] Sympathetic overdrive is seen in >62% of Indians with HF, especially in those with metabolic syndrome.[10] Therefore, drugs that inhibit SNS, RAAS, and NPS would be beneficial in the management of HF.

Further, HF is commonly associated with various comorbidities such as diabetes mellitus (61.4%), hypertension (53.4%), chronic kidney disease (CKD) with

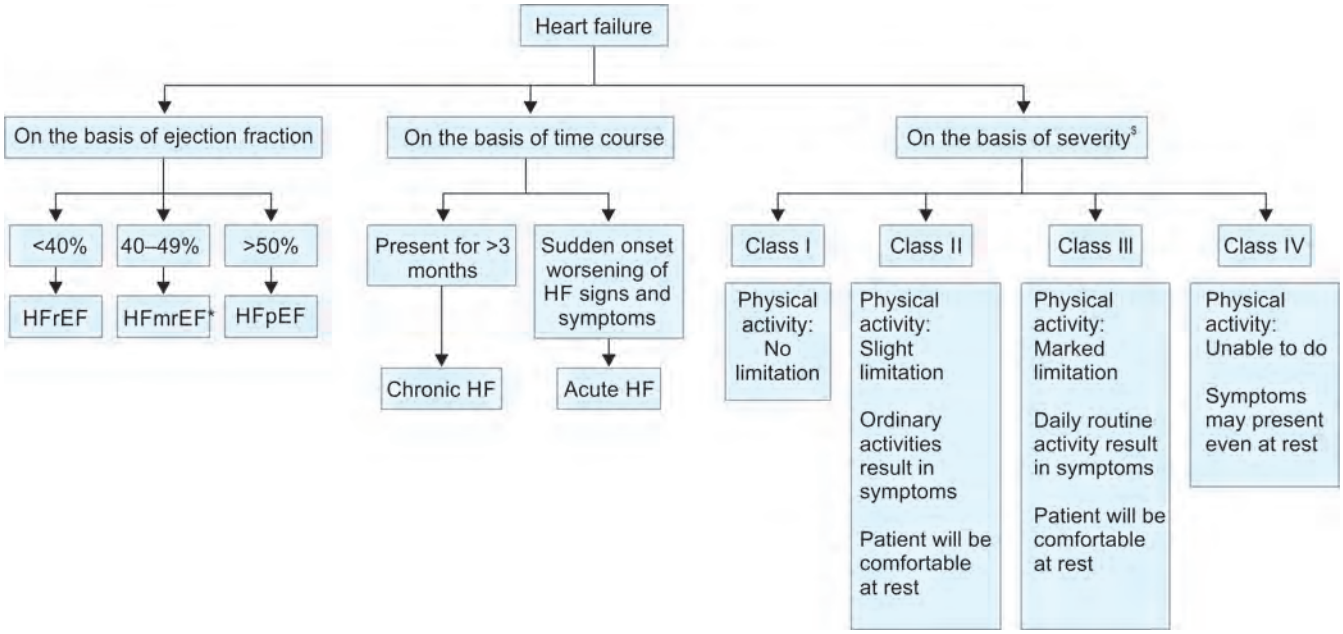


Fig. 1: Different types of HF presentations[3]; *protocol and treatment for this group are unclear but usually follow that of HFrEF; $, New York Heart Association classification (NYHA); HF, heart failure; LVEF, left ventricular ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction

estimated glomerular filtration rate (eGFR) <30 mL/minute/1.73 m^2 (15%), anemia (15%), and atrial fibrillation (AF) (14%).[4] Coronary artery disease (CAD) was the most common etiology for HF (65.7%).[3,4]

The CSI-KHFR data showed that the 5-year mortality rate in HF was 59%, and sudden cardiac death occurred in 46% of patients with HF.[4] Presence of comorbidities increases the mortality risk in HF.[3,4] The in-hospital mortality rates of HF were 7%, and 90-day mortality rates were 11%.[4] Drugs that can effectively and safely manage HF in the presence of comorbidities would be beneficial in HF.

The CSI-KHFR data showed that only 28% of these patients received guideline-directed medical therapy (GDMT).[4] Patients who received GDMT at discharge had better survival (25%).[4] β-1 selective β-blockers (BBs) have an important place in the management of HF. As compared to other GDMTs for HF, the use of BBs correlated with 43% lower 90-day mortality risk (lowest among the GDMTs), followed by RAAS blockers (40% lower risk than other GDMTs).[4]

Bisoprolol is one of the guideline-recommended β-1 super-selective BB for HF.[11–14] Bisoprolol inhibits the neurohormonal overdrive in HF that occurs due to activation of the SNS, and RAAS and has several advantages over other BBs (Table 1).[9,15,16]

This consensus from India discusses the evidence-based role of bisoprolol in the current management of HF. The consensus highlights the importance of bisoprolol in the management of HF and aims to improve the use of bisoprolol in the management of HF by identifying and highlighting the patient population and scenarios where bisoprolol can be effectively and safely used in Indian patients with HF.

Sympathetic Overdrive and RAAS Activation in HF

Cardiac injury in HF triggers a number of molecular, cellular, interstitial, mitochondrial, and genetic changes that cause adverse cardiac, renal, and vascular remodeling (Figs 2 and 3).[6,7,9,17] The adverse remodeling is mainly mediated through the overactive SNS, RAAS, and NPS.[6,9,18] The SNS and RAAS are interrelated as SNS activation in HF leads to RAAS activation, while RAAS activates the central angiotensin II type 1 receptor (AT1R), which contributes to sympathetic overdrive in HF.[5,6] Further, activated RAAS initiates the efferent renal sympathetic nerve activity, resulting in salt and water retention.[5,6] The sympathetic overdrive causes vasoconstriction, which increases blood pressure and, if this persists, causes left ventricular (LV) remodeling.[5,6] The NPS is activated in response to SNS and RAAS continued overdrive as a counter-protective mechanism.[8] However, continued SNS overdrive in HF reduces the response to NPS.[6]

Additionally, the increased cardiac sympathetic adrenergic drive in HF correlates with long-term negative impacts on myocardial function, like increased myocardial energy expenditure and possibly ischemia.[19] The stimulation of the cardiac β-1 adrenergic receptors (ARs) accelerates apoptotic cell death.[20] Further, β-1 AR stimulation reduces the contractility of myocardial cells.[21] Additionally, the sarcoplasmic reticulum is not able to properly handle the intracellular calcium.[21] All these mechanisms result in further deterioration of the failing heart.[7] Therefore, a predominant SNS blockade, combined with RAAS blockade, will be beneficial in HF.

Role of Beta-blockers in HF

Guideline-directed medical therapies (GDMTs) in HFrEF include BBs; angiotensin receptor-neprilysin inhibitors (ARNi) or angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB); mineralocorticoid receptor antagonists (MRA) and a sodium-glucose cotransporter 2 inhibitor (SGLT2i).[2,9,11–13,22,23] BBs are the cornerstones in the management of HF.

Reversing the adverse cardiovascular remodeling is critical for improving cardiac function and outcomes in HF.[9] BB has an important place in reversing cardiac remodeling (atrioventricular and vascular remodeling reversal) in HF by suppressing the β-1 AR activation and thus inhibit the neurohormonal activation seen in HF.[18,24] Further, the sympathetic overdrive in HF reduces the response to cardioprotective natriuretic peptides and thereby contributes to adverse cardiac remodeling.[6] However, substantial clinical evidence demonstrated a trend toward higher levels of natriuretic peptides with guideline-directed BB (nebivolol, bisoprolol, and carvedilol) in HF.[25–27]

Table 1: Advantages of bisoprolol over other β-1 selective blockers

Condition/comorbidity	Advantages of bisoprolol over other β-1 selective BBs (carvedilol, metoprolol or nebivolol)
HF with AF	Bisoprolol is more effective in patients with severe congestive HF with AF[69]: • Better HR control • Improved brain natriuretic peptide level • More patients defibrillated from AF to sinus rhythm • More effective in decreasing post-discharge AF incidence after CABG in patients with decreased LV function[70]
HFrEF (CIBIS-J trial)	Better HR reduction[71]
HF with COPD	Dose–response survival benefit of bisoprolol but not for carvedilol or metoprolol[72] Slightly higher peak VO2 with bisoprolol particularly in CHF patients with reduced DLCO[73] Improvement in pulmonary function and fewer adverse events[74] Better protection against inflammation, myocardial injury and better improvement in pulmonary function in chronic systolic HF[36,75]
HF patients on hemodialysis	Lower 2-year risk of death and MACEs, mainly due to lower HF and ischemic stroke risk[76]
Attaining target dose in HF patients with dizziness and hypotension	Switching from carvedilol to bisoprolol may help continue β-blocker treatment and reach target dose[77]
Prognosis in CHF	"bisoprolol > carvedilol = metoprolol succinate = nebivolol > metoprolol tartrate; (" > " means "prior to")"[38]
HF with diabetes	Bisoprolol and carvedilol do not worsen glycemic parameters and can be preferred over other BBs[39]

AF, atrial fibrillation; CABG, coronary artery bypass grafting; CHF, chronic heart failure; CIBIS, Cardiac Insufficiency Bisoprolol Study; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity of the lungs for carbon monoxide; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; MACE, major adverse cardiovascular events; VO_2, oxygen consumption

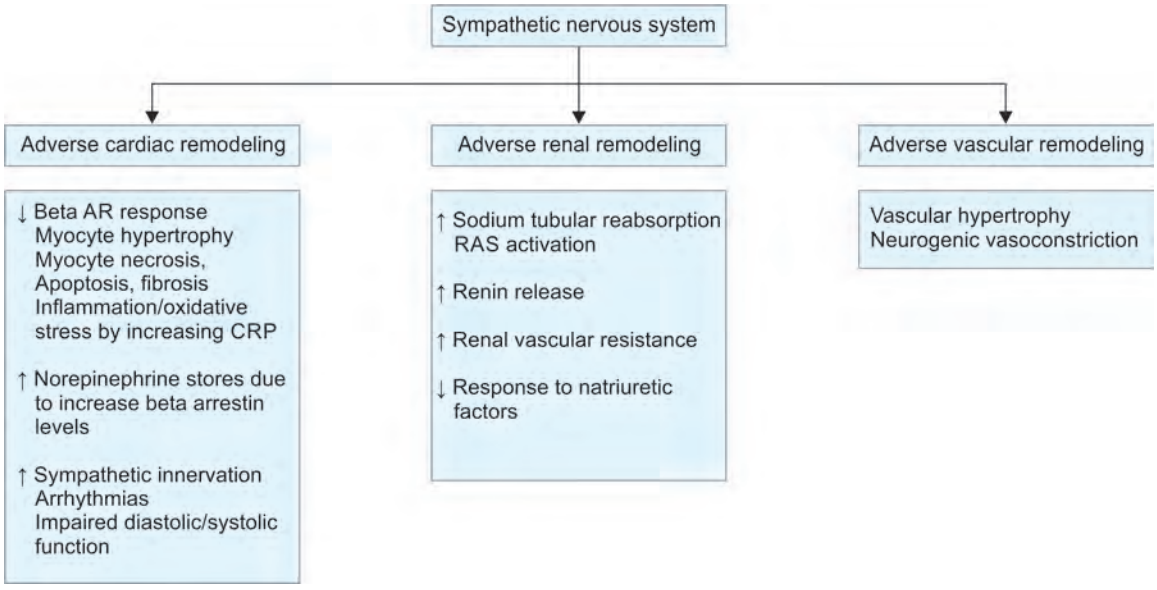


Fig. 2: Adverse cardiac, renal and vascular remodeling due to sympathetic overdrive[6,7,36,37]; AR, adrenergic receptors; NPS, natriuretic peptide system; RAS, renin angiotensin system

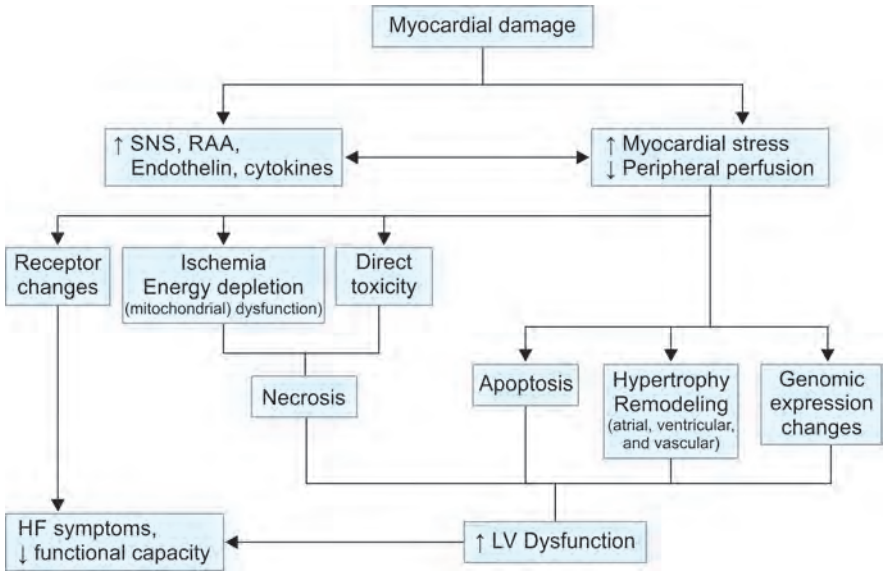


Fig. 3: Myocardial damage (adverse cardiac remodeling) in HF[6,7,17]; HF, heart failure; LV, left ventricular; RAA, renin, angiotensin, aldosterone; SNS, sympathetic nervous system

Multiple studies of BB in HF, such as MERIT-HF (with metoprolol),[28] CIBIS-II (with bisoprolol),[29] and COPERNICUS (with carvedilol)[30] highlight that adding BB to GDMT (ACEi or diuretics) reduces mortality and improves left ventricular (LV) function and volumes.[9] Further, the *post hoc* analysis of the "studies of left ventricular dysfunction" (SOLVD) showed that BB, along with enalapril, was associated with a synergistic reduction in the risk of death as compared to non-BB users.[31]

In view of this evidence, BBs can be initiated immediately in HF along with other GDMTs for rapid titration to optimal dose, thus reducing morbidity and mortality in HF.[32,33]

Guideline Recommendations for Beta-blockers in HF

Indian and International guidelines recommend β-1 blocking BBs such as bisoprolol, carvedilol, metoprolol, or nebivolol as one of the evidence-based selective BB in first-line management of HFrEF, (class I) HF with arrhythmia (class Ia for AF and I for ventricular rate), HFmrEF (class IIB), and HF with CAD (class 1) (Table 2).[2,11–13] These guidelines recommended a variety of BBs, *viz*: second-generation β-1 AR selective BBs including bisoprolol and metoprolol; third generation BB with β-1 blockade and vasodilating properties like carvedilol and nebivolol.[18]

Benefits of Bisoprolol over other Beta-blockers in HF

Current evidence highlights that bisoprolol has several advantages over other BBs recommended in the guidelines for the management of HF (Table 1). Bisoprolol targets both sympathetic overdrive and RAAS activation involved in adverse cardiac remodeling (Fig. 4).[15]

Bisoprolol is a second-generation BB that selectively blocks β_1 AR, which are mainly located in the heart, while β_2 receptors are present in vascular and airway smooth muscle, with a ratio of 119:1.[18,34,35] Bisoprolol, reduces heart contraction and heart rate (HR), leading to reduction in oxygen utilization by the cardiac cells.[15,35] Also, bisoprolol is an inverse agonist at the β_1- receptor and does not have any intrinsic sympathomimetic activity at the β_1- or β_2 ARs.[34]

Bisoprolol inhibits the activation of B1 receptors on juxtaglomerular cells and blocks RAAS, thereby preventing salt and water retention.[15,35] RAAS activation also releases noradrenaline, which has negative effects on the myocardium.[15] Thus, RAAS inhibition by bisoprolol may also reduce noradrenaline-mediated myocardial toxicity. Bisoprolol reverses cell toxicity by increasing the expression of β-arrestin levels; it also has anti-inflammatory action mediated by reduction of CRP.[36,37]

The pharmacokinetic and pharmacodynamic profile of bisoprolol confers several advantages as compared to other BBs. Compared to other BBs, bisoprolol is less lyophilic and, therefore, does not cross the blood–brain barrier and exhibits mixed

Table 2: Guideline recommendations for β-blockers/bisoprolol in HF

Guideline	*Type of HF*	*Recommendation*	*Class of recommendation*	*Level of evidence*
European Society of Cardiology (ESC) 2021[11] and 2023 ESC update[56]	HFrEF	"A β-blocker* is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death"	I	A
	HFmrEF	"A β-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death"	II	B
American Heart Association (AHA)/ACC/Heart Failure Society of America (HFSA) 2022[12]	HFrEF	"In patients with HFrEF, with current or previous symptoms, use of one of the three β-blockers** proven to reduce mortality is recommended to reduce mortality and hospitalizations"	I	A
		In patients with HFrEF, with current or previous symptoms, β-blocker therapy provides high economic value	High value statement	
	HFpEF	BB/bisoprolol is not a recommended GDMT		
ACC 2021 update[14]	HFrEF	Start evidence based BB at their initial dose; bisoprolol to start at 1.25 mg OD Consider increasing dose every 2 weeks until maximum tolerated or targeted dose (10 mg OD) is achieved Monitor HR, blood pressure and look for signs of congestion after initiation and during titration		
Heart Failure Guidelines India: 2017 update[13]	AHF	β-blockers** to be initiated only when the patient is mobile off IV diuretics and inotropes, having no systemic or pulmonary congestion, and is mobilized; Start a very low dose of any approved β-blocker** and very gradually build up the dose		
	CHF	Any approved β- blocker** Bisoprolol to be started at 1.25 mg QD and up titrated to 10 mg QD		
Indian Consensus 2020[2]	Stabilized acute decompensated HFrEF	During hospital stay: follow GDMT#[13] At discharge from hospital: "β-blockers: reduces the risk of all-cause and CV mortality but increase the risk of bradycardia and hypotension; once BP is stable, β-blockers can be safely administered. The dose should be carefully increased to reduce the HR to around 70 beats per minute"		
HFpEF Guidelines (Heart Failure Association of India, Endorsed by Association of Physicians of India) 2022[78]	HFpEF	BB should be avoided except if required for angina relief or AF rate control		
ACC consensus 2023[57]	HFpEF	The guideline notes that BB may be used in patients with "prior MI (for up to 3 years), angina, or AF, but exercise tolerance should be monitored due to the potential for chronotropic incompetence"		

*Bisoprolol, carvedilol, sustained-release metoprolol succinate, or nebivolol; **bisoprolol, carvedilol, sustained-release metoprolol succinate**; #,** as per ESC guidelines; AHF, acute heart failure; BB, β-blocker; GDMT, guideline directed medical therapy; HFmrHF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NA, not available; OD, once daily

hepatic/renal clearance.[18,35] Additionally, bisoprolol has a lower first-pass metabolism and, therefore, has a high bioavailability of 80%, higher than other BBs.[35] It also has a long half-life of 9–12 hours in healthy patients and approximately 17 hours in HF patients, and therefore suitable for once-a-day doses.[18,35,38] Bisoprolol has no intrinsic sympathomimetic activity and is, therefore, beneficial in patients with tachycardia and in post-myocardial infarction (MI) patients who exhibit increased sympathomimetic drive.[34,38] Based on the abovementioned evidence, it has been noted that bisoprolol is more effective and equally safe compared to other β-1 selective blockers such as carvedilol, metoprolol, and nebivolol.[38]

The maximum benefit of BBs is seen at the target dose.[39] Bisoprolol should be started at a low dose of 1.25 mg OD and up-titrated every 2 weeks until the target dose of 10 mg OD is reached.[11–14]

Methodology

The national consensus meeting was organized on 6th August 2023 to discuss the current evidence-based place of bisoprolol in the management of HF. A total of 77 experts from India in the fields of cardiology, nephrology, endocrinology, and intensive care specialty attended this meeting. One senior cardiologist presents the comprehensive and most updated evidence of BB in HF. The experts discussed the literary and guideline-based evidence on the rationale, benefits, and role of β-blockers, especially bisoprolol, in the management of HF. They also shared their clinical experience in managing HF with bisoprolol. The panel discussion was moderated by leading cardiologists, nephrologists, and endocrinologists. With focused discussion and deliberation, the expert opinion was formulated and accepted by all the participating faculty. This consensus

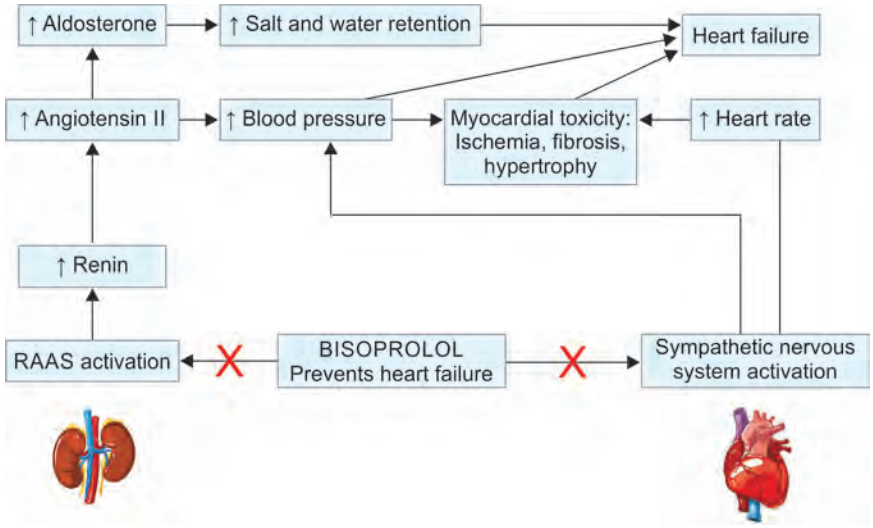


Fig. 4: Bisoprolol blocks the SNS and the RAAS involved in the development and maintenance of HF[15]

was further discussed with one expert from the United States individually by the moderator.

Panel Discussion: Role of Bisoprolol in Different Types of HF

The literary evidence on the efficacy and safety of bisoprolol in different types of HF is represented in Table 3. The randomized placebo-controlled Cardiac Insufficiency Bisoprolol Study (CIBIS) II reported that adding bisoprolol to standard GDMT in HF, such as ACEi and diuretics, improved survival.[29] This study was stopped 18 months earlier as there was a 32% reduction in all-cause mortality ($p < 0.001$).[29] A meta-analysis of the CIBIS-I and CIBIS-II studies (N =3288) confirmed that bisoprolol administration was associated with a significant reduction of overall death, cardiovascular (CV) death, and hospitalizations ($p = 0.0003$ and 0.0001, respectively).[40] The CIBIS-II trials also highlighted that the robust survival benefit with bisoprolol is seen across all dose levels, and bisoprolol withdrawal was associated with a significant increase in mortality risk.[41]

Real-world evidence also highlighted that bisoprolol with GDMT significantly improved left ventricular ejection fraction (LVEF) in patients with HFrEF or HFmrEF recovering in the acute post-acute coronary syndrome (ACS) phase.[42] Additional benefits of reduction in HR and J point ST segment deviation with no adverse effect on lipid profile or glycosylated hemoglobin (HbA1C) were noted.[42] The BISCOR Study showed that bisoprolol can be effectively and safely used at the guideline-recommended maximum doses for outpatient treatment of HF.[24]

Bisoprolol in Chronic HF

Literary evidence from various landmark trials (CIBIS-II[43]; CIBIS III[44]; BISCOR Observational Study[24]) proves the efficacy and safety of bisoprolol in CHF and has been captured in Table 3.

CIBIS-III study highlighted that first-line bisoprolol in CHF could be as efficacious and well tolerated similar to that of ACEi (enalapril), which is usually used as first-line in CHF.[44]

Further, a recent study evaluating the effectiveness and safety of four guideline-recommended BBs (bisoprolol, metoprolol, carvedilol, and nebivolol) in CHF demonstrated improved prognosis with bisoprolol as compared to carvedilol.[38] The study also demonstrated that the efficacy of bisoprolol was superior to other BBs; the effects of carvedilol were similar to metoprolol succinate and nebivolol but superior to metoprolol tartrate.[38] Evidence supports a better reduction in all-cause mortality with bisoprolol compared to carvedilol in patients with CHF. The survival benefit was consistent in Asian patients and in patients with HFrEF.[38] The survival benefit with bisoprolol was higher than that provided by metoprolol but did not reach statistical significance. Hospital readmission rates were significantly lower in patients on bisoprolol than those on metoprolol.[38]

Bisoprolol in Acute Decompensated Heart Failure (ADHF)

There have been concerns regarding the use of BBs in decompensated HF or worsening of HF.[14] However, current literary evidence supports the continued use of evidence-based BBs during acute exacerbation in HFrEF and also raises the possibility of their continued use during compromised renal function.[45,46]

A large study involving 3,817 patients hospitalized for ADHF reported that >90% of them were on evidence-based BBs at admission, of which 33.5% were on bisoprolol.[47] Patients receiving evidence-based BBs at admission had lower in-hospital mortality risk and had lower risk for CV and all-cause mortality.[47] Higher BB dose was associated with lower in-hospital mortality risk.[46] Thus, evidence-based BBs can be safely continued in ADHF.

Patients who were on evidence-based BB (including bisoprolol) at admission had a history of previous HF hospitalization, ventricular tachyarrhythmias, MI, AF, cardiomyopathy, or eGFR <30 mL/minute/1.73 m^2, or they had a history of being on ACEi, ARB, or MRA.[46]

Another retrospective review with 227 patients with ADHF on vasopressors and inotropes (Vs/Is) for cardiogenic shock also reported a lower risk for in-hospital mortality with concomitant use of BBs.[47] The patients who received BBs were younger, had HFrEF, and were more likely to have comorbidities like CAD and AF.[47] ACS was the main reason for hospital admission.

Thus, evidence-based BBs can be safely used in ADHF, confer survival benefits, and can be used across a wide range of patient profiles and combined with many drugs co-prescribed in ADHF.

The dose of evidence-based BB should be carefully monitored to keep the HR 60–70 beats per minute in HF.[2,48] While most patients with ADHF are able to tolerate evidence-based BBs, the dose may need to be down-titrated or the drug withheld if there is marked volume overload, low CO, or cardiogenic shock.[2,14,45,49] Further, dose reduction or BB withdrawal may be necessary in patients with symptomatic hypotension persisting after withdrawing other antihypertensive drugs.[50]

Bisoprolol in HF with Reduced Ejection Fraction

Since overactivation of sympathetic and RAAS systems is involved in the pathophysiology of HFrEF, pharmacological agents antagonizing the chain of events stimulated by this neurohormonal overactivation are known to reduce morbidity and mortality in HFrEF.[45,51]

Evidence-based BBs reduce mortality and morbidity and improve symptoms in

Current evidence highlights the efficacy and safety of BB in CHF as follows[38]:

Bisoprolol > carvedilol = metoprolol succinate = nebivolol > metoprolol tartrate

Where ">": Prior to; "=": equal to

patients with HFrEF when given with an ACEi and diuretic.[28–30,45,52,53] Bisoprolol is one of the guideline-recommended evidence-based BBs of choice in HFrEF.[11–14] Literary evidence on the efficacy and safety of bisoprolol in HFrEF is represented in Table 3.

Though there is no strong evidence on using an ARNi/ACEi/ARB or evidence-based BB (such as bisoprolol) as initiation of therapy, evidence-based BBs are better suited for patients who have less fluid overload and have an adequate resting HR.[14]

Table 3: Clinical evidence of bisoprolol

Trial	*N/Bisoprolol vs comparator*	*Inclusion criteria*	*Mean treatment follow-up*	*Primary endpoint results*	*Other results*	*Adverse effects*
CIBIS-II; placebo controlled RCT[43]	*N* = 2647; bisoprolol (*n* =1327 vs placebo (*n* =1320) Bisoprolol started at 1.25 mg daily and progressively increased to 10 mg daily	HFrEF (LVEF <35%) NYHA III or IV HF from ischemic to nonischemic cardiomyopathies Patients were already on ACEi or diuretics	1.3 years	Significant reduction in all-cause mortality by 34% (12% vs 17%) ($p < 0.001$)	Significant reduction in combined CV mortality or CV hospitalization rate by 21% ($p < 0.001$) Significantly lower hospital admission for worsening HF: 18 vs 12% ($p = 0{\cdot}0001$) Significant reduction in sudden death (by 44%) and pump failure deaths (by 26%)	AE other than mortality not evaluated Significant reduction in mortality
CIBIS III[44]	*N* = 1010; bisoprolol (target dose 10 mg QD; *n* = 505) or enalapril (target dose 10 mg BID; *n* = 505) for 6 months, followed by their combination for 6–24 months	Mild-to-moderate CHF HFrEF (LVEF <35%), not receiving ACEi or BB or ARB	1–2.5 years	PE of all-cause mortality or hospitalization: Bisoprolol-first treatment was noninferior to enalapril-first treatment Bisoprolol first vs enalapril first Intention-to-treat sample: 178 vs 186 PE (absolute difference:1.6%, HR 0.94). Per-protocol sample: 163 vs 165 PE (absolute difference:0.7%, HR 0.97)	Death: 65 vs 73 pts (HR 0.88) Hospitalizations: 151 vs 157 (HR 0.95) Worsening of CHF requiring hospitalization: 63 vs 51 ($p = 0.23$)	Early introduction of the second drug: 7.7 vs 7.3% ($p = 0.81$) Permanent discontinuation during monotherapy: 6.9 vs 9.7% Combined therapy phase: 4.2% permanently discontinued bisoprolol vs 10.4% discontinued enalapril
Tenacity real-world study[42]	*N* = 400; bisoprolol 1.25, 2.5, 5, or 10 mg at the discretion of physician	Post-ACS Asians patients LVD with HFmrEF and HFrEF (LVEF <50%)	1 year	Significant LVEF improvement (41.45 vs 48.73%) and HR reduction (85.06 vs 76.73 bpm) at ($p = 0.0001$)	Significant reduction in ST segment deviation at J point	No adverse effect on lipid and HbA1C
BISCOR observational study[24]	*N* = 334; bisoprolol started at 1.25 mg/day; weekly increments to 5 mg/day followed by increments every 4 weeks to a targeted doses of 10 mg/day	Chronic stable HF NYHA class II–IV outpatient setting	9 months	Maximum targeted dose achieved in 63%; mean dose at the end of follow-up was 8.5 mg	Significant improvement in functional status, quality of life and ejection fraction	Only four patients had SAE

ACS, acute coronary syndrome; CIBIS, Cardiac Insufficiency Bisoprolol Study; CHF, chronic heart failure; CV, cardiovascular; HbA1c, glycosylated hemoglobin; HF, heart failure; HFmrHF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVD, left ventricular dysfunction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PE, primary endpoint; RCT, randomized controlled trial; SAE, serious adverse events

Bisoprolol in HF with Mildly Reduced Ejection Fraction

There is no specific study evaluating β-blockade in HFmrEF. However, many patients with HFmrEF may already be on an evidence-based BB due to an underlying CV condition such as angina and AF.[11]

However, an individual patient data meta-analysis involving 11 trials suggested that evidence-based BB, including bisoprolol, reported similar reductions in CV and all-cause mortality in patients with sinus rhythm HFrEF and HFmrEF.[54]

Further, a recent exploration of results of two prospective observation studies reported lower adjusted all-cause mortality risk in HFmrEF and HFrEF (but not in HFpEF) for patients who received the highest doses of guideline-recommended BBs or ARNi/ACEi/ARB.[55] In this context, each mg bisoprolol equivalent correlated with significant incremental mortality risk reduction in patients with HFmrEF (p = 0.047).[55]

Hence, an evidence-based BB, including bisoprolol, has been considered in HFmrEF by the European guideline to reduce the risk of hospitalizations and death.[11,56]

Bisoprolol in HF with Preserved Ejection Fraction

Historically, there has been no evidence of BB translating into a recommendation for their use in HFpEF, except in specific patient populations.[57,58] A vast majority of patients with HFpEF are already on an evidence-based BB (such as bisoprolol) due to background CV diseases such as CAD, AF, and hypertension.[11] The PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) study in patients with HFpEF reported that 80% of patients were receiving a background BB therapy at baseline.[59]

The RATE-AF (Rate Control Therapy Evaluation in Permanent Atrial Fibrillation) trial highlighted that, at 6 months, bisoprolol provided similar HR control and quality of life (QoL) as digoxin in elderly patients with HFpEF and AF, at the expense of a higher rate of dizziness lethargy, and hypotension with bisoprolol at 12 months.[60]

A real-world study including 1,078 patients with HFpEF in sinus rhythm reported that BB use was not associated with 1-year mortality or HF readmission and mortality.[61]

The 2023 American College of Cardiology (ACC) consensus highlighted that BBs may be used in HF patients with prior MI (≤3 years), angina, or AF.[57] At the same time, the guideline cautioned that BBs can possibly cause chronotropic incompetence, and therefore, physicians should carefully monitor exercise tolerance.[57]

Panel Discussion: Literary Evidence for Bisoprolol in HF with Comorbidities

Patients with HF are often receiving ACEi, and/or BB or diuretics because of concomitant hypertension, ischemic heart disease (IHD), AF, CAD, or other conditions.[11,62]

Guideline Recommendations for Beta-blockers/bisoprolol in HF with Comorbidities

Table 4 gives guideline recommendations for bisoprolol in HF with comorbidities.

Heart Failure in Patients with CAD

Medical therapy with evidence-based BB (such as bisoprolol) should be considered in HFpEF for angina relief.[11,58] Evidence-based BB (such as bisoprolol) are the mainstay of therapy in patients with HFrEF and CAD because of their prognostic benefit.[11]

Table 4: Guideline recommendations for β-blockers/bisoprolol in HF with other comorbidities

Guideline	*Type of HF*	*Recommendation*	*Class of recommendation*	*Level of evidence*
European Society of Cardiology (ESC) 2021[11]	HF with arrythmia	"β-blockers* should be considered for short- and long-term rate control in patients with HF and AF"	IIa	B
		"For patients in NYHA class IIII, a β-blocker, usually given orally, is safe and therefore is recommended as first line treatment to control ventricular rate, provided the patient is euvolaemic"	I	NA
	CCS and HFrEF	β-blockers are the mainstay of therapy in patients with HFrEF andCAD because of their prognostic benefit	I	NA
ESC 2023[68]	HFrEF (NYHA class II–IV) with diabetes	One of the evidence based BBs* are recommended to reduce the risk of HF hospitalization and death	I	A
		Intensive treatment with early initiation of one of the GDMTs (which include BBs) with rapid uptitration to target dose before discharge; frequent follow-up visits in the first 6 weeks postdischarge to reduce readmissions or mortality	I	B
Heart Failure Association of the European Society of Cardiology 2021[62]	HF with CAD and angina	Evidence-based BB* may help control symptoms		
	HF with **d**iabetes	Evidence-based BB* have similar benefits in patients with diabetes as those without diabetes		
	HF with COPD/asthma	Evidence-based BB* can be given in COPD		
	HF in patients with erectile dysfunction	Evidence-based BB* may aggravate erectile dysfunction		

*Bisoprolol, carvedilol, sustained-release metoprolol succinate, or nebivolol; AF, atrial fibrillation; BB, β-blocker; CCS, Chronic coronary syndrome; COPD, chronic obstructive pulmonary disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NA, not available; NYHA, New York Heart Association

The Tenacity real-world study highlighted that bisoprolol given with other GDMTs conferred a significant 1-year improvement in LVEF and New York Heart Association class with a significant reduction in HR (Table 3).[42]

Heart Failure in Patients with Hypertension

Hypertension is the most important underlying cause of HFpEF, and the use of an evidence-based BB (such as bisoprolol) may reduce the incidence of HF in hypertensive patients.[11] However, evidence-based BB (such as bisoprolol) should be used with caution in HFpEF due to its negative chronotropic effects.[57]

Heart Failure and Arrhythmia

Evidence-based BB (e.g., bisoprolol) should be considered for short- and long-term rate control in patients with HFrEF or HFmrEF and AF.[11] These BBs improved LVEF and reduced all-cause and CV mortality in patients with HFrEF and HFmrEF but not in HFpEF.[54,63] However, bisoprolol may be used in patients with HFpEF and AF based on the results of the RATE-AF trial.[58] However, patients should be monitored strictly for adverse effects such as hypotension, dizziness, and drowsiness.

Furthermore, evidence-based BBs (e.g., bisoprolol), in their maximally tolerated dose, are often used as first-line treatment for ventricular rate control in patients with HF and ventricular arrhythmias.[11,49]

Heart Failure in Patients with Aortic Regurgitation (AR)

β-blockers should be cautiously used in patients with HF and AR as BBs prolong diastole and may worsen AR.[11]

Heart Failure in CKD Patients

The beneficial effects of evidence-based BB (e.g., bisoprolol) in reducing mortality and hospitalization for worsening HF are evident in HFrEF patients with moderate to moderately severe renal dysfunction (eGFR 45–59 mL/minute/1.73 m^2 and 30–44 mL/minute/1.73 m^2, respectively).[11,64] However, there is limited evidence of their benefit in severe renal impairment.[11] Therefore, moderate-to-moderately severe renal impairment should not limit the use of bisoprolol in patients with HF.[64]

Heart Failure and Diabetes

In India, approximately 50% of patients with CHF have coexisting type 2 diabetes mellitus (T2DM). HF is more prevalent than MI in patients with type T2DM.[1] All GDMTs recommended for HFrEF have similar efficacy in patients with or without T2DM.[1,11,62] Evidence-based BBs demonstrated a reduction in all-cause mortality in patients with HF and T2DM.[65]

The Tenacity real-world study demonstrated that bisoprolol with other GDMTs was neutral for HbA1c.[42] Bisoprolol does not worsen glycemic parameters in patients with HF and diabetes and can be safely used in this patient population.[39]

β-blockers use in T2DM may cause blunting of hypoglycemia symptoms and precipitate severe hypoglycemia in patients with T2DM.[1,66] However, the treatment benefits of HF far outweigh the risk of hypoglycemia.[67] Nonetheless, careful blood glucose monitoring should be advised for patients with HF and T2DM who are being treated with BBs.

Hence, the 2023 ESC guidelines for the management of CVD in patients with diabetes recommend the use of BB (including bisoprolol) for the management of HFrEF to reduce the risk of HF hospitalizations and mortality.[68] Further, the guideline recommends intensive and early treatment with quick up-titration to the target dose.[68]

Heart Failure in Patients with Asthma

Asthma is a known relative contraindication for the use of BB. However, the Global Initiative for Asthma (GINA) considers the use of cardio-selective BB such as bisoprolol in patients with chronic obstructive pulmonary disease (COPD)/asthma and HF.[62] Patients should be started on low-dose bisoprolol and carefully monitored for signs of airway obstruction (such as wheezing or shortness of breath with prolonged expiration).[11,62]

Pregnancy in Preexisting HF

Only evidence-based BBs such as bisoprolol should be continued, and only milder HF cases should be managed with oral drugs.[11]

Conclusion

Heart failure is a considerable health burden in India. Sympathetic overdrive is a common feature with HF. BB, one of the GDMTs for HF, plays an important and significant role in the management of sympathetic overdrive in HF. Bisoprolol is a superior BB because of its β1 super selectivity. Further, titrating the bisoprolol dose to the maximum tolerated or targeted dose (10 mg/day) helps in achieving the target HR and in cardiovascular remodelling, especially in HFrEF and HFmrEF. The drug's cardiometabolic, pharmacokinetic, and pharmacodynamic-friendly profile confers enormous mortality and morbidity benefits, including reduction in sudden cardiac death, CV mortality, all-cause mortality, and HF hospitalization. Bisoprolol has several advantages over other BBs, especially in Indian patients with HF and other comorbidities. The robust all-cause and CV survival benefits seen with bisoprolol help in improving HF prognosis. It is, therefore, proposed to incorporate bisoprolol in the management of HF in India as per the recommendations of the panel.

Consensus Statements

No.	*Consensus statements*
1	The 5-year mortality rate in HF in India is 59%; sudden cardiac death occurs in 46% of patients; those receiving GDMT at discharge had better survival
2	Sympathetic overdrive is the forerunner in HF before RAAS and NPS activation
3	Sympathetic overdrive is well documented in patients with HFrEF, HFmrEF, and HFpEF with or without significant comorbidities
4	Sympathetic overdrive is seen in 62.5% of Indians, especially in those with metabolic syndrome
5	Bisoprolol is an unique BB due to its β1 super selectivity
6	Bisoprolol has no adverse effect on lipid and glucose metabolism as compared to other BBs, pharmacokinetically and pharmacodynamically superior to other BBs, is more lyophilic, has higher bioavailability, longer half-life of up to 17 hours in CHF, and no intrinsic sympathomimetic activity
7	Sympathetic overdrive is the main cause of CV remodeling, which results in sudden cardiac death, CVD, all-cause mortality, MACE, HF hospitalization, arrhythmia, and worsening of HF
8	Bisoprolol is unique in the reduction of sudden cardiac death, CV death, all-cause mortality, and HF hospitalization (meta-analysis of CIBIS- I, CIBIS-II)
9	Bisoprolol targets both sympathetic overdrive and RAAS activation involved in cardiac remodeling

Contd....

Contd...

No.	Consensus statements
10	Bisoprolol reduces cardiac mortality by reversing cardiac (atrial, ventricular, and vascular) and renal remodeling
11	Bisoprolol reverses epinephrine-mediated cell toxicity by increasing the expression of β-arrestin and exerts anti-inflammatory action by reducing CRP
12	Bisoprolol has robust survival benefits at all dose levels in HF. (CIBIS-II)
13	Sudden bisoprolol withdrawal is associated with a significant increase in mortality risk
14	Bisoprolol is superior to other BBs in improving prognosis in HF
15	The morbidity and mortality in HF can be reduced by achieving the target HR and by optimizing elevated epinephrine and renin levels
16	Maximum benefits of bisoprolol are seen at a target HR of around 60–70/minute achieved with a dose titrated from 1.25 to 10 mg per day
17	Bisoprolol efficacy and safety are well established in both hospital and outpatient HF treatment (CIBIS II, CIBIS III, BISCOR study)
18	Bisoprolol provides a higher survival benefit than metoprolol, with a significantly lower hospital readmission rate in CHF as compared to metoprolol
19	Bisoprolol can be effectively and safely used in ADHF with a lower need for dose titration and a better tolerance profile
20	Bisoprolol is an evidence-based GDMT for HFrEF and HFmrEF but has limited evidence of efficacy in right ventricular failure secondary to LV failure
21	Bisoprolol has a compelling indication in HFpEF (as the vast majority of patients are already on bisoprolol for hypertension, CAD, AF, ventricular arrhythmia, previous infarction <3 years, and angina). It should be used with caution in the elderly as it may cause chronotropic incompetence; the drug should be monitored for exercise tolerance (PARAGON HF Study, ACC-2023)
22	Bisoprolol has prognostic benefits in patients with HF with CAD, hypertension, and arrhythmia
23	Bisoprolol confers renovascular remodeling reversal benefits in HF patients with moderately severe renal impairment
24	Bisoprolol is safe in patients with COPD and asthma; it should start at a lower dose and be monitored for signs of airway obstruction
25	Bisoprolol should be used with caution in patients with AR as it prolongs diastole and may worsen AR
26	Overall, bisoprolol is a superior β-1 super selective BB with robust survival benefits and enormous morbidity and mortality reduction in HF hospitalization, MACE, and arrhythmia, and it prevents progression to severe HF

Funding

Funding for medical writing support was provided by Alembic Pharmaceuticals Ltd.

Medical Writing Assistance

The authors thank Dr Kokil Mathur and Dr Punit Srivastava of Medication Science Pvt Ltd. for providing medical writing support in the preparation of this publication.

Conflict of Interest

Dr Onkar Swami, Dr Sanjay Jain, and Dr Priyank Shah are full-time employees of Alembic Pharmaceuticals Limited, which actively markets bisoprolol.

Acknowledgments

All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work, and have given final approval for the version to be published.

References

1. Kaul U, Ray S, Prabhakar D, et al. Consensus document: management of heart failure in type 2 diabetes mellitus. Heart Fail Rev 202;26(5):1037–1062.
2. Kaul U, Das MK, Agarwal R, et al. Consensus and development of document for management of stabilized acute decompensated heart failure with reduced ejection fraction in India. Indian Heart J 2020;72(6):477–481.
3. Mishra S, Mohan JC, Nair T, et al. Management protocols for chronic heart failure in India. Indian Heart J 2018;70(1):105–127.
4. Joseph S, Panniyammakal J, Abdullakutty J, et al. The cardiology society of India-Kerala acute heart failure registry: poor adherence to guideline-directed medical therapy. Eur Heart J 2022;43(9):908–915.
5. Zucker IH, Xiao L, Haack KK. The central RAS and sympathetic nerve activity in chronic heart failure. Clin Sci (Lond) 2014;126(10):695–706.
6. Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. Nat Rev Cardiol 2017;14(1):30–38.
7. Metra M, Nodari S, D'Aloia A, et al. A rationale for the use of beta-blockers as standard treatment for heart failure. Am Heart J 2000;139(3):511–521.
8. Kuwahara K. The natriuretic peptide system in heart failure: diagnostic and therapeutic implications. Pharmacol Ther 2021;227:107863.
9. Chopra HK, Wander GS, Nair T, et al. Angiotensin receptor-neprilysin inhibitor therapy and cardiac remodeling in heart failure: consensus statement from India. J Assoc Physicians India 2023;71(4): 11–12.
10. Chopra HK, Pancholia AK, Desai BN, et al. Beta-adrenergic blockade: is it the prudent choice against sympathetic overdrive in patients with hypertension or heart failure? J Cardiac Crit Care TSS 2022;06(3):206–209.
11. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42(36):3599–3726.
12. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. Circulation 2022;145(18):e895–e1032.
13. Seth S, Ramakrishnan S, Parekh N, et al. Heart failure guidelines for India: update 2017. J pract cardiovasc sci 2017;3(3):133–138.
14. Maddox TM, Januzzi JL, Allen LA, et al. 2021 update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2021;77(6):772–810.
15. Smith C, Fisher M, McKay G. Bisoprolol. PDI 2008;25(8):334–335.
16. Beck-da-Silva L, de Bold A, Davies R, et al. Effect of bisoprolol on right ventricular function and brain natriuretic peptide in patients with heart failure. Congest Heart Fail 2004;10(3):127–132.
17. Liu M, Lv J, Pan Z, et al. Mitochondrial dysfunction in heart failure and its therapeutic implications. Front Cardiovasc Med 2022;9:945142.
18. Bristow MR. Beta-adrenergic receptor blockade in chronic heart failure. Circulation 2000;101(5): 558–569.
19. Metra M, Nodari S, Bordonali T, et al. Bisoprolol in the treatment of chronic heart failure: from pathophysiology to clinical pharmacology and trial results. Ther Clin Risk Manag 2007;3(4):569–578.
20. Communal C, Singh K, Pimentel DR, et al. Norepinephrine stimulates apoptosis in adult rat ventricular myocytes by activation of the beta-adrenergic pathway. Circulation 1998;98(13): 1329–1334.
21. Lowes BD, Gilbert EM, Abraham WT, et al. Myocardial gene expression in dilated cardiomyopathy treated with beta-blocking agents. N Engl J Med 2002;346(18):1357–1365.
22. Sim D, Lin W, Sindone A, et al. Asian Pacific Society of Cardiology consensus statements on the diagnosis

and management of chronic heart failure. J Asian Paciffic Soc Cardiol 2022;2:e10.
23. Seferovic PM, Ponikowski P, Anker SD, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2019;21(10):1169–1186.
24. González-Juanatey JR, Alegría Ezquerra E, García Saavedra V, et al. Use of bisoprolol in heart failure. The BISOCOR observational study. Rev Esp Cardiol 2003;56(9):873–879.
25. Conraads VM, Metra M, Kamp O, et al. Effects of the long-term administration of nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with diastolic dysfunction: results of the ELANDD study. Eur J Heart Fail 2012;14(2): 219–225.
26. Düngen HD, Apostolović S, Inkrot S, et al. Titration to target dose of bisoprolol vs. carvedilol in elderly patients with heart failure: the CIBIS-ELD trial. Eur J Heart Fail 2011;13(6):670–680.
27. Bergström A, Andersson B, Edner M, et al. Effect of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function. Results of the Swedish Doppler-echocardiographic study (SWEDIC). Eur J Heart Fail. 2004 Jun;6(4):453–461.
28. MERIT-HF Study Group. Effect of metoprolol cr/xl in chronic heart failure: metoprolol cr/xl randomised intervention trial in-congestive heart failure (MERIT-HF). The Lancet 1999;353(9169):2001–2007.
29. CIBIS Investigators and Committees. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). CIBIS Investigators and Committees. Circulation 1994;90(4):1765–1773.
30. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation 2002;106(17):2194–2199.
31. Exner DV, Dries DL, Waclawiw MA, et al. Beta-adrenergic blocking agent use and mortality in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a post hoc analysis of the studies of left ventricular dysfunction. J Am Coll Cardiol 1999;33(4):916–923.
32. Packer M, McMurray JJV. Rapid evidence-based sequencing of foundational drugs for heart failure and a reduced ejection fraction. Eur J Heart Fail 2021;23(6):882–894.
33. Greene SJ, Butler J, Fonarow GC. Simultaneous or rapid sequence initiation of quadruple medical therapy for heart failure-optimizing therapy with the need for speed. JAMA Cardiol 2021;6(7):743–744.
34. AlHabeeb W, Mrabeti S, Abdelsalam AAl. Therapeutic properties of highly selective β-blockers with or without additional vasodilator properties: focus on bisoprolol and nebivolol in patients with cardiovascular disease. Cardiovasc Drugs Ther 2022;36(5):959–971.
35. Bazroon AA, Alrashidi NF. Bisoprolol. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Jul 27]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK551623/
36. Toyoda S, Haruyama A, Inami S, et al. Effects of carvedilol vs bisoprolol on inflammation and oxidative stress in patients with chronic heart failure. J Cardiol 2020;75(2):140–147.
37. Yang H, Du RZ, Qiu JP, et al. Bisoprolol reverses epinephrine-mediated inhibition of cell emigration through increases in the expression of β-arrestin 2 and CCR7 and PI3K phosphorylation, in dendritic cells loaded with cholesterol. Thromb Res 2013;131(3):230–237.
38. Liu B, Zhang R, Zhang A, et al. Effectiveness and safety of four different beta-blockers in patients with chronic heart failure. MedComm (2020) 2023;4(1):e199.
39. Masarone D, Martucci ML, Errigo V, et al. The use of β-Blockers in heart failure with reduced ejection fraction. J Cardiovasc Dev Dis 2021;8(9):101.
40. Leizorovicz A, Lechat P, Cucherat M, et al. Bisoprolol for the treatment of chronic heart failure: a meta-analysis on individual data of two placebo-controlled studies–CIBIS and CIBIS II. Cardiac insufficiency bisoprolol study. Am Heart J 2002;143(2):301–307.
41. Simon T, Mary-Krause M, Funck-Brentano C, et al. Bisoprolol dose–response relationship in patients with congestive heart failure: a subgroup analysis in the cardiac insufficiency bisoprolol study (CIBIS II). Eur Heart J 2003;24(6):552–559.
42. Sharma K, Desai H, Sharma N, et al. To evaluate the 'real world' clinical performance of bisoprolol in post-myocardial infarction with left ventricular dysfunction: tenacity study. J Assoc Physicians India 2022;70(4):11–12.
43. CIBIS-II Investigators and Committee. The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomised trial. Lancet 1999;353(9146):9–13.
44. Willenheimer R, van Veldhuisen DJ, Silke B, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized cardiac insufficiency bisoprolol study (CIBIS) III. Circulation 2005;112(16):2426–2435.
45. Hajouli S, Ludhwani D. Heart Failure and Ejection Fraction. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Jul 24]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK553115/
46. Tamaki Y, Yaku H, Morimoto T, et al. Lower in-hospital mortality with beta-blocker use at admission in patients with acute decompensated heart failure. J Am Heart Assoc 2021;10(13):e020012.
47. Ryu R, Hauschild C, Bahjri K, et al. The usage of concomitant beta-blockers with vasopressors and inotropes in cardiogenic shock. Med Sci (Basel) 2022;10(4):64.
48. Porapakkham P, Porapakkham P, Krum H. Is target dose of beta-blocker more important than achieved heart rate or heart rate change in patients with systolic chronic heart failure? Cardiovasc Ther 2010;28(2):93–100.
49. Mebazaa A, Yilmaz MB, Levy P, et al. Recommendations on pre-hospital & early hospital management of acute heart failure: a consensus paper from the heart failure association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. Eur J Heart Fail 2015;17(6):544–558.
50. Kyu HH, Abate D, Abate KH, et al. Global, regional, and national disability-adjusted life-years (dalys) for 359 diseases and injuries and healthy life expectancy (hale) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease study 2017. Lancet 2018;392(10159):1859–1922.
51. Haydock PM, Flett AS. Management of heart failure with reduced ejection fraction. Heart 2022;108(19):1571–1579.
52. Gomberg-Maitland M, Baran DA, Fuster V. Treatment of congestive heart failure: guidelines for the primary care physician and the heart failure specialist. Arch Intern Med 2001;161(3):342–352.
53. Fowler MB. Effects of beta blockers on symptoms and functional capacity in heart failure. Am J Cardiol 1997;80(11A):55L–58L.
54. Cleland JGF, Bunting KV, Flather MD, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. Eur Heart J 2018;39(1):26–35.
55. Straw S, Cole CA, McGinlay M, et al. Guideline-directed medical therapy is similarly effective in heart failure with mildly reduced ejection fraction. Clin Res Cardiol 2023;112(1):111–122.
56. McDonagh TA, Metra M, Adamo M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2023;44(37):3627–3639.
57. Kittleson MM, Panjrath GS, Amancherla K, et al. 2023 ACC expert consensus decision pathway on management of heart failure with preserved ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2023;81(18):1835–1878.
58. Jasinska-Piadlo A, Campbell P. Management of patients with heart failure and preserved ejection fraction. Heart 2023;109(11):874–883.
59. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. N Engl J Med 2019;381(17):1609–1620.
60. Kotecha D, Bunting KV, Gill SK, et al. Effect of digoxin vs bisoprolol for heart rate control in atrial fibrillation on patient-reported quality of life: the rate-af randomized clinical trial. JAMA 2020;324(24):2497–2508.
61. Formiga F, Chivite D, Nuñez J, et al. Beta-blocker use in patients with heart failure with preserved ejection fraction and sinus rhythm. Rev Port Cardiol 2022;41(10):853–861.
62. Rosano GMC, Moura B, Metra M, et al. Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2021;23(6):872–881.
63. Farmakis D, Chrysohoou C, Giamouzis G, et al. The management of atrial fibrillation in heart failure: an expert panel consensus. Heart Fail Rev 2021;26(6):1345–1358.
64. Castagno D, Jhund PS, McMurray JJV, et al. Improved survival with bisoprolol in patients with heart failure and renal impairment: an analysis of the cardiac insufficiency bisoprolol study II (CIBIS-II) trial. Eur J Heart Fail 2010;12(6):607–616.
65. Tsujimoto T, Sugiyama T, Kajio H. Effects of β-blockers on all-cause mortality in patients with type 2 diabetes and coronary heart disease. Diabetes Obes Metab 2017;19(6):800–808.
66. Tsujimoto T, Sugiyama T, Shapiro MF, et al. Risk of cardiovascular events in patients with diabetes mellitus on β-Blockers. Hypertension 2017;70(1):103–110.
67. Bashier A, Bin Hussain A, Abdelgadir E, et al. Consensus recommendations for management of patients with type 2 diabetes mellitus and cardiovascular diseases. Diabetol Metab Syndr 2019 ;11(1):80.
68. Marx N, Federici M, Schütt K, et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. Eur Heart J 2023;44(39): 4043–4140.
69. Konishi M, Haraguchi G, Kimura S, et al. Comparative effects of carvedilol vs bisoprolol for severe congestive heart failure. Circ J 2010;74(6):1127–1134.
70. Marazzi G, Iellamo F, Volterrani M, et al. Comparison of effectiveness of carvedilol versus bisoprolol for prevention of postdischarge atrial fibrillation after coronary artery bypass grafting in patients with heart failure. Am J Cardiol 2011;107(2):215–219.
71. Tsutsui H, Momomura SI, Masuyama T, et al. Tolerability, efficacy, and safety of bisoprolol vs. carvedilol in Japanese patients with heart failure and reduced ejection fraction-the CIBIS-J trial. Circ J 2019;83(6):1269–1277.
72. Su VY, Chang YS, Hu YW, et al. Carvedilol, bisoprolol, and metoprolol use in patients with coexistent heart failure and chronic obstructive pulmonary disease. Medicine (Baltimore) 2016;95(5):e2427.
73. Agostoni P, Contini M, Cattadori G, et al. Lung function with carvedilol and bisoprolol in chronic heart failure: is beta selectivity relevant? Eur J Heart Fail 2007;9(8):827–833.

74. Lainscak M, Podbregar M, Kovacic D, et al. Differences between bisoprolol and carvedilol in patients with chronic heart failure and chronic obstructive pulmonary disease: a randomized trial. Respir Med 2011;105(Suppl 1):S44–S49.
75. Toyoda S, Haruyama A, Inami S, et al. Protective effects of bisoprolol against myocardial injury and pulmonary dysfunction in patients with chronic heart failure. Int J Cardiol 2017;226:71–76.
76. Wu PH, Lin YT, Liu JS, et al. Comparative effectiveness of bisoprolol and carvedilol among patients receiving maintenance hemodialysis. Clin Kidney J 2021;14(3):983–990.
77. Taniguchi T, Ohtani T, Mizote I, et al. Switching from carvedilol to bisoprolol ameliorates adverse effects in heart failure patients with dizziness or hypotension. J Cardiol 2013;61(6):417–422.
78. S H, Oomman A, Jadhav UM, et al. Heart failure with preserved ejection fraction: management guidelines (from Heart Failure Association of India, endorsed by Association of Physicians of India). J Assoc Physicians India 2022;70(8):11–12.

Adenoid Cystic Carcinoma Mimicking Bronchial Asthma

Kranti Garg[1*], Sanjeev Kumar Binji[2]

Received: 04 May 2019; *Accepted:* 22 September 2023

A 41-year-old male presented to the Department of Pulmonary Medicine, with shortness of breath for 1 year. Though on treatment for bronchial asthma, he was not responding. The chest radiograph was normal (Fig. 1). On spirometric examination, the flow-volume curve showed flattening of the expiratory limb, suggesting variable intrathoracic obstruction. Fiber-optic bronchoscopy was, hence, done and it revealed a growth in the trachea (Fig. 2). Biopsy was deferred due to the risk of bleeding. Computed tomography (CT) of the chest also showed tracheal growth (Fig. 3). The patient was planned for rigid bronchoscopy. Meanwhile, the patient presented with expectoration of a piece of that growth. Histopathological examination revealed an adenoid cystic carcinoma (Fig. 4).

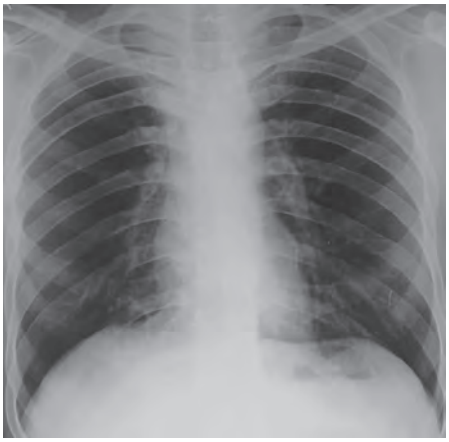


Fig. 1: Normal chest radiograph (posterior–anterior view)

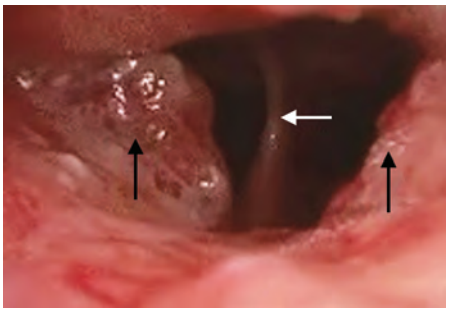


Fig. 2: Fiber-optic bronchoscopy showing growth (black arrows) in the lower end of trachea superior to carina (white arrow), causing significant luminal narrowing

Patient was referred to a higher center where debulking and coring were done with a rigid bronchoscope. Histopathology reconfirmed the diagnosis. The patient was planned for definitive surgery as there was no evidence of metastasis on detailed workup. Right, posterolateral thoracotomy showed an extraluminal component of the tumor incongruent from intraluminal growth. Intraoperative bronchoscopy revealed an involved tracheal length of around 4.5 cm. Due to positive margins on resection of this much length and the subsequent risk of anastomotic dehiscence, the procedure was abandoned. The patient received adjuvant radiotherapy with a dose of 50 Gy in 25 fractions over 5 weeks on the linear accelerator. He tolerated radiotherapy well without any treatment breaks. CT of the chest at 4 months follow-up showed circumferential thickening of the trachea (Fig. 5). At follow-up at 12 months, the patient is stable, with no evidence of recurrence.

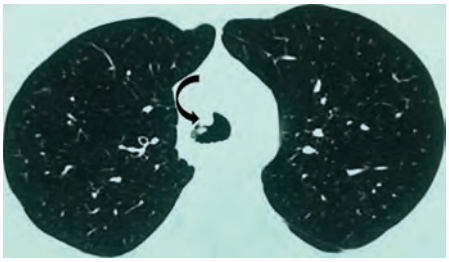


Fig. 3: Contrast-enhanced computed tomography (CECT) chest axial section showing growth in the trachea (black curved arrow) causing partial occlusion

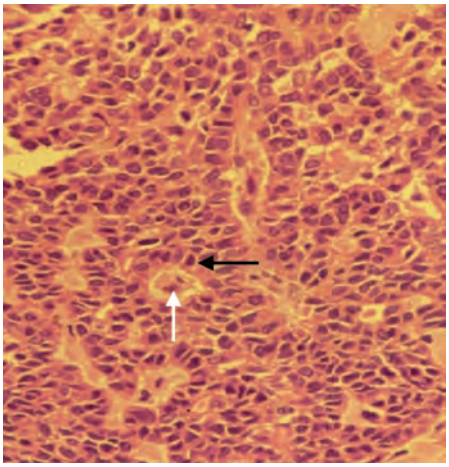


Fig. 4: Basaloid-appearing tumor cells (black arrow) along with eosinophilic material in the lumen (white arrow) (hematoxylin and eosin, 400x)

Our case restrengthens the adage "all that wheezes is not asthma."[1,2] A young male, with presenting complaints of shortness of breath, findings of wheeze on examination, and an absolutely normal chest radiograph, was diagnosed and treated as an asthmatic. In view of uncontrolled symptoms, the patient was reevaluated and reasons for the same were looked for. A simple spirometry gave a valuable lead for the evaluation of the central airways. Subsequent detailed workup ultimately led to an early definitive diagnosis of an uncommon tracheal tumor.[1,3,4] This case thus highlights how a simple investigation can be of immense help. It also highlights that localized airway obstructions should be considered a differential in asthmatic patients not responding to treatment. Had an early bronchoscopy not been done, the airway obstruction due to a tumor could have

[1]Assistant Professor; [2]Ex-Junior Resident, Department of Pulmonary Medicine, Government Medical College and Hospital, Chandigarh, India; *Corresponding Author

How to cite this article: Garg K, Binji SK. Adenoid Cystic Carcinoma Mimicking Bronchial Asthma. J Assoc Physicians India 2023;71(12):89–90.

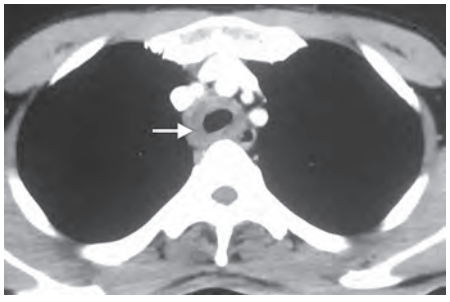


Fig. 5: Contrast-enhanced computed tomography (CECT) chest axial section at 4 months follow-up showing circumferential thickening of the trachea with luminal compromise (white arrow)

progressed, with this patient presenting in advanced stages of the disease.[1,3,4]

Acknowledgments

Dr R P S Punia, Professor, Department of Pathology, corroborating the diagnosis.

References

1. Kokturk N, Demircan S, Kurul C, et al. Tracheal adenoid cystic carcinoma masquerading asthma: a case report. BMC Pulm Med 2004;4:10.
2. https://ginasthma.org/wp-content/uploads/2019/01/2010-GINA.pdf. accessed on February 25, 2019.
3. Kapatia G, Gupta K, Shrestha O, et al. An autopsy report of an adenoid cystic carcinoma arising in the trachea. Head Neck Pathol 2018;13(2):243–246.
4. Qi D, Feng L, Li J, et al. Primary adenoid cystic carcinoma of the trachea with thyroid invasion: a case report and literature review. Onco Targets Ther 2016;9:6291–6296.

Phakomatosis Pigmentovascularis: A Rare Disease

Ashish Singh[1], Yash Chandan[2], Amar R Pazare[3*]

Received: 28 July 2023; *Accepted:* 18 August 2023

[1,2]Juniour Resident; [3]Professor and HOU, Department of Medicine, KJ Somaiya Medical Institute and Hospital, Mumbai, Maharashtra, India; *Corresponding Author

How to cite this article: Singh A, Chandan Y, Pazare AR. Phakomatosis Pigmentovascularis: A Rare Disease. J Assoc Physicians India 2023;71(12):91–92.

Case History

A 19-year-old female, Mrs. XYZ, resident of Mumbai came with complaints of fever and cough with whitish expectorate of 12 days duration. The patient had a bright red erythematous patches on bilateral cheeks and chin (Fig. 1). Hyperpigmented patches seen over the body at multiple sites since birth.

X-ray chest and chest computed tomography scan shows haziness in the right lower lobe (Fig. 2), Sputum for AFB by CBNAAT was positive (rifampicin sensitive). Blood sugar was normal. Test for hepatitis B surface antigen, anti-hepatitis C antibody, and human immunodeficiency virus-was negative. Antinuclear antibodies (ANA) and double- stranded DNA (dsDNA) were negative.

On general examination, she had hyperpigmented patches (extensive dermal Melanesia) (Figs 3 and 4). Clinically she was diagnosed as phakomatosis pigmentovascularis (PPV).

Discussion

Phakomatosis pigmentovascularis (PPV) is a rare congenital disorder, predominantly characterized by the coexistence of vascular and pigmentary birthmarks.[1]

The PPV is a mosaic pattern abnormality of vasomotor nerves and melanocytes that results in cutaneous manifestations like port wine stain, patches of hyperpigmentation, *cafe au lait spots*, moles, nevus of ota, and extensive dermal melanosis. Few patients have associated systemic features involving muscular, or ocular abnormality.[2–4]

This disease is so rare that the prevalence is currently unknown. It is thought to be more common in those of Asian ethnicity with no family history of PPV.[1]

The PPV is a mosaic developmental abnormality of the vasomotor nerves and melanocytes. It is found in a study that PPV is caused by somatic mutations in guanosine nucleotide-binding protein alpha-11 and

Fig. 1: Showing erythematous lesion on the face

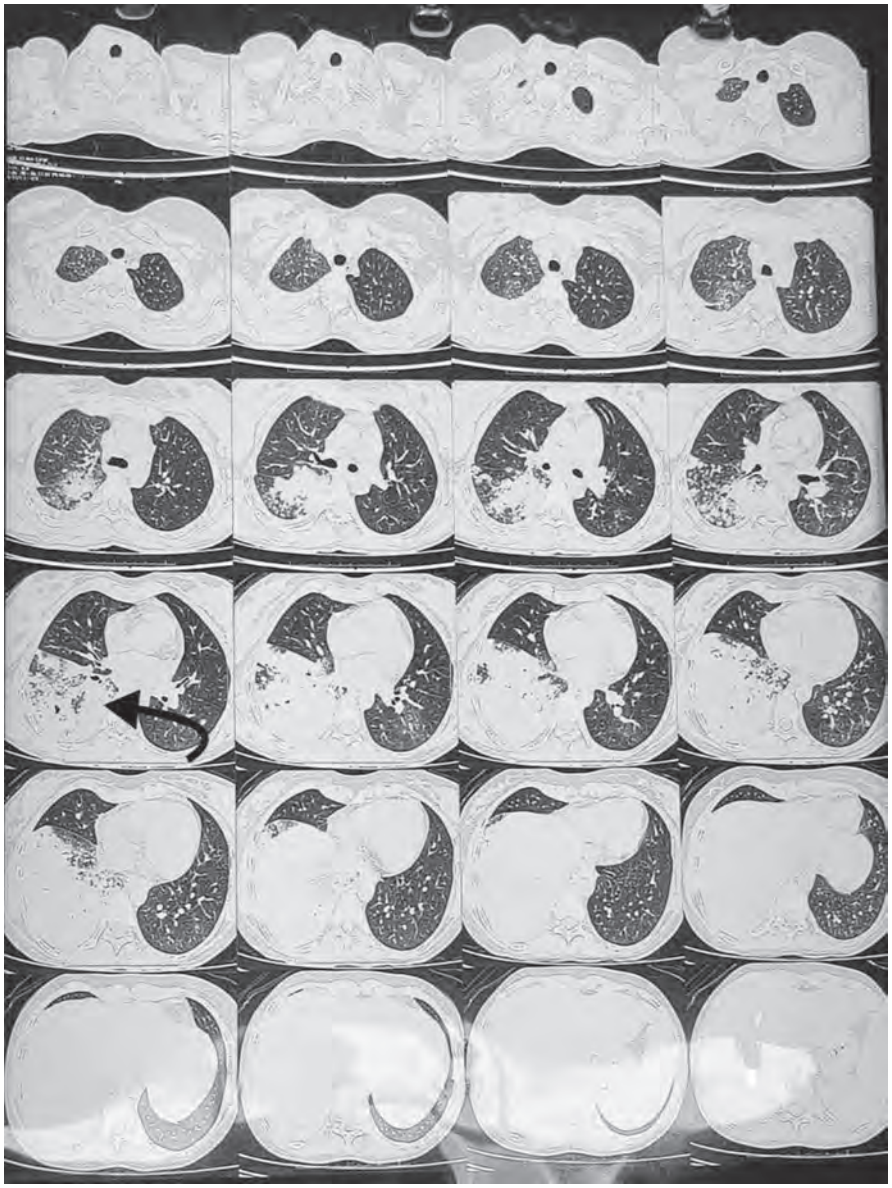


Fig. 2: High-resolution computed tomography chest showing the atypical path in the right lower lobe

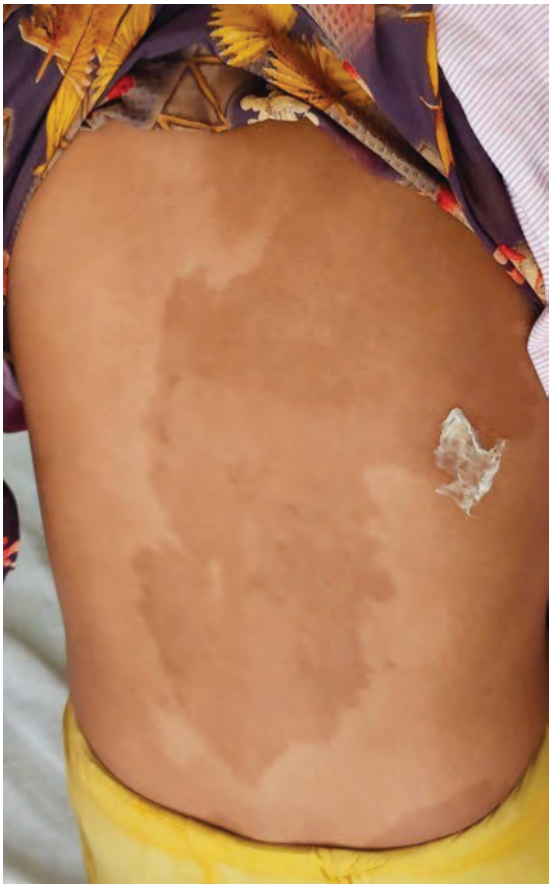


Fig. 3: Hyperpigmented patch in back

guanosine nucleotide-binding protein Q gene genes, which encode Gα subunits of heterotrimeric G proteins, a mosaic G protein disorder joining the family of McCune–Albright syndrome and Sturge–Weber syndrome. These somatic genetic mutations have been only detected in affected tissues, but undetectable in blood and unaffected organs, which means PPV is non inheritable mutation disorder.[5]

Fig. 4: Hyperpigmented lesion in the forearm

Acknowledgment

Department of Dermatology, KJ Somaiya Medical Institute and Hospital, Mumbai, Maharashtra, India.

References

1. Fernández-Guarino M, Boixeda P, de Las Heras E, et al. Phakomatosis pigmentovascularis: clinical findings in 15 patients and review of the literature. J Am Acad Dermatol 2008;58(1):88–93.
2. Happle R. Phacomatosis pigmentovascularis revisited and reclassified. Arch Dermatol 2005;141(3):385–388.
3. Shin H, Kim YG, Kim YE, et al. Clinical characteristics and treatment of 52 cases of phakomatosis pigmentovascularis. J Dermatol 2019;46(10):843–848.
4. Tran C, Alward WLM. Phakomatosis pigmentovascularis. Ophthalmol Glaucoma 2021;4(3):250.
5. Thomas AC, Zeng Z, Rivière JB, et al. Mosaic activating mutations in GNA11 and GNAQ are associated with phakomatosis pigmentovascularis and extensive dermal melanocytosis. J Invest Dermatol 2016;136(4):770–778.

CASE SERIES

A Case Series of Snakebite Presenting with Renal Syndromes

M Ananthakrishna[1*], Himamani[2]

Received: 25 March 2023; *Accepted:* 07 June 2023

Abstract

Snakebite is one of the common causes of acute kidney injury (AKI), mainly in Southeast Asia. The toxin can cause a variety of pathological types of AKI. The study shows 17 cases of snakebite with renal impairment, proving different pathological subtypes of AKI.

Journal of the Association of Physicians of India (2023): 10.59556/japi.71.0362

Introduction

It has been observed that there were 0.5–2 million cases of snakebite annually, with the highest burden in Southeast Asia.[1]

Snakebite is one of the common causes of acute kidney injury (AKI) in India. Around 13–33% of snakebite produces AKI. It can develop in hours to as late as 96 hours after the incident.[2] Renal dysfunction is usually seen with hemotoxic and myotoxic snakebites and is really rare with neurotoxic snakebites.[3,4] Renal dysfunction in snakebite can be due to different causes. The most common is acute tubular necrosis (ATN), which can be secondary to direct toxin injury or sepsis-induced or pigmental nephropathy-induced (rhabdomyolysis) or due to DIC. Rare cases are present with typical haemolytic uremic syndrome (HUS)—induced renal injury with associated hemolysis, the outcomes of which are highly variable. A typical HUS shows the response to early initiation of Plasma exchange with complete resolution of renal injury, according to some studies but some other studies have shown them going into dialysis dependent state. Rare cases can persist to have nonoliguric renal failure due to acute cortical necrosis. Very rarely there can be glomerulonephritis due to toxin-antibody complex deposition.[5–9]

Studies on the prevalence of different renal syndromes in snakebite cases are lacking. The present study is observational in nature, on what are the causes of renal syndrome presentation in snakebite cases and their outcome on treatment. This is a study of snakebite cases with renal impairment, admitted in a tertiary hospital in South India during 6 months period.

Materials and Methods

A total of 17 cases of snakebite with renal impairment, admitted in a tertiary hospital in South India were taken for the present study.

Results

Five of the cases had ATN. One case had ATN on biopsy, the patient has been on regular hemodialysis for the last 1 month. Five cases with toxin/sepsis-induced prerenal AKI. Two cases presented with TMA with hemolysis. One case presented went into nonoliguric AKI secondary to cortical necrosis. One case of ATN secondary to pigment cast nephropathy. One case of acute interstitial nephritis (AIN).

One case with hypertension showed features of glomerulonephritis, the patient was not improving with routine antibiotics and hemodialysis. The patient was planned for renal biopsy after being clinically stable but was taken to another hospital by the attendees. Pathology of AKI looked multifactorial in view of sepsis, toxin-significant proteinuria and preexisting hypertension. A preexisting glomerulosclerosis may be there or a rare chance of toxin antibody complex-mediated glomerulonephritis.

Five of the cases were viper bites, other cases being unknown snakebites. The majority of the cases showed local or systemic signs of hematotoxicity snake venom toxicity. None of the cases showed neurotoxic manifestations.

- Prerenal AKI: Five cases of the study, presented with hemodynamic instability had AKI on the day or 1 day after admission. These patients had an oliguric presentation. On routine investigations this group showed a rise in urea more than creatine (>20:1). The urine routine of this group didn't yield any significant abnormality. The fractional excretion of sodium (FeNa) of these cases were <20. Thus a diagnosis of prerenal AKI was put on clinical to biochemical basis.
  All these patients were given fluid therapy with antibiotic coverage. All the patients in this group improved after this management within 3–4 days, with a total reversal of renal function.
- ATN: Seven cases presented with oliguric AKI.This group of patients had a broad spectrum presentation, some presented to the hospital on the day of the snakebite with AKI on the same day to some presented after 1 week of the snakebite with AKI.
  Five of these cases were clinicobiochemically diagnosed as acute tubular necrosis. These cases had an RFT showing a rise in urea and creatinine in a ratio <20:1, with urine routine showing the epithelial cast in the majority of cases, with a FeNa >40. All these five cases were given IV antibiotics and other supportive care, they showed a delayed recovery of renal parameters by around 1–2 weeks.
  One case in the group didn't show recovery in the oliguric AKI and was started on hemodialysis for the same. A renal biopsy was done for the case to confirm ATN on histopathology (Fig. 1).
  The case had an outcome of a dialysis-dependent state with weekly two times dialysis.
  One case of similar presentation with a urine routine showing red blood cells (RBCs) and serum C-reactive protein (CPK) significantly high, was biopsied for confirmation of the diagnosis of ATN secondary to pigment cast

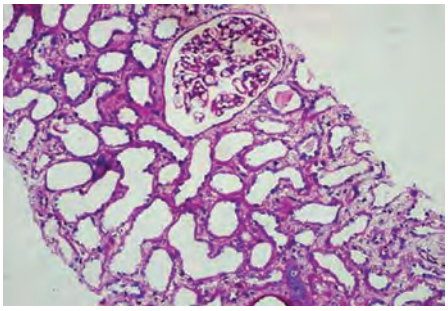
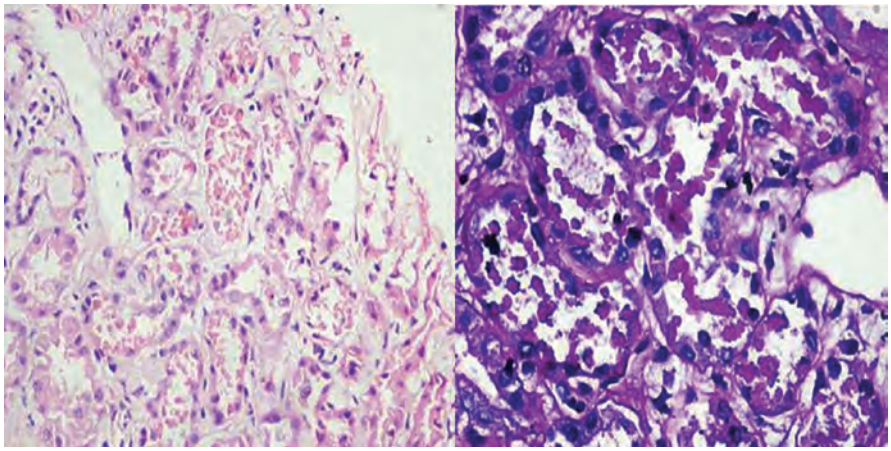


Fig. 1: ATN

[1]Junior Resident, Department of General Medicine; [2]Professor and Head, Department of Nephrology, MMCRI, Mysuru, Karnataka, India; *Corresponding Author

How to cite this article: M A, S H. A Case Series of Snakebite Presenting with Renal Syndromes. J Assoc Physicians India 2023;71(12):93–94.



Figs 2A and B: Pigment cast nephropathy. (A) Hematoxylin and eosin staining; (B) Periodic acid–Schiff staining

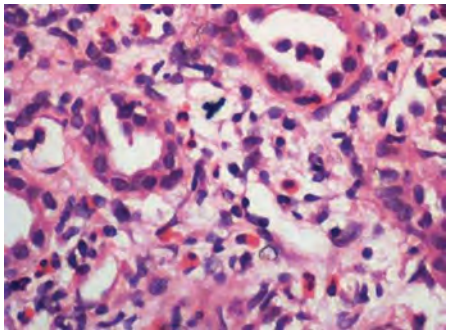


Fig. 3: AIN

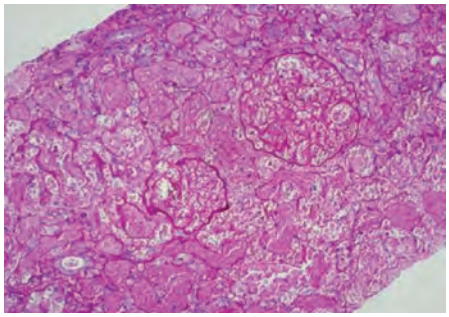


Fig. 4: Diffuse cortical necrosis

nephropathy. The case was also initiated on hemodialysis, the patient on follow-up showed improvement and is dialysis-free after 3 months of illness (Fig. 2).

- AIN: One case who presented after 1 week of snakebite with oliguric AKI, with further evaluation showed a urine routine with WBC and eosinophil cast, a high erythrocyte sedimentation rate (ESR) and CRP. The case on renal biopsy showed interstitial infiltrate, proving the diagnosis of acute interstitial nephritis. The case was treated with IV steroid pulse and hemodialysis. The patient showed improvement with complete recovery in renal function after around 1 week of therapy (Fig. 3).
- Atypical HUS: Two cases presented to the hospital after 1 and 4 days, respectively after snakebite, developed oliguric AKI. These cases had high blood pressure during this period. They were investigated, which showed hemolytic anemia with thrombocytopenia with a significant lactate dehydrogenase (LDH) rise. The peripheral smear of these cases showed schistocytes.

A diagnosis of thrombotic microangiopathy was made on a clinicpathological basis. These cases were given plasma exchange in five sections, after which patients showed gradual improvement in renal function, with total recovery by around 1 month.

- Renal cortical necrosis: One case presented after 6 days of snakebite had a nonobliguric AKI. The patient on routine evaluation had albumin, pus cells and RBC in urine This patient was biopsied which showed diffuse cortical necrosis.

  The patient ended up being dialysis dependent, with weekly thrice hemodialysis (Fig. 4).
- Immune glomerular nephritis: One case with hypertension who presented after 1 day of snakebite with oliguric AKI. The patient showed significant proteinuria (4+) and RBC in urine, with very high ESR. The patient didn't show improvement with antibiotics and other supportive care and hence initiated on hemodialysis, which was planned for renal biopsy after the patient stabilized, but the patient was lost to follow-up.

The differential diagnoses provisionally kept were:

- The AKI with multifactorial ethiology (sepsis, toxin) with underlying hypertensive glomerulosclerosis.
- Toxin antibody-mediated glomerulonephritis.

Discussion

- Snakebite-related renal syndrome is a major challenge in India. It can present a wide variety of pathology.
- We analyzed the clinical presentation and correlated it with the investigation was able to reach the conclusion on different pathological causes of AKI in snakebite cases.

Conclusion

- Snakebite causing renal impairment is a common complication.
- Renal impairment due to snakebite can be due to different pathologies.
- AKI–ATN being the most common.
- The outcome of patients presenting with renal impairment due to snakebite depends on the pathology underlying.
- From rapid recovery in prerenal AKI to a dialysis-dependent state cortical necrosis can occur secondary to snakebite.
- Late presentation to the hospital has shown more frequency of severe pathology causing AKI.

References

1. White J. Bites and stings from venomous animals: a global overview. Ther Drug Monit 2000;22(1):65–68.
2. Chugh KS. Snake-bite-induced acute renal failure in India. Kidney Int 1989 Mar;35(3):891–907.
3. Chugh KS, Pal Y, Chakravarty RN, et al. Acute renal failure following poisonous snakebite. Am J Kidney Dis 1984;4(1):30–38.
4. Kohli HS, Sakhuja V. Snake bites and acute renal failure. Saudi J Kidney Dis Transpl 2003;14(2):165–176.
5. Chugh KS, Aikat BK, Sharma BK, et al. Acute renal failure following snakebite. Am J Trop Med Hyg 1975;24(4):692–697.
6. Sitprija V. Animal toxins and the kidney. Nat Clin Pract Nephrol 2008;4(11):616–627.
7. Godavari KS. Hemolytic uremic syndrome-an unusual complication of snake envenomation. UJM 2016;2(2).
8. Noutsos T, Currie BJ, Lek RA, et al. Snakebite associated thrombotic microangiopathy: a systematic review of clinical features, outcomes, and evidence for interventions including plasmapheresis. PLoS Negl Trop Dis 2020;14(12):e0008936.
9. Dineshkumar T, Dhanapriya J, Sakthirajan R, et al. Thrombotic microangiopathy due to viperidae bite: two case reports. Ind J Nephrol 2017;27(2):161–164.

CASE REPORT

Serum Sickness like Reaction Postequine Rabies Immunoglobulins

Mansi Shah[1], Vinus Taneja[2*], Pooja Khosla[3]

Received: 01 March 2023; *Accepted:* 08 May 2023

Abstract

A 30-year-old, previously healthy adult male received equine rabies immunoglobulins (Ig) (ERIG) along with anti-rabies vaccinations as per protocol for postexposure prophylaxis after an unprovoked rabid dog bite of grade three wound over the shin of the left lower limb. On the 8th day, he developed urticarial rashes beginning from the site of the wound, which gradually became a widespread maculopapular rash. Development of the rash was followed by low-grade fever, nonspecific arthralgias and soreness in the throat. A diagnosis of serum sickness-like illness was made based on history, temporal correlation of administration of ERIG and development of symptoms. He responded well to antihistaminic and a short course of injectable steroids. The purpose of this article is to increase awareness regarding the clinical presentation and management of this rare yet potentially curable adverse event if identified timely.

Journal of the Association of Physicians of India (2023): 10.59556/japi.71.0345

Introduction

Rabies, a neurological catastrophic illness caused by the genus *Lyssavirus* belonging to the family *Rhabdoviridae*, has the potential to become rapidly fatal in the absence of prompt postexposure prophylaxis. Rabies is responsible for 18,000–20,000 deaths per year in India alone. For previously unvaccinated individuals, bitten by a rabid animal with a bite wound extending beyond the dermis or involving oozing of blood (category three), rabies immunoglobulins (Igs) are the cornerstone of acute management along with local wound care and scheduled anti-rabies vaccinations.[1] In developing countries like India, equine preparations are found to be cost-effective.[2] However, due to the presence of heterologous proteins, incidents of serum sickness-like illness have been noted with equine preparations.

Case Description

A 30-year-old healthy male was bitten by a stray rabid dog on the shin of his left lower limb just below the knee. Minor bleeding was noted from the wound site while providing local wound care with soap and water. Since no prior immunization against rabies was received, equine rabies Igs (ERIG) (40 units/kg) were locally infiltrated into the wound and the remaining dose was injected intramuscularly into the right gluteal region along with the administration of the first dose of anti-rabies vaccination (day 0) over right deltoid muscle. He was prescribed amoxicillin as an antibiotic prophylaxis. However, he developed 2–3 episodes of loose stools after postantibiotic intake, and it was stopped. He completed his subsequent doses of anti-rabies vaccination (days 3 and 7); during this phase, he was clinically unremarkable.

On 9th day, he developed an urticarial rash around the wound site initially, which gradually evolved over the next day into generalized, erythematous, pruritic, maculopapular, partially blanchable rash involving the upper trunk, abdomen, and bilateral upper and lower limbs with sparing the mucous membranes (Fig. 1). The next day he developed low-grade fever with soreness and irritation in throat associated with occasional dry cough, chest discomfort and nonspecific polyarthralgia. On examination, he was afebrile, blood pressure (130/90 mm Hg), pulse rate (94/minute), and respiratory rate (16/minute) were within normal limits. His oxygen saturation with pulse oximetry was recorded at 93% on room air. Rhonchi were heard over bilateral lung fields, and other systemic examinations were unremarkable. The wound was partially healed with the initiation of scab formation, linear in shape of approximately 1.5 cm. There was no pus discharge, swelling or local tenderness. A complete blood count showed mild leucocytosis. Renal and liver function tests were within normal limits. Markers for inflammation were raised (erythrocyte sedimentation rate 60 mm in 1st hour, C-reactive protein 169 mg/dl). Serum procalcitonin was normal (0.04 ng/dL). A fever workup was done to rule out common causes of such presentation. Urine routine, dengue dengue nonstructural protein 1 antigen, thick and thin peripheral smears for malaria, typhidot Ig M, IgM scrub typhus, and antinuclear antibody detection by Immunofluorescence were all negative. Serum complement levels were low [serum complement (C) 3: 645 mg/L, serum C4: 70 mg/L).

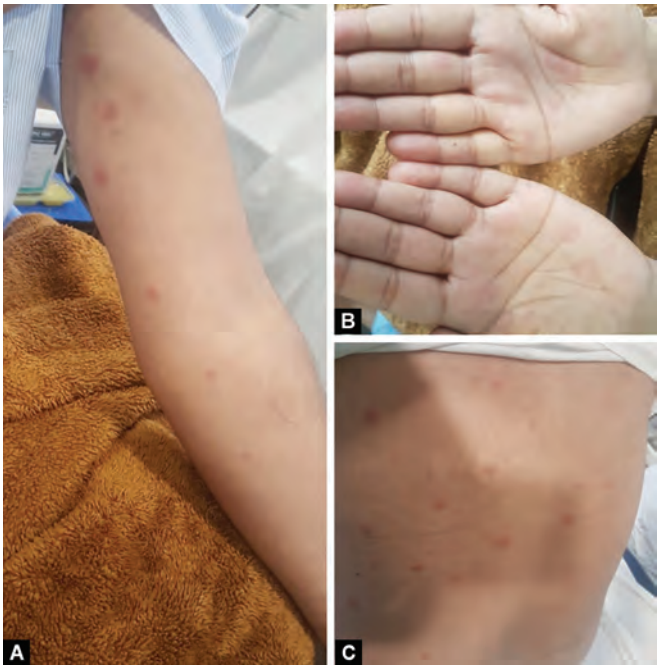
He was admitted, and antihistaminic, low-dose corticosteroids, along with supportive treatment, including nebulizations and minimal intermittent oxygen inhalation, were initiated. He showed dramatic improvement with the treatment over the course of the next 2 days. The rash was resolved without any ulcer or scar formation. He was later discharged in stable condition with advice for completion of anti-rabies vaccination as per the schedule.

Discussion

Serum sickness was initially described for diphtheria antitoxin by Von Pirquet as antigen-antibody complex, also known as toxic bodies formation triggered by exposure to a heterologous protein leading to a cascading immune reaction, which now categorized as delayed or type 3 hypersensitivity reaction.[3] The common clinical features are rashes, arthralgia, fever, malaise, headache, or gastrointestinal symptoms, in severe cases, may cause shock and death. In India, approximately 15 million people are bitten by animals, primarily dogs, every year and require postexposure prophylaxis, yet surprisingly, only 22.5% had good awareness regarding rabies prevention in a cross-sectional study conducted by Kapoor et al.[4] In developing countries like ours, ERIGs for the cornerstone of postexposure prophylaxis as its more cost-effective and affordable than human preparations. The incidence of serum sickness-like illness postadministration of equine preparations ranges from 0.87 to 6.19% due to varying concentrations of protein in the

[1]Post Graduate DNB Medicine Trainee; [2]Associate Consultant; [3]Vice-Chairperson, Senior Consultant, Department of Medicine, Sir Ganga Ram Hospital, Delhi, India; *Corresponding Author

How to cite this article: Shah M, Taneja V, Khosla P. Serum Sickness like Reaction Postequine Rabies Immunoglobulins. J Assoc Physicians India 2023;71(12):95–97.



Figs 1A to C: Upper limb forearm, back, and palm; showing widespread erythematous maculopapular rash

preparation and differences in the purification process.[5] It is, however, noteworthy that similar cases have been noted even with low protein (1 mg/dL) preparations.[6]

While the standard definition for serum sickness-like illness is yet to be established, and exact pathogenesis is not clearly understood, the diagnosis remains chiefly clinical. The temporal relation between the exposure of a suspected causative agent and the delayed reaction observed at 1–2 weeks beginning from the site of Ig administration with compatible clinical features is the classic history clincher that helps us to differentiate it from any acute hypersensitivity reaction as a response from concomitantly administered antibiotics or vaccine. The absence of reaction to subsequent doses of anti-rabies vaccination strongly implicates Igs to be the cause. In countries with a high burden of infectious disease, likely causes for such a presentation should be ruled out. Viral exanthems such as dengue, acute rheumatic fever, scarlet fever, scrub typhus and noninfectious causes such as systemic lupus erythematosus and cutaneous vasculitis can have similar presentation.

Complement levels are classically expected to be on the lower side, given the widely accepted underlying hypothesis for pathogenesis involving activation of the complement cascade. Lawley et al. demonstrated that C3 and C4 levels can decrease to 29–100% and 19–100% from the baseline values with nadir values at 10 days postadministration of the drug.[7] However, complement levels can vary depending on the timing of blood collection and the severity of the reaction. Similarly, in cases with predominant dermatological features, a skin biopsy may demonstrate leukocytoclastic vasculitis. However, they are nonspecific and do not help with identifying the causative agent or guide further management. Thus, at present, it is not recommended by World Health Organization (WHO).

In localities with high prevalences of dog bites, routine preexposure prophylaxis with anti-rabies vaccination should be carried out. In the case of category three wound in a previously unvaccinated person, Igs should be locally infiltrated as early as possible up to day 7 as beyond that, seroconversion from the first (day 0) vaccine is expected. Human preparations can be done whenever possible. Hypersensitivity reaction testing by intradermal inoculation prior to administrating the ERIG has poor predictability for anaphylactic or serum sickness-like reactions. At present, the WHO does not recommend it due to a lack of scientific background. Thus, a positive test should not preclude the patient from receiving ERIG, and it can be perhaps considered as a warning sign for possible adverse events; close monitoring should be done while keeping in mind that a negative test does not rule out anaphylaxis or serum sickness.

There is no consensus on standard management of serum sickness-like illness post ERIG at present. A cross-sectional study in 1548 patients demonstrated that serum sickness-like illness had an incidence of 3.1% with a median interval of presentation at the 7th-day post-ERIG administration and rash being the most common clinical feature. Only one case required steroids, while the rest showed improvement with antihistaminics alone.[8] Data available across literature shows that oral prednisone (0.5–1 mg/kg/day) or intravenous methylprednisone (1–2 mg/kg/day) shows dramatic resolution of symptoms even in severe cases. While there are concerns for decreased effectiveness of anti-rabies vaccination due to glucocorticoid administration (cumulative dose of prednisone 20 mg/day or more), the effect is unlikely to be clinically significant with a shorter course (<2 weeks). Therefore, while serum sickness-like illness can occur post-ERIG administration, it can be easily managed and should not be avoided when indicated as it is a lifesaving treatment.

Thus, despite all possible precautions that can be taken, close monitoring, a high index of suspicion and prompt management are required for acute as well as delayed manifestations of Igs, with timely reporting of adverse drug reactions monitoring centres. With regular preexposure and prompt postexposure prophylaxis goal of the "National Action Plan for Dog Mediated Rabies Elimination by 2030" can surely be achieved.

Conclusion

In cases with category three wounds from an unprovoked rabid animal, postexposure prophylaxis chiefly consists of local wound care, anti-rabies vaccinations and administration of Igs. This combination strategy offers nearly complete prophylaxis against developing fatal rabies. However, close monitoring is warranted for both acute and delayed manifestations of administrating Igs to offer prompt care and rehabilitation to the patients in case of any adverse event. The temporal correlation remains the most important clue to identify these cases, and it must be emphasized that dosing of anti-rabies vaccination should be completed as per schedule.

References

1. O'Brien KL, Nolan T, SAGE WG on Rabies. The WHO position on rabies immunization - 2018 updates. Vaccine 2019;37 (Suppl 1):A85–A87.
2. Satpathy D, Sahu T, Behera T. Equine rabies immunoglobulin: a study on its clinical safety. J Indian Med Assoc 2005;103(4):238, 241–242.
3. Von Pirquet C, Schick B. *Die Serumkrankheit*. Wien: Franz Deutike; 1905.
4. Kapoor P, Baig VN, Kacker S, et al. A cross-sectional study of knowledge regarding rabies among

attendees of anti-rabies clinic of a teaching hospital, Jaipur. J Family Med Prim Care 2019;8(1):194–198.
5. Wilde H, Chomchey P, Punyaratabandhu P, et al. Purified equine rabies immune globulin: a safe and affordable alternative to human rabies immune globulin. Bull World Health Organ 1989;67(6):731–736.
6. Khomvilai S, Daviratanasilpa S, Pornmuttakun D, et al. Production of equine rabies immune globulin of high purity, potency, and safety. In: Rupprecht C, Nagarajan T, editors. Current laboratory techniques in rabies diagnosis, research and prevention. San Diego, CA: Academic Press; 2015;2:293–303.
7. Lawley TJ, Bielory L, Gascon P, et al. A study of human serum sickness. J Invest Dermatol 1985;85 (1 Suppl):129s–132s.
8. Maharana S, Behera T, Pattanaik N. Serum sickness in patients receiving equine rabies immunoglobulin. J Commun Dis 2018;50(2):30–33.

Association of Physicians of India
Election Results of API, PRF and ICP

Results of the Election of the Association of Physicians of India (API), Physicians Research Foundation (PRF) and Indian College of Physicians (ICP) for 2024–2027

ASSOCIATION OF PHYSICIANS OF INDIA

President-Elect: Dr. Jyotirmoy Pal, Barrackpore - unopposed

Vice President: Dr. M.P.S. Chawla, New Delhi - unopposed

Governing Body Members (Six Posts)

1. Dr. Nihar Mehta, Mumbai
2. Dr. Aditya Prakash Misra, New Delhi
3. Dr. Nandini Chaterjee, Kolkata
4. Dr. Gautam Bhandari, Jodhpur
5. Dr. A. K. Gupta, Agra
6. Dr. L. Srinivasa Murthy, Bengaluru

PHYSICIANS RESEARCH FOUNDATION

Director-Elect: Dr. A. Muruganathan, Tirupur - unopposed

Board Members (Two posts)

1. Dr. Devendra Prasad Singh, Bhaghalpur
2. Dr. Puneet Rijhwani, Jaipur

INDIAN COLLEGE OF PHYSICIANS

Dean-Elect

Dr. Kamlesh Tewary, Muzaffarpur - unopposed

Vice Dean

Dr. Sanjeev Maheshwari, Ajmer - unopposed

Faculty Council Members (Four posts)

1. Dr. Munish Prabhakar, Gurugram
2. Dr. S. Sreenivasa Kamath, Kochi
3. Dr. E. Prabhu, Chennai
4. Dr. Sekhar Chakraborty, Siliguri

Dr. Milind Nadkar
Chairman – Election Committee

CASE REPORT

An Unusual Case of Recurrent Raised Intracranial Pressure Headache

Sivaroja Yellaturi[1*], Sowmini Perumal[2], Malcolm Jeyaraj[3], Sakthi Velayutham[4], Viveka Saravanan R[5], Mugundhan Krishnan[6]

Received: 27 December 2022; *Revised:* 20 April 2023; *Accepted:* 12 May 2023

Abstract

Introduction: Raised intracranial pressure (ICP) can be due to varied etiology. Differentiating among these various etiologies is crucial in making appropriate therapeutic decisions. A patient with a known past history of the primary or secondary headache of any etiology, when presenting with new onset severe headache, needs to be evaluated with imaging to rule out an alternative diagnosis.

Discussion: Here, we describe the case details of a young lady who presented with recurrent raised ICP headaches due to three different etiologies. At her third visit, isolated intracranial hypertension (IH) was the only manifestation of cerebral venous sinus thrombosis (CVST), which could have been missed if a repeat magnetic resonance imaging (MRI) brain and venogram were not done.

Conclusion: Our case highlights the importance of having a high degree of suspicion for CVST in the clinical setting of raised ICP headache in view of its crucial therapeutic implications.

Journal of the Association of Physicians of India (2023): 10.59556/japi.71.0371

Introduction

Raised intracranial pressure (ICP) can be due to various causes like intracranial mass lesions, disturbances in cerebrospinal fluid (CSF) circulation and ventricular system, obstruction of venous outflow like in cerebral venous sinus thrombosis (CVST), and diffuse cerebral edema due to meningeal pathology.[1] Idiopathic intracranial hypertension (IIH) is a diagnosis of exclusion after ruling out all other causes.[2] Differentiating among these various etiologies is crucial in making appropriate therapeutic decisions.

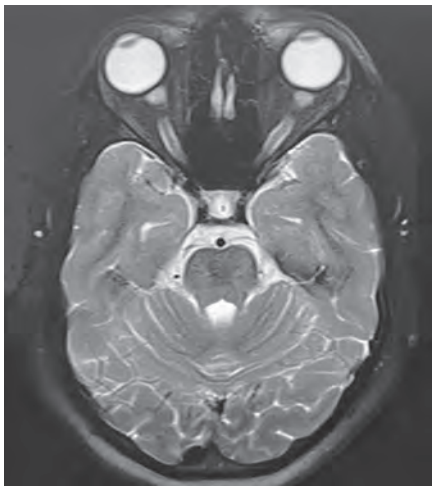


Fig. 1: Magnetic resonance imaging (MRI) brain axial T2 image showing tortuous optic nerves, prominent perioptic CSF spaces with flattening of the posterior globe

Case Description

A 25-year-old lady with a history of tuberculous meningitis 3 years back received antitubercular therapy (ATT) for 12 months and improved symptomatically. About 1 year and 6 months after the completion of ATT, the patient presented again with raised ICP headache and bilateral established papilloedema on examination without neck stiffness or other neurological deficits. Magnetic resonance imaging (MRI) of the brain showed tortuous optic nerves, prominent perioptic CSF spaces with flattening of the posterior globe (Fig. 1), and normal MR venogram (Fig. 2). Lumbar puncture showed elevated opening pressure of 79 cm of H_2O, normal CSF analysis, including CSF polymerase chain reaction for tuberculosis. A diagnosis of IIH was made and started on acetazolamide therapy. She improved within a month and discontinued therapy by herself.

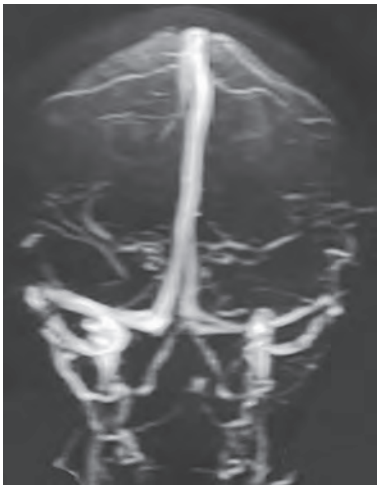


Fig. 2: Normal MR venogram

The patient was asymptomatic for the next 6 months when she presented again with raised ICP headache. She had bilateral established papilledema, and the rest of the examination was normal. MRI of the brain with venogram showed thrombosis in the superior sagittal sinus, right transverse sinus, and right sigmoid sinus (Figs 3 and 4). Bilateral perioptic spaces were widened with the flattening of the posterior sclera. Routine blood investigations, coagulation profile, and vasculitis profile were normal. The patient was started on anticoagulation therapy, improved clinically and is on regular follow-up.

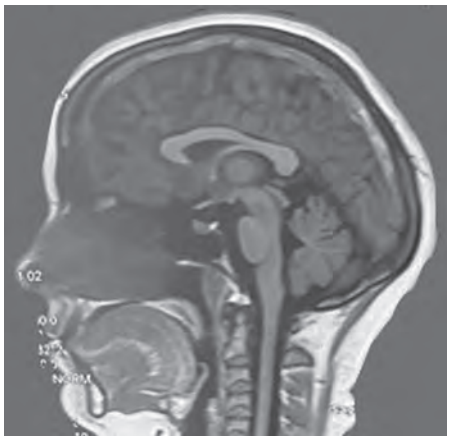


Fig. 3: Magnetic resonance imaging (MRI) brain sagittal image showing thrombosis of superior sagittal sinus

[1]Neurology Resident; [2–5]Assistant Professor of Neurology; [6]Professor and HOD of Neurology, Department of Neurology, Stanley Medical College (SMC), Chennai, Tamil Nadu, India; *Corresponding Author

How to cite this article: Yellaturi S, Perumal S, Jeyaraj M, *et al.* An Unusual Case of Recurrent Raised Intracranial Pressure Headache. J Assoc Physicians India 2023;71(12):98–99.

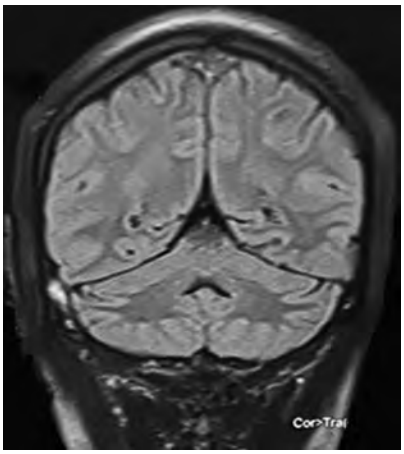


Fig. 4: Magnetic resonance imaging (MRI) brain coronal fluid-attenuated inversion recovery image showing thrombosis of right transverse sinus and sigmoid sinus

Discussion

This young lady presented with three different etiologies of raised ICP headache over a period of 3 years. At her third presentation, our initial consideration was incompletely treated IIH. She was taken up for a repeat MRI brain with a venogram, which surprisingly showed CVST. Isolated IH could be the only manifestation of CVST, which could have been missed in our patient if a repeat MRI brain and venogram had not been done. This case highlights the importance of having a high degree of suspicion for CVST in the clinical setting of raised ICP headaches in view of its crucial therapeutic implications. Any patient with a known history of primary or secondary headache of any etiology, when presenting with new onset severe headache, needs to be evaluated with imaging to rule out alternative diagnosis.

References

1. Dunn LT. Raised intracranial pressure. J Neurol Neurosurg Psychiatry 2002;73(Suppl 1):i23–i27.
2. Thurtell MJ, Wall M. Idiopathic intracranial hypertension (pseudotumor cerebri): recognition, treatment, and ongoing management. Curr Treat Options Neurol 2013;15(1):1–12.

CASE REPORT

Myokymia in a Patient with Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Pavan Kumar Reddy Pedda Gangula[1], Pramod Kumar Samarla[2], Malcolm Jeyaraj Krishnasamy[3], Sakthi Velayutham Saravanan[4], Sowmini Padmaja Raman[5], Kannan Vellaichamy[6], Viveka Saravanan Raju[7], Mugundhan Krishnan[8*]

Received: 24 December 2022; *Revised:* 19 August 2023; *Accepted:* 23 August 2023

Abstract

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired, immune-mediated neuropathy affecting peripheral nerves and nerve roots. It is characterized by symmetric weakness involving both proximal and distal muscles; it can be relapsing-remitting or progressive in course. The clinical manifestations of CIDP are various and may present with atypical features, like myokymia, tremor, or tremor-like phenomena, which may mislead the clinician in diagnosis.

Journal of the Association of Physicians of India (2023): 10.59556/japi.71.0408

Case Vignette

A 45-year-old man, an agricultural coolie, with no known comorbidities presented with complaints of symmetrical progressive muscle weakness of 4 months duration associated with flailness, initially started in the lower limbs, followed by the upper limbs, involving both proximal and distal muscles, and twitching of muscles mainly in the bilateral thigh and shoulder muscles and also numbness and tingling sensation of all four limbs, without any bowel or bladder symptoms.

On examination, vitals were stable. Neurological examination revealed ulnar clawing of both hands (Fig. 1) and hypotonia of all 4 limbs with wasting of the bilateral thenar, shoulder and thigh muscles, and distal power of two out of five and proximal power of four out of five in the upper limbs and four out of five in both the proximal and distal lower limbs. All reflexes were absent. We noticed undulating and rippling movements in bilateral thighs and shoulders suggestive of myokymia. Sensory examination revealed decreased touch, pain temperature in a nonlength-dependent pattern, diminished vibration sense, absent position sense, and Romberg's sign. Nerve conduction studies revealed demyelinating with secondary axonal changes in all four limbs. Electromyography (EMG) of the left vastus lateralis and deltoid showed spontaneous, repetitive continuous motor unit activity discharge in doublets, (Fig. 2), and occasionally triplets suggestive of myokymic discharges.[2] The firing frequency of these myokymic bursts ranged from 5 to 15 Hz, recurring regularly at 0.1–1 second intervals (Fig. 3). There was no spontaneous activity recorded in the distal muscles of the upper and lower limbs. The patient was started on treatment with intravenous methylprednisolone and showed a dramatic response within 5 days; myokymia disappeared clinically in 2 days after starting steroids; sensory symptoms and motor weakness improved; and we discharged the patient on oral steroids. He is on follow-up.

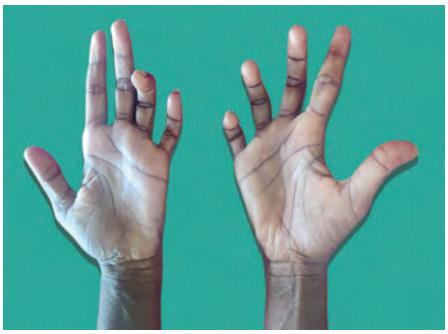


Fig. 1: Claw hand

Discussion

Myokymia is defined as the involuntary, spontaneous, persisting rippling movement of muscles or bundles within a muscle. Myokymia is seen in both peripheral nervous

[1,2]Resident; [3–5]Assistant Professor; [6,7]Associate Professor; [8]Professor and HOD, Department of Neurology, Stanley Medical College, Chennai, Tamil Nadu, India; *Corresponding Author

How to cite this article: Pedda Gangula PKR, Samarla PK, Krishnasamy MJ, *et al.* Myokymia in a Patient with Chronic Inflammatory Demyelinating Polyradiculoneuropathy. J Assoc Physicians India 2023;71(12):100–101.

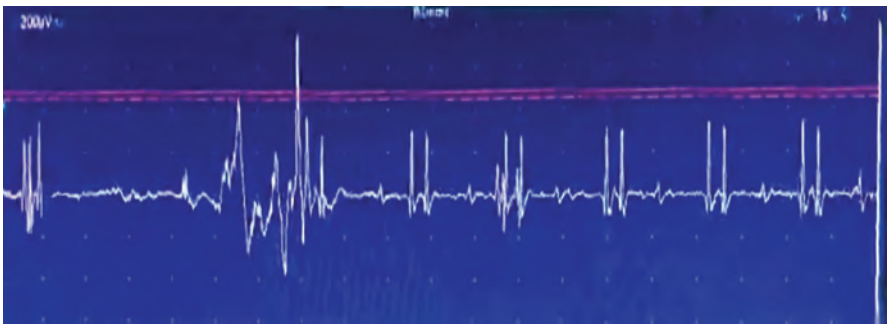


Fig. 2: Electromyography (EMG) of right deltoid showing continuous motor unit activity discharging in doublets

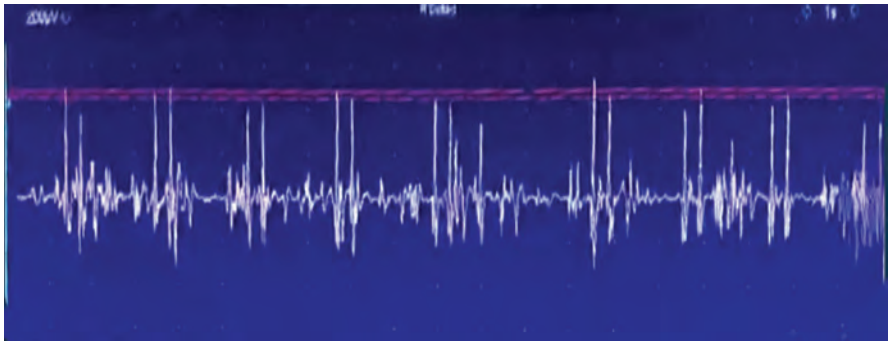


Fig. 3: Myokymia with firing frequency of 5–15 Hz and interfering interval of 0.1–1 seconds in right deltoid

system and central nervous system disorders. Myokymias are generated by a primarily axonal process or by segmental demyelination with secondary axonal dysfunction.[1] Even though myokymia is usually seen in peripheral nerve hyperexcitability syndromes, generalized myokymia has been seen in acute inflammatory neuropathies such as Guillain–Barre syndrome (GBS) or chronic inflammatory neuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP).

In electromyography, myokymic and neuromyotonic discharges may be seen in patients with peripheral nerve hyperexcitability. However, neuromyotonic discharges are specific for peripheral nerve hyperexcitability syndromes, whereas focal or generalized myokymic discharges are seen in many peripheral nerve disorders like radiation plexopathy, carpal tunnel syndrome, GBS, and CIDP.[2] In patients with acute inflammatory demyelinating polyneuropathy and CIDP, myokymia can be seen in either proximal or distal muscles at sites of focal demyelination, and the continuous motor activity in EMG at these sites of demyelination is due to ephaptic transmission.[3]

Conclusion

Atypical features like myokymia may be the presenting feature of CIDP, which makes the diagnosis difficult. We want to highlight the importance of recognizing the unusual and atypical presentation of inflammatory neuropathies, which is crucial for timely diagnosis and intervention.

References

1. Mansour M, Ouerdiene A, Riahi A, et al. An atypical form of chronic inflammatory demyelinating polyneuropathy presenting with initial isolated bulbar weakness. Curr J Neurol 2020;19(2):93–95.
2. Meriggioli MN, Sanders DB. Conduction block and continuous motor unit activity in chronic acquired demyelinating polyneuropathy. Muscle Nerve 1999;22(4):532–537.
3. Chhibber S, Greenberg SA. Teaching video neuroimages: widespread clinical myokymia in chronic inflammatory demyelinating polyradiculoneuropath. Neurology 2011;77(5):e33.

Milstein and Kohler: Monoclonal Antibodies

J V Pai-Dhungat

Cesar Milstein Nobel Prize Medicine 1984; Argentina, 2005

César Milstein (1927–2002) was born in Bahía Blanca, Argentina. He was a chemistry student educated at the University of Buenos Aires, obtaining his degree in biochemistry in 1952. He completed his PhD in 1957 at the same University and also received the British Council research scholarship to the biochemistry department at the University of Cambridge. Under the direction of the distinguished biochemist Frederick Sanger, Milstein completed a second dissertation, a study of the enzyme, earning his PhD in 1960 and joining the scientific staff of the Medical Research Council (MRC). He then worked at the National Institute of Microbiology in Buenos Aires from 1961 to 1963 until political turmoil led him to resign and return to Cambridge to work with Sanger at the newly formed MRC Laboratory of Molecular Biology. Now, he shifted his focus from enzymes to antibodies. By the early 1970s, he was an internationally recognized leader in the field and was able to attract talented, young researchers, including Georges Köhler, to the MRC. In 1983, Milstein was named head of the Protein and Nucleic Acid Chemistry Division of the MRC, a position he held until his retirement in 1995. He died in Cambridge, England, in 2002 at the age of 74.

George Kohler (1946–1995) was a German biologist born in Munich. He started a postdoctoral research fellowship at the Laboratory in Cambridge, United Kingdom, where he began working with César Milstein to develop a laboratory tool that could help them investigate the diversity of antibodies. They devised their *hybridoma* technique for the production of antibodies. Köhler continued his collaboration on the technique and joined the Basel Institute of Immunology in 1974. Köhler remained at the Basel Institute for another 9 years. In 1986, Köhler became the director of the Max Planck Institute of Immunobiology, where he worked until his death in 1995, aged 48. He died in Freiburg in Breslau as the consequence of a heart condition.

George Kohler Nobel Prize; Medicine 1984 Grenada, 1995

Sir Macfarlane Burnet Nobel Prize; Medicine for Immunology, 1960; Dominica, 1995

Milstein and Köhler overcame difficulty of growing antibody-producing B cells in culture by fusing spleen cells derived from mice immunized with a specific antigen to immortalize myeloma cells, a technique that enabled production of antigen-specific antibody in culture indefinitely. Their innovative *hybridoma* technique became a cornerstone of immunology and molecular biology research. After mastering how to produce specific antibodies reliably and efficiently in culture, Milstein turned his attention to fostering the use of monoclonal antibodies as a fundamental research tool. The ability to make monoclonal antibodies at will in the test tube and in unlimited quantities to any sort of antigen—whether an interesting chemical, infectious microorganism, cancer, or normal cells—opened numerous new and unforeseen avenues for research; many are used as treatment modalities in clinical medicine today.

Niel K Jerne (1911–1994), a Danish immunological theorist, proposed the first selection theory of antibody formation in 1955, which was expanded by Sir Macfarlane Burnet.

The 1984 Nobel Prize in Physiology or Medicine was awarded jointly to César Milstein, Georges Köhler, and Niel Jerne. "*For theories concerning the specificity in development and control of the immune system and the discovery of principle for production of monoclonal antibodies*."

Milstein and Köhler won the prize for developing the hybridoma method of producing monoclonal antibodies.

Professor of Medicine (Retd), Department of Medicine, Topiwala National Medical College and Bai Yamunabai Laxman Nair Charitable Hospital; Honorable Physician, Bhatia Hospital, Mumbai, Maharashtra, India

How to cite this article: Pai-Dhungat JV. Milstein and Kohler: Monoclonal Antibodies. J Assoc Physicians India 2023;71(12):102–102.

The Deadly Duo of Hypertension and Diabetes in India: Further Affirmation from a New Epidemiological Study

Shailendra Kumar Singh[1], Rina Singh[2], Pradeep Kumar Rai[3], Abhishek Kumar Singh[4]

[1]Endocrinologist, Department of Endocrinology; [2]Pediatrician, Department of Pediatrics, Endocrine Clinic; [3]Nephrologist, Department of Nephrology, Opal Hospital; [4]Senior Physician, Central Jail Hospital, Varanasi, Uttar Pradesh, India

Sir,

We read with great interest the article "the deadly duo of hypertension and diabetes in India: further affirmation from a new epidemiological study" by Metri et al.[1] They rightly pointed out that the prevalence of hypertension in Indian patients with type 2 diabetes patients is high and therefore early screening and management of hypertension should be included in the treatment of patients with type 2 diabetes. We wish to share our study findings on the prevalence of hypertension in newly onset diabetes mellitus (DM). We find that the prevalence of hypertension in all males and females with DM was 44.59, 44.34, and 45.16%, respectively.[2] This is similar to what was observed by Metri et al. in their study. In our study, the prevalence of hypertension was numerically higher in females than in males.[2,3] But, in a study by Metri et al. males were more hypertensive than females. All know that the prevalence of hypertension in the general population is higher in males than females but in newly onset DM opposite is true. This is because adult female develops DM at a higher body mass index (BMI) than male.[3] In our study, BMI and prevalence of central obesity were higher in females as compared to males.[3] That's why females have a higher risk of cardiovascular disease than males in DM. We also find that serum uric acid is independently associated with hypertension in newly onset DM.[2] We further propose that in a hypertensive diabetic patient routine measurement of serum uric acid is essential as it is closely and independently associated with it.

References

1. Metri KG, Raghuram N, S Ram CV, et al. The deadly duo of hypertension and diabetes in India: further affirmation from a new epidemiological study. J Assoc Physicians India 2022;70(7):14–17.
2. Singh SK, Singh R, Singh SK, et al. Prevalence of hyperuricemia and the relationship between serum uric acid and hypertension in new onset diabetic patients: a cross-sectional Indian study. Diabetes Metab Syndr Obes 2022;15:1809–1817.
3. Singh SK, Singh R, Singh SK. Gender difference in cardiometabolic risk factor in newly onset type 2 diabetes mellitus: a cross sectional study. J Assoc Physicians India 2022;70(1):11–12.

Etiology and Clinical Profile of Patients with a Tree-in-bud Appearance on High-resolution Computed Tomogram of the Thorax

Vyshak Uddur Surendra[1], Ann Roy Febi[2], Mohan K Manu[3], Aswini Kumar Mohapatra[4], Koteshwara Prakashini[5], Vishnu Prasad Shenoy[6], Kiran Chawla[7]

[1]Assistant Professor; [2]Senior Resident; [3,4]Professor, Department of Respiratory Medicine; [5]Professor, Department of Radiodiagnosis; [6]Associate Professor; [7]Professor, Department of Microbiology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Udupi, Karnataka, India

Sir,

The tree-in-bud (TIB) opacities are small, clustered, branching, and nodular opacities that resemble a budding tree which we frequently find on thoracic computed tomogram (CT). It represents mucus impaction in terminal airways with adjacent peribronchiolar inflammation. The tree portion represents the intralobular inflamed bronchiole, and the bud portion represents alveolar ducts filled with inflammatory exudates.[1] Initially, the reports equated TIB to the endobronchial spread of *Mycobacterium tuberculosis (*MTB). Currently, the pattern is recognized as a cause of diverse pathologies. It can be CT manifestation of endobronchial spread of various infections (bacterial, fungal, viral, or parasitic), allergic bronchopulmonary aspergillosis, congenital airway disorders like ciliary dyskinesia or cystic fibrosis, idiopathic disorders (obliterative bronchiolitis, panbronchiolitis), aspiration or inhalation of foreign substances, immunologic disorders, connective tissue disorders and peripheral pulmonary vascular diseases such as pulmonary tumor emboli.[2] Though it is most commonly caused by MTB, the frequency of various other etiologies of TIB opacities is not entirely known in our setting. We aimed to identify the frequency of multiple causes of TIB opacities through a prospective observational study.

We studied 44 patients above 18 years old who had TIB opacities on thoracic CT and underwent bronchoscopy. Our study was approved by the Institutional Ethics Committee. We excluded four patients due to lack of consent and six due to incomplete data. Thus, finally, we analyzed 34 patients, of which 21 (61.76%) were male. The males were aged 51.3 ± 16.8 and the females 53.9 ± 18.8. Four of the subjects (11.8%) had pulmonary tuberculosis in the past. Diabetes mellitus was present in nine subjects (26.5%), and one patient (2.9%) tested positive for human immunodeficiency virus. The aerobic culture of sputum was done in 29 patients, of which 22 (64.7%) yielded normal oropharyngeal flora, two samples grew *Streptococcus pneumoniae* (5.9%), and one each grew *Klebsiella pneumoniae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa* (2.9%). Cultures of two sputum samples yielded two organisms (*Moraxella catarrhalis* and *Haemophilus influenzae*, *Klebsiella pneumoniae* and *Escherichia coli*).

Ziehl–Neelsen staining of bronchial washing was positive in three (8.8%) patients. MTB was detected by culture in five (14.7%) cases. Xpert MTB/RIF using cartridge-based nucleic acid amplification test was performed in 32 bronchial washing samples, of which six (18.8%) had MTB. No rifampicin resistance was identified in the above samples. The aerobic culture of bronchial washing showed no growth in 22 patients (64.7%), *Streptococcus pneumoniae* in four (11.8%), *Klebsiella pneumoniae* in three (8.8%), and *Pseudomonas aeruginosa* in two (5.9%) cases. Growth of *Escherichia coli*, *Haemophilus parahaemolyticus*, and Methicillin-resistant *Staphylococcus aureus* was identified in one patient each (2.9%). The fungal culture of bronchial washing ($n = 28$) showed no growth in the majority ($n = 27$, 79.4%). Only one patient's sample grew *Aspergillus fumigatus*.

Bacterial infections were the most common cause of TIB opacities in our study. MTB was our study's most common single infectious agent causing TIB appearance. In contrast to this finding, a retrospective study conducted in the United States of America by Miller and Panosian showed that nontubercular *Mycobacterium*, *Mycobacterium avium* complex was the most common infectious cause of TIB opacities.[3] The low incidence of MTB may explain this in the USA compared to India, which is one among the eight countries that accounted for two-thirds of global TB incidence in 2021.[4] The TIB opacities in tuberculosis are due to caseation necrosis and granulomatous inflammation within and surrounding the terminal bronchioles, respiratory bronchioles, and alveolar ducts. TIB opacities usually disappear after 5 months of antituberculous treatment.[5]

In our study, only one patient had *Aspergillus fumigatus* in the culture of

bronchoalveolar lavage fluid. The sample size was smaller, and the number of immunocompromised individuals in our study was minimal; this could explain the lower incidence of fungal infection in the study. Viral polymerase chain reaction was not done in our study patients, even though the incidence of TIB due to viral infection ranges about 3% as per literature.[1] Influenza virus, *Cytomegalovirus*, and respiratory syncytial virus in children are known to cause TIB.[3,5]

Primary ciliary dyskinesia and cystic fibrosis cause repeated airway infection and inflammation leading to TIB opacities. Other uncommon causes for such opacities include chronic rejection in lung transplants, graft-versus-host disease in bone marrow transplants, or cryptogenic organizing pneumonia.[3] We have yet to come across any such patients in our study, which may be attributed to the smaller sample size.

All patients underwent bronchoscopy. Hence, the respiratory samples collected were of better quality, which was the strength of our study. Only 20 patients had a definitive diagnosis, and no further investigations were done on the rest, which was a limitation. The study was conducted in a hospital setting, so the findings cannot be generalized.

To conclude, TIB opacities can be due to infectious and noninfectious causes. Our study found that diverse bacterial infections were causing TIB proving that all TIBs are not pulmonary tuberculosis. Hence, a thorough investigation of every patient with TIB is essential to reach a definitive diagnosis.

References

1. Im JG, Itoh H. Tree-in-bud pattern of pulmonary tuberculosis on thin-section ct: pathological implications. Korean J Radiol 2018;19(5):859–865.
2. Bhalla N, Chang CF, Lee C. Special considerations for tree-in-bud nodules. Ann Am Thorac Soc 2019;16(5):636–638.
3. Miller WT Jr, Panosian JS. Causes and imaging patterns of tree-in-bud opacities. Chest 2013;144(6): 1883–1892.
4. World Health Organization. Global tuberculosis report 2021. World Health Organization; 2021 Licence: CC BY-NC-SA 3.0 IGO.
5. Gosset N, Bankier AA, Eisenberg RL. Tree-in-bud pattern. AJR Am J Roentgenol 2009;193(6): W472–W477.

RNI NO. 11552/57
Postal Reg. No. MCW/80/2021-2023
MR/TECH/WPP-248/WEST/2021-23 licensed to post without prepayment
Posted at Mumbai Patrika Channel Sorting Office, Mumbai 400 001 on 1st and 2nd of every month

IF UNDELIVERED PLEASE RETURN TO
Office: Turf Estate, Unit No. 006/007, Opp. Shakti Mill Compound, Off Dr. E. Moses Road, Near Mahalaxmi Station (W), Mumbai 400 011. • Tel.: 91-22-6666 3224