Journal of The Association of Physicians of India

VOL NO. 73 | ISSUE NO. 8 | AUGUST 2025 | ISSN : 0004 - 5772

WITH SUPPLEMENT 36 PAGES

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 (2025–2026)

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 (2025–2026)

President-Elect
G Narsimulu (Hyderabad) (2026)

President
Jyotirmoy Pal (Barrackpur) (2026)

Past President
Milind Nadkar (Mumbai) (2026)

Vice Presidents

NP Singh (New Delhi) (2026)

MPS Chawla (New Delhi) (2027)

Puneet Saxena (Jaipur) (2028)

Hon. General Secretary
Agam C Vora (Mumbai) (2028)

Jt. Secretary (HQ)
Rakesh Bhadade (Mumbai) (2028)

Hon. Treasurer
Amit Saraf (Mumbai) (2026)

Members

Naval Chandra (Hyderabad)	(2026)	**Nihar Mehta** (Mumbai)	(2027)	**Soumitra Ghosh** (Kolkata)	(2028)
SS Dariya (Jaipur)	(2026)	**Aditya Prakash Misra** (New Delhi)	(2027)	**Pradeep Bhaumik** (Agartala)	(2028)
DG Jain (New Delhi)	(2026)	**Nandini Chatterjee** (Kolkata)	(2027)	**Sangram S Biradar** (Gulbarga)	(2028)
Udas Ghosh (Kolkata)	(2026)	**Gautam Bhandari** (Jodhpur)	(2027)	**Anupam Prakash** (New Delhi)	(2028)
R Chandni (Kozhikode)	(2026)	**AK Gupta** (Agra)	(2027)	**M Pavan Kumar** (Warangal)	(2028)
BK Singh (Aurangabad)	(2026)	**L Srinivasa Murthy** (Bengaluru)	(2027)	**Pramod Kumar Sinha** (Gaya)	(2028)

Zonal Members

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

Invited Members

Editor-in-Chief, API Textbook
KK Pareek (Kota)

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

Chairman, API House Committee
Shashank Joshi (Mumbai)

Ex-Officio Members

Dean, ICP
Kamlesh Tewary (Muzaffarpur)

Director, PRF
A Muruganathan (Tirupur)

Co-opted Members

Jt. Secretary (President's Place)
Saikat Dutta (Darjeeling)

Armed Forces Medical Services
Vivek Hande (Mumbai)

Organizing Secretary, APICON 2026 (Patna)
Kamlesh Tewary (Muzaffarpur)

Organizing Secretary, APICON 2025 (Kolkata)
Sekhar Chakraborty (Siliguri)

Indian College of Physicians

FACULTY COUNCIL (2025–2026)

Chairman
Jyotirmoy Pal (Barrackpur) (2026)

Dean
Kamlesh Tewary (Muzaffarpur) (2026)

Dean-Elect
Girish Mathur (Kota) (2026)

Vice Deans
Jayanta Kumar Panda (Cuttack) (2026)
Sanjeev Maheshwari (Ajmer) (2027)
V Palaniappen (Dindigul, TN) (2028)

Hon. Gen. Secretary
Agam C Vora (Mumbai) (2028)

Past Dean
RK Singal (New Delhi) (2026)

Jt. Secretary (HQ)
Rakesh Bhadade (Mumbai) (2028)

Jt. Secretary (Dean's Place)
Sanjay Kumar (Patna) (2026)

Hon. Treasurer
Amit Saraf (Mumbai) (2026)

Elected Members

Prakash Keswani (Jaipur)	(2026)	**Munish Prabhakar** (Gurugram)	(2027)	**Sandeep Garg** (New Delhi)	(2028)
S Chandrasekar (Chennai)	(2026)	**S Sreenivasa Kamath** (Kochi)	(2027)	**Hem Shankar Sharma** (Bhagalpur)	(2028)
NK Soni (Greater Noida)	(2026)	**E Prabhu** (Chennai)	(2027)	**Ashis Kumar Saha** (Kolkata)	(2028)
Devi Ram (Purnia)	(2026)	**Sekhar Chakraborty** (Siliguri)	(2027)	**Suresh V Sagarad** (Raichur)	(2028)

Ex-Officio Members

President-Elect
G Narsimulu (Hyderabad)

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

Director, PRF
A Muruganathan (Tirupur)

Editor-in-Chief, API Textbook
KK Pareek (Kota)

Physicians Research Foundation

BOARD OF DIRECTORS (2025–2026)

Chairman
Jyotirmoy Pal (Barrackpur) (2026)

Director
A Muruganathan (Tirupur) (2027)

Past Director
GS Wander (Ludhiana) (2026)

Hon. General Secretary
Agam C Vora (Mumbai) (2028)

Jt. Secretary (Director's Place)
R Rajasekaran (Kumbakonam) (2027)

Hon. Treasurer
Amit Saraf (Mumbai) (2026)

Members

Prabhat Pandey (Durg)	(2026)	**Devendra Prasad Singh** (Bhagalpur)	(2027)	**Sudhir Mehta** (Jaipur)	(2028)
Liyakhat Ali Gouri (Jaipur)	(2026)	**Puneet Rijhwani** (Jaipur)	(2027)	**Ghanshyam Pangtey** (New Delhi)	(2028)

Invited Members

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

Dean, ICP
Kamlesh Tewary (Muzaffarpur)

Editor-in-Chief, API Textbook
KK Pareek (Kota)

EDITORIAL

"Responsible Use of Artificial Intelligence in Clinical Medicine" or "Ethical Integration of Artificial Intelligence in India's Healthcare System": A Framework for Responsible Innovation

Shriram V Kulkarni[1*], Alok Modi[2]

The rapid evolution of artificial intelligence (AI) has ushered in transformative changes in healthcare systems globally, and India stands at the threshold of leveraging this technology to address longstanding disparities in access, efficiency, and quality of care. While the potential of AI is undeniable, its integration into healthcare must be guided by a strong ethical framework that ensures equity, accountability, and trust. In this context, the synthesized framework for ethical AI integration in India's healthcare system presents a comprehensive and timely guide that aligns with both global standards and India's unique demographic and infrastructural realities.

Data Privacy and Security

India's healthcare data infrastructure remains fragmented, with digitization uneven across regions and facilities. Paper-based records, duplicate patient identifiers, and unstandardized formats continue to pose serious risks to patient confidentiality. The Digital Personal Data Protection Act (2023) lays foundational principles, but implementation gaps persist. To mitigate these risks, the framework calls for robust anonymization of training datasets, secure encryption protocols during data transmission and storage, and stringent enforcement of privacy regulations. These safeguards are essential as AI models increasingly rely on large-scale data to train algorithms, particularly in the development of clinical decision support systems.[1,2]

Algorithmic Bias and Equity

Artificial intelligence algorithms trained predominantly on urban-centric datasets risk perpetuating or even exacerbating healthcare disparities. The heterogeneity of India's population—with its wide variations in disease prevalence, sociocultural determinants, and healthcare access—necessitates inclusive, representative datasets. For instance, a diabetes risk prediction tool calibrated only on urban, well-nourished individuals may fail to detect atypical presentations in undernourished rural populations. Regular bias audits using frameworks such as IBM's AI Fairness 360 and investment in rural data acquisition are imperative to prevent algorithmic inequities.[3,4]

Transparency and Explainability

The so-called "black box" nature of advanced AI models like deep learning has created skepticism among clinicians. Lack of interpretability hinders clinical adoption and undermines patient trust. Explainable AI (XAI) techniques such as LIME (Local Interpretable Model-agnostic Explanations) and SHAP (SHapley Additive exPlanations) offer transparency by elucidating the rationale behind algorithmic predictions. The framework further emphasizes the need to communicate these insights in patient-friendly formats and local languages, fostering shared decision-making between patients and healthcare providers. As demonstrated in contemporary literature, explainability remains a prerequisite for responsible AI deployment in clinical practice.[2]

Accountability and Regulation

A significant ethical conundrum lies in determining liability for AI-generated medical errors, particularly in underserved regions where overburdened health workers may follow AI-generated recommendations without critical evaluation. The proposed framework recommends establishing a centralized regulatory body modeled after the EU's AI Act and WHO's global guidelines. This entity would audit algorithmic performance, mandate transparency reports, and adjudicate grievances, thereby fostering a culture of responsible innovation and redressal.[4,5]

Equity and Accessibility

The digital divide remains a formidable barrier to equitable AI deployment. Despite mobile penetration, only 34% of rural India has reliable internet access. Consequently, even the most advanced AI solutions risk becoming tools of exclusion if not designed for accessibility. The framework encourages the development of low-cost, low-bandwidth AI solutions, and endorses public–private partnerships, such as Niramai's affordable cancer screening tools and Tata Elxsi's tribal telemedicine models. These exemplify frugal innovation aligned with the principles of universal health coverage.[2,4]

Human–AI Collaboration

Artificial intelligence is not a replacement for clinical judgment but a complement to it. Institutions such as Apollo Hospitals already integrate AI in preliminary radiologic triaging, with final decisions resting with trained specialists. The framework rightly promotes AI literacy among healthcare professionals through structured training programs, enabling them to critically appraise AI outputs and retain clinical autonomy. Empowering frontline health workers, particularly in primary and secondary care settings, will be pivotal to successful integration.[3]

Multistakeholder Partnerships

Ethical AI development requires co-creation across disciplines. Initiatives like Elsevier's Responsible AI Advisory Board and the Global

[1]HOD Medcine Department, MGM Medical College, Panvel, Navi Mumbai; [2]Senior Consultant Physician and Diabetologist, Department of Diabetology, Kaiwalya Hospital and Jupiter Hospital, Thane, Maharashtra, India; [*]Corresponding Author

How to cite this article: Kulkarni SV, Modi A. "Responsible Use of Artificial Intelligence in Clinical Medicine" or "Ethical Integration of Artificial Intelligence in India's Healthcare System": A Framework for Responsible Innovation. J Assoc Physicians India 2025;73(8):11–12.

Digital Health Partnership exemplify such collaborative governance. The framework urges the creation of platforms that bring together technologists, ethicists, clinicians, patients, and policymakers to shape AI applications that are contextually relevant and ethically sound.[4,5]

Policy Recommendations for 2025

To operationalize this vision, the framework recommends:

1. Pilot explainable AI tools in 10 rural districts to evaluate performance, acceptance, and clinician trust.
2. Launch a National Health Data Repository of anonymized, standardized records to enable inclusive algorithm training.
3. Mandate AI-specific healthcare regulations, including algorithmic audits, transparency disclosures, and independent oversight.
4. Allocate 15% of Ayushman Bharat Funds to develop AI infrastructure in underserved regions.

As AI technologies continue to advance, India's healthcare system has a unique opportunity to leapfrog traditional barriers through ethically grounded, socially inclusive innovation. This framework provides a pragmatic roadmap for doing so—prioritizing privacy, equity, and trust while embracing the transformative potential of AI. It is not merely a technical blueprint but a moral imperative to ensure that no patient is left behind in the digital age.

References

1. Johnson D, Goodman R, Patrinely J, et al. Assessing the accuracy and reliability of AI-generated medical responses: an evaluation of the Chat-GPT model. Res Sq 2023:rs.3.rs-2566942.
2. Wójcik S, Rulkiewicz A, Pruszczyk P, et al. Beyond ChatGPT: what does GPT-4 add to healthcare? The dawn of a new era. Cardiol J 2023;30(6):1018–1025.
3. Javaid M, Haleem A, Singh RP. ChatGPT for healthcare services: an emerging stage for an innovative perspective. BenchCouncil Trans Benchmarks Stand Eval 2023;3(1):100105.
4. Kharat PB, Dash KS, Rajpurohit L, et al. Revolutionizing healthcare through Chat GPT: AI is accelerating medical diagnosis. Oral Oncol Rep 2024;9:100222.
5. Tustumi F, Andreollo NA, Aguilar-Nascimento JE. Role of ChatGPT in healthcare. Arq Bras Cir Dig 2023;36:e1727.

OBITUARY

Dr RB Pandit (1938–2025)

It is with profound sadness we announce the passing of Dr RB Pandit, a revered physician, dedicated mentor, Past President of Association of Physicians of India (API) and beloved figure in the medical community, who left us for a divine abode on July 11, 2025, at the age of 87.

Born on January 1, 1938, Dr Pandit embarked on a remarkable medical journey that spanned over five decades. He received his MBBS from the Government Medical College and Hospital, Nagpur, in 1961, and further specialized, earning his MD in General Medicine from Grant Medical College and Sir JJ Hospital, Mumbai, in 1967.

He began his distinguished career in 1965 at the Railway Hospital, where he served with unwavering commitment until his retirement in 1996. Following his retirement from the Railway Hospital, he continued to serve the community tirelessly, practicing Internal Medicine at Lions Hospital in Kopar Khairane, Navi Mumbai, for many years, touching countless lives with his expertise and compassionate care.

A highly respected member of the Maharashtra Medical Council, he was a prominent and influential voice in the medical fraternity. He served as the President of the Association of Physicians of India (API) in 1996, a testament to his leadership and standing among his peers. He remained a very active member of API throughout his life and was also a proud Fellow of the Indian College of Physicians (ICP). His dedication to the advancement of medicine was further exemplified by his role as a founder member of the API House.

He will be remembered not only for his exceptional diagnostic skills and extensive medical knowledge but also for his genuine empathy, kindness, and unwavering commitment to his patients' well-being. He leaves behind a legacy of selfless service and inspiration to generations of medical professionals.

He will be deeply missed by his family, friends, colleagues, and the countless patients whose lives he positively impacted. May his soul rest in peace.

Prof Dr Shashank R Joshi
Prof Dr Mangesh Tiwaskar

ORIGINAL ARTICLE

Use of Ambulatory Glucose Profile in Monitoring and Improved Control of Gestational Diabetes Mellitus When Compared to Self-monitoring of Blood Glucose

Mohammad Sabah Siddiqui[1], Superior Kawale[2], Rohini Rokkam[3*], Sarita Agrawal[4], Amritava Ghosh[5]

Received: 25 September 2024; *Accepted:* 25 April 2025

Abstract

Introduction: Gestational diabetes mellitus (GDM) is hyperglycemia diagnosed for the first time during the second or third trimester of pregnancy. It often leads to neonatal complications. Effective management of GDM is crucial to mitigate such risks. This study evaluates the effectiveness of ambulatory glucose profile (AGP) vs self-monitoring of blood glucose (SMBG) in managing GDM.

Methods: This 18-month observational study was conducted at All India Institute of Medical Sciences, Raipur, India, involving 65 pregnant women diagnosed with GDM. Thirty-two patients wore the flash glucose monitoring system (AGP group) and 33 performed SMBG (SMBG group). Blood glucose levels were monitored using AGP and SMBG, with data collected on fasting, postprandial glucose levels, and hypoglycemic events till 15 days after enrollment. Statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) version 21.

Results: The AGP group showed significant reductions in blood glucose levels across all measured times. Mean blood glucose concentrations decreased significantly in both groups from enrollment till 15 days, with no significant intergroup differences. The AGP group had a higher mean time in range (92 vs 90%) and lower time above range (4 vs 6%) compared to the SMBG group. Hypoglycemic events were fewer in the AGP group.

Conclusion: AGP demonstrated superior effectiveness in managing GDM by providing continuous glucose monitoring, improving glycemic control, and reducing hypoglycemic events compared to SMBG. AGP is recommended for better glucose management in GDM patients.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1064

Introduction

Gestational diabetes mellitus (GDM) is caused by glucose intolerance with onset or first recognition during pregnancy.[1] This metabolic disorder typically arises in the second or third trimester when the insulin requirements of the body increase significantly. The prevalence of GDM is widely influenced by genetic, demographic, and lifestyle factors. Globally, >14% of pregnancies are complicated by GDM.[2] However, this prevalence can be higher in certain populations, such as those with a higher incidence of type 2 diabetes mellitus (T2DM). For example, studies have shown that women of South Asian, African, and Hispanic descent are at a higher risk compared to Caucasian women.[3] In India, GDM has a high prevalence of 16.55%.[4] Additionally, factors such as obesity, advanced maternal age, and a family history of diabetes also contribute to the increased likelihood of developing GDM.[5]

Gestational diabetes mellitus often leads to several neonatal complications. Macrosomia arises from maternal hyperglycemia, leading to fetal hyperinsulinemia, thereby accelerating somatic growth.[6] This excessive fetal growth is associated with increased risks of birth injuries, such as shoulder dystocia, brachial plexus injury, and clavicular fractures. Moreover, infants of mothers with GDM are predisposed to preterm delivery, with resultant complications from immature organ systems, most notably the respiratory system. The heightened risk of respiratory distress syndrome in these neonates is attributed to the delayed production of surfactant, a crucial component for pulmonary function.[7] Postnatally, the sequelae of maternal hyperglycemia manifest as neonatal hypoglycemia, due to persistent hyperinsulinemia, posing risks for seizures and neurological impairments if not promptly managed.[8] These neonates also exhibit an elevated incidence of jaundice secondary to hyperbilirubinemia, and polycythemia, which can lead to hyperviscosity syndrome. Electrolyte disturbances, particularly hypocalcemia and hypomagnesemia, are additional concerns, potentially precipitating neuromuscular irritability and convulsions. Long-term health consequences for infants include an increased risk of obesity and metabolic syndrome, such as T2DM and cardiovascular diseases, later in life.[9] The intrauterine environment and genetic predisposition contribute to these risks.

Effective management of GDM is essential in mitigating these adverse outcomes. Therapeutic strategies include meticulous glycemic control through dietary modifications, physical activity, and pharmacotherapy, including insulin administration when necessary.[10] Intensive treatment is crucial; however, overly stringent glycemic control in GDM can lead to hypoglycemia in up to 71% of cases.[11] While self-monitoring of blood glucose (SMBG) can help manage blood glucose levels, it often misses postprandial (PP) hyperglycemia and hypoglycemia due to the lack of 24-hour monitoring.[12] The National Institute for Health and Care Excellence (NICE) recommends testing blood sugar levels four to eight times daily, a challenging frequency to maintain.[13] Continuous glucose monitoring (CGM) systems offer a more comprehensive glucose profile without the discomfort of frequent finger pricks.[12] One of the most substantial benefits of CGM is its ability to provide real-time glucose monitoring. Unlike SMBG, which only provides snapshot readings at specific times, CGM offers a comprehensive view of glucose trends and fluctuations throughout the day and night. This continuous monitoring helps users understand how different factors such as food, exercise, and insulin affect their glucose levels, allowing for more precise adjustments in therapy. CGM systems also come with alerts and alarms that notify users of high or low glucose levels.[14] These real-time alerts enable timely interventions to prevent hyperglycemia or hypoglycemia,

[1]Additional Professor; [2]Resident; [3]Assistant Professor, Department of General Medicine; [4]Professor, Department of Obstetrics and Gynecology; [5]Associate Professor, Department of Endocrinology, All India Institute of Medical Sciences, Raipur, Chhattisgarh, India; [*]Corresponding Author

How to cite this article: Siddiqui MS, Kawale S, Rokkam R, *et al.* Use of Ambulatory Glucose Profile in Monitoring and Improved Control of Gestational Diabetes Mellitus When Compared to Self-Monitoring of Blood Glucose. J Assoc Physicians India 2025;73(8):15–20.

which is particularly beneficial during sleep or activities when frequent testing is not feasible. Studies have shown that CGM use can significantly reduce the frequency and severity of hypoglycemic events by providing early warnings and detailed glucose trends, whereas SMBG may miss detecting hypoglycaemia. Flash glucose monitoring (FGM) was introduced in 2014, which features a subcutaneous sensor that tracks glucose levels in real-time. The FreeStyle Libre Pro system, which can be used for up to 14 days without finger-prick calibration, offers detailed glucose data but lacks automatic alarms.[15]

The ambulatory glucose profile (AGP) is a transformative tool in diabetes management, which offers a standardized, single-page report that visualizes CGM data.[16] AGP simplifies the complex data from CGM systems into an easy-to-interpret format. It shows daily glucose patterns, variability, and target ranges. This user-friendly report enhances patient understanding and engagement by clearly indicating periods of hypoglycemia and hyperglycemia. For healthcare providers, AGP facilitates efficient analysis and personalized treatment planning, leading to better clinical outcomes.[17] Despite its advantages, the 24-hour glycemic profile using AGP has not been extensively studied in GDM patients in India. The current study aims to evaluate the glycemic profiles of GDM patients using AGP and its effectiveness in managing GDM at a tertiary healthcare center in Central India.

The primary objective of this study was to compare the effectiveness and safety of the AGP with the SMBG profile in the monitoring and control of GDM. Additionally, the study aimed to assess glycemic variability (GV) in GDM patients and the user acceptability of AGP among individuals with GDM, gauging patient comfort and satisfaction with this monitoring method.

Methods

Study Design and Setting

This hospital-based observational study was conducted over a period of 18 months at the All India Institute of Medical Sciences (AIIMS), Raipur. The study was performed at the Antenatal Care (ANC) clinic, Medicine Outpatient Department (OPD), and Endocrinology OPD of AIIMS Raipur.

Methodology

- We selected two groups of patients. The first group had an AGP sensor attached, and the second group was on SMBG monitoring as directed by their treating physician.
- The day patients were enrolled was counted as day 1 (D1). The patients were followed up on days 7 and 15.
- The first group of participants wore the AGP sensor (on the back of their upper arm) for 14 days. Throughout this period, participants were asked to perform usual premeal capillary blood glucose (SMBG) tests daily.
- The second group of participants was asked to perform usual premeal capillary blood glucose (SMBG) tests daily.
- At clinic visits on days 7 and 15, data from the device were uploaded, frequency of SMBG tests was reviewed, and any adverse events (AEs) experienced or concomitant medication changes done by the treating physician were recorded. On day 15, the reader sensors were removed.
- The second contact, i.e., the D7 of enrollment was considered as the point of intervention, when the treatment was revised based on the initial 7-day glucose readings of the patient. The changes were done by the treating physician. None of the interventions were done as part of our research protocol.

Study Population

Sample Size

The sample size was calculated using the formula:

$$n = \frac{Z^2 PQ}{e^2}$$

Here, $Z = 1.96$, $P = 16.55$, $Q = 83.45$, and $e = 10\%$. Using this formula, the calculated sample size was 53. Accounting for a 10% nonresponse and refusal rate, the sample size was adjusted to 60, which was divided into two groups: (1) AGP and (2) SMBG.

Inclusion Criteria

Pregnant women aged >18 years, diagnosed with GDM according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria.

Exclusion Criteria

Women aged ≤18 year, with a preexisting diagnosis of type 1 diabetes mellitus (DM) or type 2 DM, history of allergic reactions to AGP materials, adhesives, chlorhexidine, or alcoholic antiseptic solutions, presence of local site infection or any abnormality, and who refused to provide consent were excluded from the study.

Operational Definitions

Gestational diabetes mellitus was diagnosed using the IADPSG criteria. These criteria include specific blood glucose thresholds during an oral glucose tolerance test (OGTT). According to these criteria, a fasting glucose level of 92 mg/dL or higher is indicative of GDM. Additionally, if the 1-hour glucose level reaches or exceeds 180 mg/dL, or if the 2-hour glucose level is 153 mg/dL or higher, the diagnosis of GDM is confirmed.

Target blood sugar levels were defined to ensure stable glucose management. For fasting blood sugar (FBS), the target was set at <95 mg/dL. For postprandial (PP) measurements, the target was <140 mg/dL at 1-hour PP and <120 mg/dL at 2-hour PP.

Glycemic variability, which measures fluctuations in blood glucose levels, was defined by the coefficient of variation (CV). The goal was to maintain a CV of <36% to ensure more stable blood glucose levels, reducing the risk of both hyperglycemia and hypoglycemia.

The primary metrics for managing blood glucose levels were time in range (TIR), time above range (TAR), and time below range (TBR). For TIR, which represents the percentage of time that blood glucose levels remain within the desired range, the target was set at >90%. For TAR, which measures the percentage of time that blood glucose levels are above the target range, the objective was to keep this value below 5%. Similarly, the target for TBR, which indicates the percentage of time that blood glucose levels fall below the target range, was also set at <5%.

Study Variables and Data Collection

A detailed history and clinical examination of the patients were recorded. Hemogram and metabolic profiles were documented. The AGP monitor (FreeStyle Libre Pro Flash Professional; Abbott Diabetes Care Ltd, Range Road, Witney, Oxon, UK) was applied to the back of the left upper arm for 14 days. Patients maintained a chart documenting the timing of major meals (breakfast, lunch, and dinner) while the AGP monitor was in place. Additionally, all women were instructed to perform SMBG four times a day (preferably seven times a day) and document the timings in their chart. Both AGP and SMBG were used for monitoring and control of GDM as per the study plan.

Data Analysis

The collected data were entered into a Microsoft Excel Sheet and analyzed using IBM SPSS version 21. Quantitative data were summarized using mean and standard

deviation (SD). The Chi-square test was used for comparison of categorical variables, while *t*-tests and Fisher's exact tests were applied for quantitative (continuous) variables as appropriate. A Likert scale was used for user questionnaires. Differences between variables were considered statistically significant when the *p*-value was <0.05.

Results

Demography and Baseline Clinical Details of the Participants

The participants were divided into two groups: (1) the AGP group ($n = 32$) and (2) the SMBG group ($n = 33$). The majority of patients were aged 26–30 years in both groups. The mean age was 28.93 ± 3.60 years in the AGP group and 29.06 ± 3.91 years in the SMBG group.

The mean FBS levels were 107.54 ± 13.03 mg/dL in the AGP group and 101.45 ± 8.68 mg/dL in the SMBG group. The mean 1-hour PP blood sugar levels were 190.74 ± 27.94 mg/dL in the AGP group and 179.60 ± 20.38 mg/dL in the SMBG group. The mean 2-hour PP blood sugar levels were 157.96 ± 23.60 mg/dL in the AGP group and 144.27 ± 22.81 mg/dL in the SMBG group.

In the AGP group, 28.1% ($n = 9$) patients were primigravida, and 71.9% ($n = 23$) were multigravida. In the SMBG group, 36.4% ($n = 12$) were primigravida, and 63.6% ($n = 21$) were multigravida. Among the multiparous women, 25% ($n = 8$) in the AGP group and 24.2% ($n = 8$) in the SMBG group had a history of GDM in a previous pregnancy. In the AGP group, 28.1% ($n = 9$) patients had a family history of DM, while in the SMBG group, 30.3% ($n = 10$) patients had a family history of DM. In the AGP group, one patient had hypertension, seven patients had hypothyroidism, and two patients had both conditions. In the SMBG group, one patient had hypertension, nine patients had hypothyroidism, and one patient had both conditions.

Diagnosis and Treatment

Most patients were diagnosed with GDM at 24–25 weeks of gestation. In the AGP group, 11 patients received medical nutrition therapy, while 21 patients received pharmacotherapy: 17 treated with insulin, 2 with insulin and metformin, and 2 with metformin alone. In the SMBG group, 12 patients received medical nutrition therapy, and 21 patients received pharmacotherapy: 17 treated with insulin, 2 with insulin and metformin, and 2 with metformin alone.

Measurement of Blood Glucose

In the AGP cohort, the mean blood glucose concentration prior to breakfast was 88.72 ± 12.93 mg/dL during the initial 7-day period (preintervention) and decreased significantly to 85.41 ± 5.87 mg/dL postintervention during the final 7 days ($p = 0.046$). The mean PP blood glucose level following breakfast was 114.10 ± 20.82 mg/dL in the first 7 days (preintervention) and significantly decreased to 106.37 ± 11.45 mg/dL postintervention ($p = 0.002$). Similarly, the mean PP blood glucose level after lunch was 120.03 ± 20.53 mg/dL preintervention and decreased significantly to 111.13 ± 10.40 mg/dL postintervention ($p = 0.001$). The mean PP blood glucose level following dinner was 125.65 ± 19.22 mg/dL preintervention and decreased significantly to 115.48 ± 10.36 mg/dL postintervention ($p = 0.001$). The findings are summarized in Table 1.

In the SMBG cohort, the mean blood glucose concentration before breakfast was 92.15 ± 9.65 mg/dL during the preintervention period and decreased significantly to 88.48 ± 5.47 mg/dL in the postintervention period ($p = 0.002$). The mean PP blood glucose level following breakfast was 114.57 ± 15.96 mg/dL preintervention and decreased significantly to 108.63 ± 10.62 mg/dL postintervention period ($p = 0.020$). Similarly, the mean PP blood glucose level after lunch was 117.63 ± 14.40 mg/dL preintervention and decreased significantly to 112.75 ± 8.64 mg/dL postintervention ($p = 0.012$). The mean PP blood glucose level following dinner was 124.27 ± 16.66 mg/dL preintervention and decreased significantly to 114.57 ± 10.98 mg/dL in the postintervention period ($p = 0.001$). The findings are summarized in Table 2.

Table 1: Comparison of the blood glucose in different timings between the first 7 days (preintervention) and last 7 days (postintervention) in the AGP group

Timing		*Mean*	*SD*	*t-value*	*p-value*
Before breakfast	Preintervention	88.72	12.93	1.98	0.046*
	Postintervention	85.41	5.87		
After breakfast	Preintervention	114.10	20.82	–2.50	0.002*
	Postintervention	106.37	11.45		
After lunch	Preintervention	120.03	20.53	2.67	0.001*
	Postintervention	111.13	10.40		
After dinner	Preintervention	125.65	19.22	2.40	0.001*
	Postintervention	115.48	10.36		

* Significant when $p < 0.05$

Table 2: Comparison of the blood glucose in different timings between the first 7 days (preintervention) and last 7 days (postintervention) in the SMBG group

Timing		*Mean*	*SD*	*t-value*	*p-value*
Before breakfast	Preintervention	92.15	9.65	3.67	0.002*
	Postintervention	88.48	5.47		
After breakfast	Preintervention	114.57	15.96	2.56	0.020*
	Postintervention	108.63	10.62		
After lunch	Preintervention	117.63	14.40	2.78	0.012*
	Postintervention	112.75	8.64		
After dinner	Preintervention	124.27	16.66	3.87	0.001*
	Postintervention	114.57	10.98		

* Significant when $p < 0.05$

The mean variation in fasting blood glucose levels from the preintervention to the postintervention period was 3.31 mg/dL in the AGP cohort and 3.66 mg/dL in the SMBG cohort, with an intergroup difference of 0.35 mg/dL. The mean change in PP blood glucose levels following breakfast from preintervention to the postintervention period was 7.72 mg/dL in the AGP cohort and 5.93 mg/dL in the SMBG cohort, resulting in an intergroup difference of 2.79 mg/dL. The mean change in PP blood glucose levels following lunch from preintervention to the postintervention period was 8.90 mg/dL in the AGP cohort and 4.87 mg/dL in the SMBG cohort, with an intergroup difference of 4.13 mg/dL. The mean variation in PP blood glucose levels following dinner from preintervention to the postintervention period was 10.17 mg/dL in the AGP cohort and 9.69 mg/dL in the SMBG cohort, resulting in an intergroup difference of 0.48 mg/dL. However, the intergroup variations were not statistically significant at any time interval. The findings are summarized in Table 3.

Time in Range

As shown in Table 4, in the AGP group, the mean time within the target range was 84% during the preintervention period and significantly increased to 92% postintervention ($p < 0.001$). The mean time below the target range was 3% during the preintervention period and decreased significantly to 2% during the postintervention period ($p = 0.008$). The mean time above the target range was 12% during the preintervention period and decreased significantly to 4% postintervention ($p < 0.001$).

Hypoglycemic Events

In the AGP group, three patients experienced symptomatic hypoglycemia, while eight patients experienced asymptomatic hypoglycemia. In contrast, in the SMBG group, four patients experienced symptomatic hypoglycemia, with no cases of asymptomatic hypoglycemia recorded. The results of the Chi-square test for hypoglycemic events in the AGP and SMBG groups are summarized in Table 5. In the AGP group, 9.37% of patients experienced symptomatic hypoglycemia compared to 12.12% in the SMBG group ($p = 0.01$). This indicates a significant difference in the occurrence of symptomatic hypoglycemia between the two groups.

Glycemic Variability

The GV (% CV) in the AGP group was calculated to be 16.81 ± 4.22 in the preintervention period and 14.15 ± 3.08 in the postintervention period. Paired *t*-test indicated a statistically significant difference between the preintervention and postintervention values ($p = 0.005$), suggesting an improvement in GV following the intervention (Table 6).

Table 3: Comparison of the mean change in the blood glucose at different times of measurement during preintervention and postintervention period between the AGP and SMBG groups

Timings		*Mean change*	*Difference*	*p-value*
Before breakfast	AGP	3.31	0.35	0.468
	SMBG	3.66		
After breakfast	AGP	7.72	2.79	0.646
	SMBG	5.93		
After lunch	AGP	8.90	4.13	0.216
	SMBG	4.87		
After dinner	AGP	10.17	0.48	0.971
	SMBG	9.69		

Table 4: Comparison of the various times between the first 7 days and last 7 days in the AGP group

Timing		*Mean*	*SD*	*p-value*
Time in target	Preintervention	0.84	0.10	<0.001*
	Postintervention	0.92	0.03	
Time below target	Preintervention	0.03	0.02	0.008*
	Postintervention	0.02	0.01	
Time above target	Preintervention	0.12	0.09	<0.001*
	Postintervention	0.04	0.03	

* Significant when $p < 0.05$

Table 5: Comparison of hypoglycemic events in AGP and SMBG groups

Hypoglycemic events	*Group AGP*		*Group SMBG*		*p-value*
	N = 32	*%*	*N = 33*	*%*	
Symptomatic	3	9.37	4	12.12	0.01*
Asymptomatic	8	25	0	0	

Chi-square test; *Significant when $p < 0.05$

Table 6: Comparison of glycemic variability in the AGP group

Coefficient of variability	*Mean*	*SD*	*p-value*
Preintervention	16.81	04.22	0.005*
Postintervention	14.15	03.08	

Paired *t*-test; *Significant when $p < 0.005$

User Acceptability

In the AGP group, 10.34% of the patients responded with "agree" (indicating that the device was almost painless) regarding the acceptability of the device. A significant majority, 89.66%, responded with "strongly agree" (indicating that the device was painless) for the acceptability of the device. Notably, none of the patients provided responses of "neither agree nor disagree" (indicating slight pain), "disagree" (indicating moderate pain), or "strongly disagree" (indicating severe pain) on the user acceptability questionnaire that was given to them. No AEs were observed with the AGP monitor.

Discussion

There is a growing demand for advanced tools to monitor and regulate alterations in 24-hour blood glucose levels. Among the first continuous, albeit invasive, monitoring systems introduced are the continuous glucose monitoring system (CGMS) and FGM system. The CGMS facilitates periodic recording of comprehensive blood glucose profiles and important statistics for diabetic patients. Given the availability of this technology, it is essential to evaluate its accuracy, reproducibility, and ability to detect critical glycemic events as well as blood glucose patterns. In a systematic review, Aggarwal et al. analyzed 26 clinical and 12 economic studies and revealed that CGMS effectively reduces hypoglycemic events and improves glucose and HbA1c levels, while also impacting direct and indirect management costs.[18] Another systematic review by Majewska et al. found that CGM provides better glycemic control than SMBG and improves qualification for insulin therapy. However, most studies do not show CGM's impact on neonatal outcomes, indicating a need for further research.[19]

In this study, significant reductions in mean blood glucose levels were observed postintervention compared to preintervention across various meal timings in both the SMBG and AGP groups. For instance, before breakfast, mean blood glucose levels decreased significantly in both the AGP and SMBG groups. Similar reductions were noted after breakfast, lunch, and dinner in both groups. However, there was no significant difference in the mean change in blood glucose levels between the AGP and SMBG groups across different meal timings. These findings suggest that while both AGP and SMBG interventions effectively reduced mean blood glucose levels across various meal timings, there was no significant advantage of one method over the other in terms of mean blood glucose level reduction. Thus, our study demonstrated that both AGP and SMBG are effective in detecting and managing hyperglycemia in GDM patients. The detailed data provided by AGP allow for the comprehensive assessment of hyperglycemic episodes. Conversely, the frequency of SMBG recordings plays a crucial role in identifying hyperglycemic episodes, often missed due to less frequent testing.

Alfadhli et al. conducted a prospective open-label randomized controlled study at the Maternity and Children Hospital, Medina, Saudi Arabia, evaluating the impact of a real-time continuous glucose monitoring system (RT-CGMS) as an educational tool in 130 pregnant women diagnosed with GDM. Participants were randomized into two groups: (1) SMBG alone and (2) SMBG with RT-CGMS application shortly after diagnosis. Despite improvements in glucose variability metrics, the study found no significant enhancements in overall glycemic control or pregnancy outcomes with RT-CGMS use.[20] Lane et al. conducted a randomized controlled trial to assess whether RT-CGMS improves glycemic control over intermittent SMBG in GDM. They reported that despite RT-CGM providing continuous feedback, there was no significant difference in mean sensor glucose levels between the groups after 4 weeks. Additionally, there were no notable differences in glycemic target achievement, maternal, or neonatal outcomes. However, patients perceived CGM, particularly real-time feedback, as beneficial for managing GDM, suggesting its role as a motivational tool.[21] These findings are similar to those reported in the current study.

However, some studies indicate that AGP may be more effective in managing hyperglycemia. Yogev et al. assessed the utility of CGM in managing insulin therapy for GDM. They reported that adjustments based on CGM data improved glycemic control, highlighting its potential in managing diabetic pregnancies effectively.[22] García-Moreno et al. reviewed 457 studies and included six randomized clinical trials involving 482 patients in their meta-analysis. The findings indicate that CGM use led to lower HbA1c levels at the end of pregnancy, reduced gestational weight gain in mothers, and lower birth weights in infants compared to blood glucose monitoring (BGM).[23]

In the AGP group, there was a significant increase in the mean TIR in the postintervention period (92%) compared to that of preintervention (84%), alongside reductions in TBR and TAR. In contrast, TIR calculation was not feasible in the SMBG group. This demonstrates the advantage of AGP in assessing glycemic profile, which can be detrimental to both the patient and fetus. They often go unchecked in SMBG-managed patients but can be effectively addressed through AGP profiling. Regarding hypoglycemia, three patients in the AGP group and four in the SMBG group experienced symptomatic hypoglycemia (blood glucose < 60 mg/dL), all occurring at night and in patients receiving insulin. AGP detected eight additional asymptomatic hypoglycemia cases, managed through dietary and insulin dose modifications. This demonstrates the efficacy of AGP in identifying asymptomatic and nocturnal hypoglycemic episodes, which are often missed by SMBG. In a randomized trial, Ólafsdóttir et al. studied the impact of CGM on hypoglycemia in diabetes patients using multiple daily insulin injections (MDIs). Results showed a significant reduction in nocturnal hypoglycemia (48% for <70 mg/dL and 65% for <54 mg/dL) and daytime hypoglycemia. CGM use also improved hypoglycemia-related confidence in social situations and overall life quality, with participants feeling more capable of detecting and responding to low glucose levels.[24]

Assessing GV in the current study was possible in the AGP group, with mean GV decreasing from 16.81% CV during the preintervention period to 14.15% CV postintervention. While definitive GV targets for GDM are yet to be established, our findings suggest lower GV in GDM patients compared to type 1 and type 2 DM. AGP provides a comprehensive glycemic profile, aiding GV assessment, whereas SMBG's data sufficiency depends on testing frequency. User acceptability of CGM in the AGP group was high, with 89.66% of patients rating it as painless and no adverse reactions reported. This aligns with the study by Scott et al., who highlighted the FreeStyle Libre System's acceptability among pregnant women with diabetes. This study evaluated the accuracy, clinical safety, and acceptability of the system in pregnant women with diabetes. Sensor glucose values were compared to SMBG values taken at least four times daily. Results showed as high as 99.8% of sensor readings. User feedback indicated high satisfaction, and no device-related AEs were reported, demonstrating the safety and accuracy of the system for pregnant women with diabetes.[25] Similarly, Pikee et al. reported a preference for FGM over SMBG among patients. They assessed the FGM system for GV, patient satisfaction, and clinical utility in pregnant women with diabetes. They reported that FGM detected more hypoglycemic episodes (92.9 vs 45.7%) and identified hyperglycemia in more women (74 vs 52%) compared to SMBG.

All participants preferred FGM, highlighting its sensitivity and patient satisfaction.[26]

Limitations of the Study

The study has a few limitations that may impact its generalizability and reliability. The relatively small sample size limits the applicability of the findings to a broader population, and the single-center setting at AIIMS Raipur may not reflect different patient demographics and clinical practices elsewhere. Additionally, the study did not control for all potential confounding variables, and the technological limitations of the AGP device could affect data accuracy. The effectiveness of SMBG heavily depends on participant adherence, which can vary widely.

Conclusion

This study compares the effectiveness of AGP and SMBG in managing gestational GDM. Both monitoring methods significantly improved glycemic control, with notable reductions in fasting and PP blood glucose levels. The AGP group demonstrated a more significant reduction in blood glucose levels postintervention compared to the SMBG group, particularly after meals, although the intergroup differences were not statistically significant. The AGP group's mean time within the target glucose range increased from 84% to 92%, indicating better overall glucose management compared to the SMBG group. Additionally, the AGP group had a more substantial decrease in the time spent above the target glucose range, which suggests improved control over hyperglycemia. Moreover, the study highlights the practical advantages of AGP, such as CGM without frequent finger pricks, which enhances patient compliance and comfort. The real-time data and trend analysis provided by AGP help in making timely adjustments to the treatment regimen, potentially reducing the risk of AEs associated with GDM. However, both methods showed efficacy in reducing the incidence of hypoglycemia, with AGP also identifying asymptomatic hypoglycemia episodes that SMBG might miss. AGP appears to offer a more comprehensive and patient-friendly approach to glucose monitoring in GDM management, potentially leading to better clinical outcomes. These findings support the integration of AGP into routine GDM care, particularly in settings where continuous monitoring can provide significant benefits over traditional SMBG methods.

Acknowledgment

Authors acknowledge the expert English editing and writing assistance from Papyruscript Private Limited (https://www.papyruscript.com/), Delhi, India.

Sources of Support

The AGP machine was provided by the General Medicine Department. The study did not receive any external funding.

Conflict of Interest

None.

Orcid

Rohini Rokkam https://orcid.org/0000-0001-8001-3933

Amritava Ghosh https://orcid.org/0000-0001-6798-3222

References

1. Sweeting A, Wong J, Murphy HR, et al. A clinical update on gestational diabetes mellitus. Endocr Rev 2022;43(5):763–793.
2. Mazumder T, Akter E, Rahman SM, et al. Prevalence and risk factors of gestational diabetes mellitus in Bangladesh: findings from Demographic Health Survey 2017-2018. Int J Environ Res Public Health 2022;19(5):2583.
3. Yuen L, Wong VW. Gestational diabetes mellitus: challenges for different ethnic groups. World J Diabetes 2015;6(8):1024–1032.
4. Li KT, Naik S, Alexander M, et al. Screening and diagnosis of gestational diabetes in India: a systematic review and meta-analysis. Acta Diabetol 2018;55(6):613–625.
5. Mirabelli M, Tocci V, Donnici A, et al. Maternal preconception body mass index overtakes age as a risk factor for gestational diabetes mellitus. J Clin Med 2023;12(8):2830.
6. Kc K, Shakya S, Zhang H. Gestational diabetes mellitus and macrosomia: a literature review. Ann Nutr Metab 2015;66(Suppl. 2):14–20.
7. Yildiz Atar H, Baatz JE, Ryan RM. Molecular mechanisms of maternal diabetes effects on fetal and neonatal surfactant. Children (Basel) 2021;8(4):281.
8. De Leon DD, Thornton P, Stanley CA, et al. Hypoglycemia in the newborn and infant. In: Sperling MA (Ed). Pediatric Endocrinology. Philadelphia: Elsevier; 2021. pp. 175–201.
9. Mitanchez D, Yzydorczyk C, Siddeek B, et al. The offspring of the diabetic mother—short- and long-term implications. Best Pract Res Clin Obstet Gynaecol 2015;29(2):256–269.
10. Rasmussen L, Poulsen CW, Kampmann U, et al. Diet and healthy lifestyle in the management of gestational diabetes mellitus. Nutrients 2020;12(10):3050.
11. Di Cianni G, Lencioni C, Lacaria E, et al. Hypoglycemia in diabetic pregnancy. In: Lapolla A, Dalfrà MG, Lencioni C, Di Cianni G (Eds). Textbook of Diabetes and Pregnancy, 3rd edition. Boca Raton (FL): CRC Press; 2018. pp. 432–440.
12. Reddy N, Verma N, Dungan K. Monitoring technologies-continuous glucose monitoring, mobile technology, biomarkers of glycemic control. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000.
13. Sibal L, Home PD. Management of type 2 diabetes: NICE guidelines. Clin Med (Lond) 2009;9(4):353–357.
14. Cappon G, Vettoretti M, Sparacino G, et al. Continuous glucose monitoring sensors for diabetes management: a review of technologies and applications. Diabetes Metab J 2019;43(4):383–397.
15. Fokkert MJ, van Dijk PR, Edens MA, et al. Performance of the FreeStyle Libre Flash glucose monitoring system in patients with type 1 and 2 diabetes mellitus. BMJ Open Diabetes Res Care 2017;5(1):e000320.
16. Johnson ML, Martens TW, Criego AB, et al.Utilizing the ambulatory glucose profile to standardize and implement continuous glucose monitoring in clinical practice. Diabetes Technol Ther 2019;21(S2):S217–S225.
17. Gibb FW, Jennings P, Leelarathna L, et al. AGP in daily clinical practice: a guide for use with the FreeStyle Libre flash glucose monitoring system. Br J Diabetes 2020;20(1):32–40.
18. Aggarwal A, Pathak S, Goyal R. Clinical and economic outcomes of continuous glucose monitoring system (CGMS) in patients with diabetes mellitus: a systematic literature review. Diabetes Res Clin Pract 2022;186:109825.
19. Majewska A, Stanirowski PJ, Wielgoś M, et al. Efficacy of continuous glucose monitoring on glycaemic control in pregnant women with gestational diabetes mellitus—a systematic review. J Clin Med 2022;11(10):2932.
20. Alfadhli E, Osman E, Basri T. Use of a real time continuous glucose monitoring system as an educational tool for patients with gestational diabetes. Diabetol Metab Syndr 2016;8:48.
21. Lane AS, Mlynarczyk MA, de Veciana M, et al. Real-time continuous glucose monitoring in gestational diabetes: a randomized controlled trial. Am J Perinatol 2019;36(9):891–897.
22. 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.
23. García-Moreno RM, Benítez-Valderrama P, Barquiel B, et al. Efficacy of continuous glucose monitoring on maternal and neonatal outcomes in gestational diabetes mellitus: a systematic review and meta-analysis of randomized clinical trials. Diabet Med 2022;39(1):e14703.
24. Ólafsdóttir AF, Polonsky W, Bolinder J, et al. A randomized clinical trial of the effect of continuous glucose monitoring on nocturnal hypoglycemia, daytime hypoglycemia, glycemic variability, and hypoglycemia confidence in persons with type 1 diabetes treated with multiple daily insulin injections (GOLD-3). Diabetes Technol Ther 2018;20(4):274–284.
25. Scott EM, Bilous RW, Kautzky-Willer A. Accuracy, user acceptability, and safety evaluation for the freestyle libre flash glucose monitoring system when used by pregnant women with diabetes. Diabetes Technol Ther 2018;20(3):180–188.
26. Pikee S, Khushbu K, Anupam P, et al. New innovation: use of flash glucose monitoring for evaluating glycaemic variability, patient satisfaction and clinical utility in pregnant women with diabetes. J Obstet Gynaecol India 2021;71(2):136–142.

ORIGINAL ARTICLE

Cardiovascular Metrics in Hospitalized Male Patients with Acute Coronary Syndrome

Meenaxi Sharda[1], Nisa Susan Thomas[2*], Yogesh Kumar Bareth[3], Setu Jain[4], Dheeraj Krishna[5], Hemant Vimlani[6], Arjun Deepak Tanup[7]

Received: 30 October 2024; *Accepted:* 21 March 2025

Abstract

Background: Coronary artery disease (CAD) is the leading cause of mortality globally, with a pronounced impact in India. Acute coronary syndrome (ACS), which includes unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI), is a manifestation of CAD. In 2010, the American Heart Association (AHA) introduced Life's Simple 7 (LS7) to improve cardiovascular health (CVH) by emphasizing disease prevention and lifestyle changes. This study aims to find the prevalence and distribution of LS7 metrics in hospitalized male patients with ACS compared to healthy individuals.

Methods: An observational case–control study was conducted at Government Medical College, Kota, between December 2022 and 2023, involving 50 male cases of ACS and 100 male controls, in the age-group 21–50. The Life's Simple 7 score was calculated by recording blood pressure, fasting blood glucose, total cholesterol, body mass index (BMI), diet, physical activity, and smoking/tobacco use. Scores were categorized into three groups, with 10–14 having ideal CVH, 5–9 as intermediate, and 0–4 as poor. Data were analyzed using SPSS 25.0, employing Chi-square, ANOVA, and calculating odds ratios and relative risk.

Observations: In this study, ACS cases had a mean LS7 score of 7.68, lower than the control group's 9.39, showing poorer CVH. High prevalence rates of hypertension (28%), diabetes (12%), and dyslipidemia (4%) were significant contributors to ACS, with odds ratios of 2.2, 1.94, and 1.94, respectively, and relative risks of 1.67, 1.83, and 1.83. Smoking was highly prevalent among ACS cases (96%), with an odds ratio of 12.77 and a relative risk of 1.47. Ideal BMI was present in only 48% of cases, with an odds ratio of 2.5 and a relative risk of 2.29. STEMI (78%) was prevalent among ACS cases, with single-vessel disease most common in angiographic findings.

Conclusion: The ACS cases studied had suboptimal CVH metrics compared to controls. These findings highlight the critical role of healthy lifestyles and managing modifiable risk factors in reducing ACS incidence and improving CVH outcomes.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1080

Introduction

In India, cardiovascular diseases (CVDs) have become the prime cause of mortality.[1] CVD affects the Indian population at least a decade earlier and in their most productive midlife years compared to the European population.[2] About 23% of CVD deaths occur before the age of 70 years in Western countries, whereas in India, this number is 52%, indicating the magnitude of the disease burden in the country.[3] Even though cardiovascular disease is preventable, the use of nicotine, decreased physical activity, and poor nutrition practices are leading to an increase in its prevalence in several countries.[4] Acute coronary syndrome (ACS) is a manifestation of coronary artery disease (CAD) and occurs as a result of plaque disruption in coronary arteries or vasospasm. It encompasses unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI).[5]

In 2010, the American Heart Association (AHA) introduced the concept of positive health promotion to improve cardiovascular health (CVH) in society, rather than focusing solely on the treatment of disease. To implement this vision, a model of ideal CVH was devised—Life's Simple 7 (LS7). Ideal CVH is defined by four health behaviors and four health factors. The behaviors include abstinence from smoking, body mass index (BMI) <25 kg/m^2, physical activity at goal levels, and a healthy diet. The ideal health factors described are nonsmoking within the last year, untreated total cholesterol <200 mg/dL, untreated blood pressure <120/80 mm Hg, and fasting blood glucose <100 mg/dL. Smoking was considered as one single component. Thus, seven health metrics were described. For each health metric, a study participant could either score 0 (poor), 1 (intermediate), or 2 (ideal) points. A total score of 0–4 points is considered poor, 5–9 intermediate, and 10–14 ideal for CVH.[6]

By examining the LS7 score in ACS, this study contributes to understanding the prevalence of cardiovascular metrics in the younger population and the importance of lifestyle modifications and preventive measures to reduce the risk of ACS.

Methods

This observational case–control study was conducted at the medicine ward, intensive care unit, and intensive coronary care unit (ICCU) of Government Medical College, Kota, Rajasthan, from December 2022 to 2023. A total of 150 male participants aged 21–50 were enrolled, including 50 cases diagnosed with ACS and 100 healthy controls. Cases were selected based on the history of typical cardiac chest pain, electrocardiogram (ECG) evidence of acute myocardial infarction, or elevated cardiac biomarkers, with no prior history of cardiovascular or cerebrovascular disease. Controls were healthy males with no history of ACS or previous cardiovascular conditions. Vital parameters, including pulse rate, blood pressure, respiratory rate, and oxygen saturation, were recorded. A 12-lead ECG, fasting blood glucose, total cholesterol, and troponin T levels were measured. Participants' lifestyle factors, including diet, physical activity, smoking, and tobacco use, were documented. The LS7 score was calculated and data analysis was performed using SPSS version 25.0. Statistical methods included Chi-squared test, ANOVA, *post hoc* Tukey test, odds ratio, and relative risk calculations, with a significance level set at $p < 0.05$.

Results

The mean age of cases was 43.08 and the standard deviation was 6.24. The distribution of ACS cases across different age-groups shows 70% of cases in the 41–50 age-group, 4% in the 21–30 age-group, and 26% in the 31–40

[1]Senior Professor; [2–5,7]Junior Resident; [6]Assistant Professor, Department of General Medicine, Government Medical College, Kota, Rajasthan, India; *Corresponding Author

How to cite this article: Sharda M, Thomas NS, Bareth YK, *et al.* Cardiovascular Metrics in Hospitalized Male Patients with Acute Coronary Syndrome. J Assoc Physicians India 2025;73(8):21–24.

age-group. This age distribution is statistically significant, with a p-value < 0.00001 ($\chi^2 = 33.91$), indicating a strong correlation between age and the occurrence of ACS. In contrast, the control group shows 33% of controls in the 21–30 age-group, 29% in the 31–40 age-group, and 38% in the 41–50 age-group. The p-value for the control group ($\chi^2 = 1.22$, $p = 0.543$) suggests no significant difference in age distribution.

Table 1: Mean values of age and cardiovascular metrics in ACS cases compared to controls

Mean (n)	*Cases*	*Controls*
Age	43.08 ± 6.24	36.3 ± 9.48
LS7 score	7.68 ± 1.92	9.39 ± 2.24
Systolic blood pressure	128.7 ± 19.7	121.2 ± 18.8
Diastolic blood pressure	82.8 ± 14.1	79.4 ± 9.9
Fasting blood sugar	101.06 ± 49.5	90.1 ± 35.31
Total cholesterol	178.94 ± 64.4	145.9 ± 36.2

Table 1 summarizes the mean values of various cardiovascular metrics in cases of ACS compared to controls. The data show that ACS cases are older and have lower LS7 scores, as well as higher levels of systolic and diastolic blood pressure, fasting blood sugar, and total cholesterol compared to controls.

Table 2 shows the distribution of CVH metrics among ACS cases and controls, highlighting the differences in adherence to LS7.

Figure 1 shows that among cases, fasting blood glucose, total cholesterol, and BMI have the highest number of participants with ideal scores. The participants with the lowest ideal scores are healthy diet, followed by smoking or tobacco consumption. The LS7 metric with the largest proportion of participants in the poor category is smoking or tobacco chewing, followed by healthy diet and blood pressure.

As shown in Figure 2, among controls, fasting blood glucose, total cholesterol, and BMI have the highest number of participants with ideal scores. The number of participants having the lowest ideal score is a healthy diet, followed by physical activity, smoking/tobacco use, and blood pressure. The LS7 metric with the largest proportion of participants in the poor category was smoking or tobacco chewing, followed by blood pressure and healthy diet.

Table 3 shows the odds ratios and relative risks for cardiovascular metrics for ACS cases and controls.

In our study, the majority of ACS cases are STEMI (78%), followed by UA (18%), and NSTEMI (4%). The majority of cases have single-vessel disease (72%), followed by double-vessel disease (20%), and a smaller proportion have no vessel involvement or recanalization (8%). Notably, no individuals have triple-vessel disease based on angiographic findings.

Table 2: Distribution of CVH metrics among ACS cases and controls

Metrics	*Cases*	*Controls*
1. LS7 score		
Poor	5 (10%)	6 (6%)
Intermediate	39 (78%)	36 (36%)
Ideal	6 (12%)	58 (58%)
2. Blood pressure		
Poor	19 (38%)	24 (24%)
Intermediate	12 (24%)	23 (23%)
Ideal	19 (38%)	53 (53%)
3. Fasting blood glucose		
Poor	8 (16%)	5 (5%)
Intermediate	0 (0%)	7 (7%)
Ideal	41 (82%)	88 (88%)
4. Total cholesterol		
Poor	5 (10%)	6 (6%)
Intermediate	8 (16%)	8 (8%)
Ideal	37 (74%)	86 (86%)
5. Smoking/tobacco consumption		
Poor	48 (96%)	62 (62%)
Intermediate	0 (0%)	5 (5%)
Ideal	2 (4%)	33 (33%)
6. Physical activity		
Poor	1 (2%)	0 (0%)
Intermediate	33 (66%)	77 (77%)
Ideal	16 (32%)	23 (23%)
7. Healthy diet		
Poor	21 (42%)	20 (20%)
Intermediate	29 (58%)	79 (79%)
Ideal	0 (0%)	1 (1%)
8. BMI		
Poor	4 (8%)	5 (5%)
Intermediate	22 (44%)	20 (20%)
Ideal	24 (48%)	75 (75%)

Table 3: Odds ratios and relative risks for cardiovascular metrics for ACS cases and controls

S. no.	*Metric*	*Odds ratio*	*Relative risk*
1.	Blood pressure	2.2	1.67
2.	Fasting blood glucose	1.94	1.83
3.	Total cholesterol	1.93	1.82
4.	Smoking/tobacco chewing	12.77	1.47
5.	Healthy diet	2.86	2.08
6.	Physical activity	0.61	0.73
7.	BMI	2.5	1.83

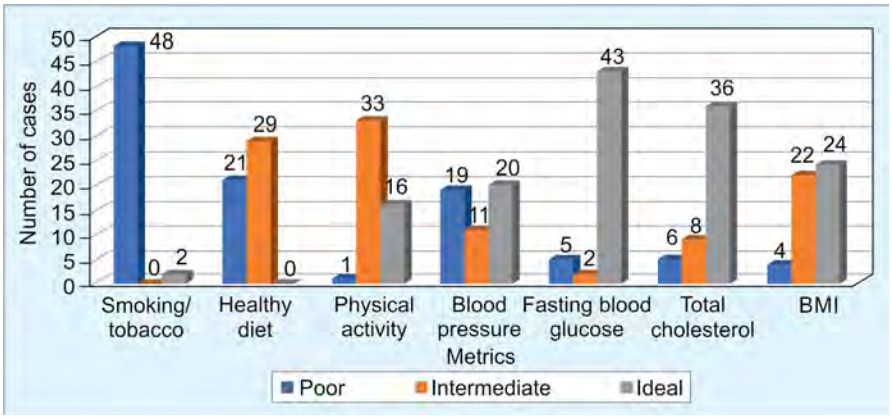


Fig. 1: Distribution of individual components of LS7 score in cases

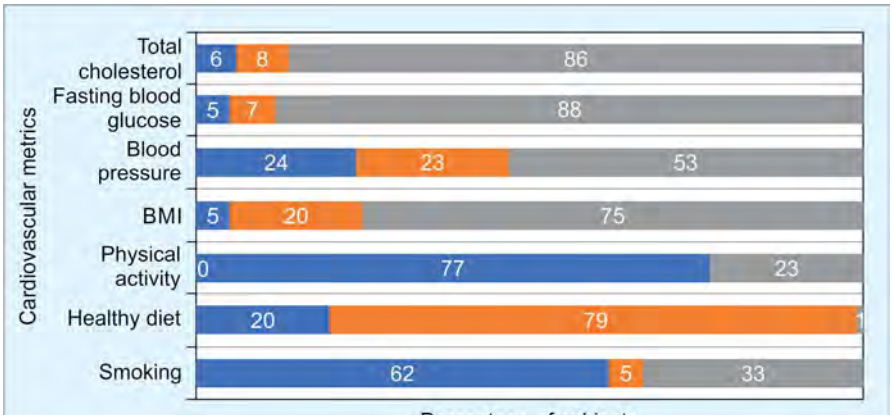


Fig. 2: Distribution of individual components of LS7 score in controls

Discussion

This study aimed to find the prevalence and distribution of LS7 score in young males with ACS, compare it to controls, and investigate the impact of modifiable risk factors in ACS. As age, sex, and family history of cardiovascular disease are nonmodifiable risk factors for ACS, males older than 50 years and female gender were excluded to avoid confounding. Vitale et al. reported a higher incidence of cardiovascular disease in men compared to women of similar age, along with highlighting the increase in cardiovascular disease among postmenopausal women.[7] Bugiardini et al. described that high-risk factor prevalence causes an earlier incidence of ACS in men as compared to women with similar risk factor burden, as atherosclerosis occurs later in women than men.[8] These demonstrate the gender-related differences that promote cardiovascular disease. Ranthe et al. reported a family history of myocardial infarction as an important independent marker of increased MI risk among individuals.[9] These findings support the exclusion of nonmodifiable risk factors from our study.

About 70% of cases were in the 41–50 age-group, with the mean age being 43.08 years, indicating the middle-aged population as more affected. The age-wise distribution in our study shows a high degree of significance, suggesting that increasing age is a critical factor for the prevalence of the disease. The odds of ACS were significantly higher for the age-group 41–50 compared to controls. Similarly, Gupta et al. and Shen et al. found that ideal cardiovascular metrics declined with aging, $p < 0.01$ and $\chi^2 = 106.746$, $p = 0.000$, respectively.[10,11]

The maximum distribution of cases belongs to the intermediate LS7 score, followed by ideal and then poor category. In contrast, a majority of the controls had an ideal score (58%), followed by intermediate (36%) and poor (6%). The LS7 score in cases ranged from 2 to 10, with a mean of 7.68 (SD 1.92), indicating suboptimal CVH. Controls had a higher mean LS7 score of 9.39 (SD 2.24), reflecting better CVH. The significant difference in LS7 score distributions between cases and controls ($p < 0.00001$) highlights the impact of CVH metrics on the risk of developing ACS.

In our study, ideal cardiovascular metrics were highest in fasting blood glucose (82%), total cholesterol (74%), and BMI (48%). The poorest metrics were seen in smoking or tobacco use (96%), healthy diet (42%), and blood pressure (38%). Physical activity showed moderate scores in 66% of cases, while none had an ideal diet. Only 4% of cases had five ideal metrics, with none achieving all seven. Similarly, Gupta et al. found that <1% of the study population involving Indian subjects had all seven ideal health factors, with most having poor CVH.[10]

The mean systolic and diastolic blood pressure among ACS cases was 128.7 and 82.8 mm Hg, respectively, with 38% having poor blood pressure metrics. Controls had lower averages of 121.2 mm Hg systolic and 79.4 mm Hg diastolic. The odds of ACS in cases with poor blood pressure metrics were 2.2 times higher than in controls, with a relative risk of 1.67. Dong et al. found that higher blood pressure significantly increased the risk of cardiovascular disease and mortality.[12] Janković et al. also noted a decline in ideal CVH as blood pressure increased, especially with age.[13]

In our study, 82% of participants had ideal LS7 scores for fasting blood glucose, compared to 88% in controls. The odds of ACS in cases with poor glucose control were 1.94 times higher, with a relative risk of 1.83, underscoring the importance of glycemic

control in CVH. Miao et al. and Ding et al. also found higher fasting glucose levels to be negatively associated with CVH scores.[14,15]

Among cases, 74% had ideal LS7 scores for total cholesterol, while 10% had poor metrics. The odds of ACS for those with poor LS7 scores were 1.93 times higher, and the relative risk was 1.82 times higher compared to controls. Elevated total cholesterol is associated with poorer CVH, as described by Leopold and Antman.[16]

In our study, 96% of cases had poor smoking metrics, compared to 62% in controls, highlighting a strong link to ACS. The odds ratio for ACS in smokers vs nonsmokers is 12.77, and the relative risk is 1.47, indicating significantly higher ACS risk in smokers. In Leopold and Antman, participants with CVD were more likely to be current or prior smokers compared to those without CVD ($p < 0.01$).[16] Additionally, young adults with CVD were more likely to be current or former smokers than older adults (50.4 vs 40.1%, $p < 0.01$).

About 42% of ACS cases had poor diet metrics, 58% had intermediate, and none had ideal metrics. Controls showed better dietary habits, with fewer having poor diets (20 vs 42% in cases). The odds ratio of 2.86 and relative risk of 2.08 indicate a significantly higher ACS risk with poor diet. Both cases and controls lacked ideal diet metrics. This highlights a critical gap in achieving optimal dietary habits across both groups, suggesting a universal need for dietary improvement to support CVH. Younus et al. reported poor diet as the lowest-scoring metric across studies, with many reporting <1% prevalence of an ideal diet.[17] Harrison et al. described diet metric as the least prevalent of "ideal" scores at 4.8%.[18] Gupta et al., in their study across 11 cities in the Indian population, described the ideal diet in 10% of the population.[10] Educational programs that focus on the benefits of a balanced diet rich in fruits, vegetables, whole grains, and decreased salt intake could significantly improve the LS7 scores and CVH outcomes.

The odds ratio and relative risk between cases and controls of 0.61 and 0.73, respectively, for ideal vs intermediate physical activity indicate that those with ideal physical activity levels are less likely to develop ACS than those with intermediate physical activity. Leopold and Antman described differences in physical activity between young adults with and without cardiovascular disease and reported fewer minutes of vigorous exercise per week ($p < 0.01$).[16] These findings emphasize the strong correlation between higher physical activity levels and better LS7 scores.

The mean BMI among cases was 24.67 compared to 23.08 in controls. The odds ratio and relative risk among cases were 2.5 and 1.83, compared to controls, indicating a substantial risk in cases. Leopold and Antman demonstrated that BMI was higher in young adults with cardiovascular disease than those without the disease (31.4 ± 8.7 vs 29.3 ± 8.0 kg/m^2, $p < 0.01$).[16]

In our study, 78% of the cases were STEMI. Allouche et al. in their study mentioned the predominance of ST elevation MI in 69% of young patients presenting with myocardial infarction.[19] Angiographic findings showed the prevalence of single-vessel disease, particularly the left anterior descending artery. Zimmerman et al. described in their study that young patients were more likely to have single-vessel disease, whereas older patients more often had multiple-vessel disease ($p < 0.0001$).[20]

Conclusion

Our study comprehensively analyses Life's Simple 7 score, its implications, and its prevalence in ACS. Suboptimal cardiovascular metrics were documented among the ACS cases compared to healthy controls. This disparity underlines the critical impact of maintaining ideal LS7 scores for reducing risk for ACS. The higher odds ratio and relative risk for ACS among cases with hypertension, diabetes mellitus, and dyslipidemia, as compared to controls, highlight the need for early detection and treatment of these risk factors. Smoking, tobacco consumption, and poor dietary habits were prevalent among ACS cases and strongly associated with lower LS7 scores, emphasizing the urgent need for lifestyle modifications for risk reduction. Higher physical activity levels demonstrated a protective effect, correlating with better LS7 scores and lower ACS incidence.

References

1. Reddy KS, Shah B, Varghese C, et al. Responding to the threat of chronic diseases in India. Lancet 2005;366(9498):1744–1749.
2. Joshi P, Islam S, Pais P, et al. Risk factors for early myocardial infarction in South Asians compared with individuals in other countries. JAMA 2007;297(3):286–294.
3. Leeder S, Raymond S, Greenberg H, et al. A Race against Time: The Challenge of Cardiovascular Disease in Developing Economies. New York: Columbia University; 2004. p. 24.
4. Danaei G, Ding EL, Mozaffarian D, et al. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. PLoS Med 2009;6(4):e1000058.
5. Kumar A, Cannon CP. Acute coronary syndromes: diagnosis and management, part I. Mayo Clin Proc 2009;84(10):917–938.
6. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation 2010;121(4):586–613.
7. Vitale C, Mendelsohn ME, Rosano GMC. Gender differences in the cardiovascular effect of sex hormones. Nat Rev Cardiol 2009;6(8):532–542.
8. Bugiardini R, Cenko E, Yoon J, et al. Traditional risk factors and premature acute coronary syndromes in South Eastern Europe: a multinational cohort study. Lancet Reg Health Eur 2024;38:100824.
9. Ranthe MF, Petersen JA, Bundgaard H, et al. A detailed family history of myocardial infarction and risk of myocardial infarction—a nationwide cohort study. PLoS One 2015;10(5):e0125896.
10. Gupta B, Gupta R, Sharma KK, et al. Low prevalence of AHA-defined ideal cardiovascular health factors: a study of urban Indian men and women. Global Heart 2017;12(3):219–225.
11. Shen SW, Lu Y, Qi HJ, et al. The prevalence of ideal cardiovascular health metrics in Southeast Chinese middle-aged men. Zhonghua Xin Xue Guan Bing Za Zhi 2016;44(10):885–890.
12. Dong Y, Hao G, Wang Z, et al. Ideal cardiovascular health status and risk of cardiovascular disease or all-cause mortality in Chinese middle-aged population. Angiology 2019;70(6):523–529.
13. Janković J, Marinković J, Stojisavljević D, et al. Sex inequalities in cardiovascular health: a cross-sectional study. Eur J Public Health 2016;26(1):152–158.
14. Miao C, Bao M, Xing A, et al. Cardiovascular health score and the risk of cardiovascular diseases. PLoS One 2015;10(7):e0131537.
15. Ding EY, Mehawej J, Abu H, et al. Cardiovascular health metrics in patients hospitalized with an acute coronary syndrome. Am J Med 2021;134(11):1396–1402.
16. Leopold JA, Antman EM. Ideal cardiovascular health in young adults with established cardiovascular diseases. Front Cardiovasc Med 2022;9:814610.
17. Younus A, Aneni EC, Spatz ES, et al. A systematic review of the prevalence and outcomes of ideal cardiovascular health in US and non-US populations. Mayo Clin Proc 2016;91(5):649–670.
18. Harrison S, Couillard C, Robitaille J, et al. Assessment of the American Heart Association's "Life's simple 7" score in French-speaking adults from Québec. Nutr Metab Cardiovasc Dis 2019;29(7):684–691.
19. Allouche E, Ghariani A, Ahmed HB, et al. Infarctus du myocarde chez le sujet jeune en Tunisie: caractéristiques cliniques, aspects thérapeutiques et complications intra-hospitalières [Myocardial infarction in the young: clinical characteristics, therapeutic aspects and in-hospital complications.]. Ann Cardiol Angeiol (Paris) 2022;71(2):90–94.
20. Zimmerman FH, Cameron A, Fisher LD, et al. Myocardial infarction in young adults: angiographic characterization, risk factors and prognosis (Coronary Artery Surgery Study Registry). J Am Coll Cardiol 1995;26(3):654–661.

ORIGINAL ARTICLE

Circadian Blood Pressure Profile and Associated Cardiovascular Risk Factors in Prehypertensive Patients and Its Relationship with Urinary Albumin-to-Creatinine Ratio

Jaldu Krishna Pavan[1], Ashok Kumar[2*], Gutti Prasanth[3], Shubha Laxmi Margekar[4], Shivani Bansal[5]

Received: 03 November 2024; *Accepted:* 21 March 2025

Abstract

Background: Prehypertension is characterized by a systolic blood pressure (SBP) ranging from 120 to 139 mm Hg and a diastolic blood pressure (DBP) between 80 and 89 mm Hg, acting as a precursor to hypertension and potentially increasing cardiovascular risks. This study investigates the circadian patterns of blood pressure (BP), dipper status, and associated cardiovascular risk factors in prehypertensive individuals, with a particular focus on the relationship with the urinary albumin-to-creatinine ratio (UACR) as a marker of kidney and vascular health.

Objective: To assess the circadian rhythm of BP in prehypertensive patients and examine its relationship with UACR and other cardiovascular risk factors.

Methods: In this research involving systematic observation, a total of 101 participants were included, 57.4% of whom were identified as prehypertensive. Prehypertensive participants were grouped into "dippers" or "nondippers" based on a nocturnal BP reduction threshold of greater than or <10%, respectively. UACR, high-sensitivity C-reactive protein (Hs-CRP), lipid profiles, and additional biochemical parameters were measured. Statistical analysis included *t*-tests and analysis of variance (ANOVA) were utilized to examine associations.

Results: Prehypertensive subjects demonstrated significantly higher mean 24-hour SBP and DBP than normotensive controls ($p < 0.001$). Dipper status was identified in 55.2% of prehypertensives, with nondippers exhibiting elevated nighttime SBP and DBP ($p < 0.001$). UACR and nondipper status were found to be significantly correlated ($p = 0.034$), with nondippers also displaying elevated Hs-CRP levels, indicating greater systemic inflammation.

Conclusion: Circadian BP variability and dipper status in prehypertensive patients correlate with UACR and Hs-CRP levels, suggesting that nondippers may be at increased cardiovascular risk. Ambulatory blood pressure monitoring (ABPM) offers valuable insights into early hypertension risk and can aid in identifying prehypertensive individuals requiring closer monitoring and intervention.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1067

Background

Blood pressure (BP) is a continuous variable, and elevated BP measurements have been associated with heightened cardiovascular risk. Although the definition of hypertension is a rise of BP ≥140/90 mm Hg, a category termed "prehypertension" (BP: 120–139/80–89 mm Hg) has been established to recognize individuals at heightened risk of progression to hypertension. Prehypertension is often asymptomatic yet poses significant cardiovascular and renal risks, including an increased likelihood of developing myocardial infarction and cerebrovascular disease.[1,2]

Importance of Circadian Blood Pressure Patterns

Circadian variations in BP follow predictable daily rhythms, with typical patterns involving a morning surge, minor afternoon dip, and a more substantial nocturnal decline. In prehypertensive individuals, these circadian patterns may be disrupted, especially in those classified to be "nondippers" (with <10% nocturnal BP reduction). Nondipping patterns have been linked to greater cardiovascular risks and target organ damage than seen in "dippers," who exhibit typical BP declines at night. Ambulatory blood pressure monitoring (ABPM) allows for the precise assessment of 24-hour BP patterns, including these variations, offering valuable insights into cardiovascular risks in prehypertensive individuals.[3,4]

Link between Blood Pressure Patterns and Cardiovascular Risk Factors

Increasing evidence correlates BP patterns with multiple cardiovascular risk factors, including higher urinary albumin-to-creatinine ratio (UACR) and high-sensitivity C-reactive protein (Hs-CRP) levels. UACR signifies renal involvement and vascular health, whereas Hs-CRP functions as an inflammatory marker frequently raised in individuals with cardiovascular disease (CVD).

Nondippers have been shown to exhibit higher UACR and Hs-CRP levels, indicating greater systemic inflammation and renal stress, both of which may contribute to adverse cardiovascular outcomes.[5]

Study Rationale

The present study seeks to characterize circadian BP profiles in prehypertensive patients, determine their dipper status, and explore associations between BP patterns and cardiovascular risk factors, particularly UACR and Hs-CRP.

Methodology

Study Design and Population

This observational study included 101 consecutive adult patients aged 18–60 years, recruited from the outpatient department of the Medicine Department. Participants were categorized as normotensive (BP < 120/80 mm Hg) or prehypertensive [systolic blood pressure (SBP) 120–139 mm Hg, diastolic blood pressure (DBP) 80–89 mm Hg] according to the mean of three office BP measures recorded 5 minutes apart.

[1]Resident; [2]Professor and HOD; [3]Resident, Department of General Medicine, Santosh Medical College, Santosh Deemed to be University, Ghaziabad, Uttar Pradesh; [4]Professor, Department of Medicine, Lady Hardinge Medical College, Delhi; [5]Professor, Department of General Medicine, Santosh Medical College, Santosh Deemed to be University, Ghaziabad, Uttar Pradesh, India; *Corresponding Author

How to cite this article: Pavan JK, Kumar A, Prasanth G, *et al.* Circadian Blood Pressure Profile and Associated Cardiovascular Risk Factors in Prehypertensive Patients and Its Relationship with Urinary Albumin-to-Creatinine Ratio. J Assoc Physicians India 2025;73(8):25–30.

According to office measurements, persons with prehypertension, characterized when having a SBP of 120–139 mm Hg and a DBP of 80–89 mm Hg, between the ages of 18 and 60, are eligible to participate in this study. Exclusion criteria encompass individuals who are nonambulatory or have experienced a myocardial infarction, stroke, or undergone surgery within the past 6 months. Additionally, subjects with a history of chronic liver disease, renal disease, endocrine disorders, or secondary hypertension are excluded from participation.

Monitoring of Blood Pressure and Dipper Status Classification

Ambulatory blood pressure monitoring was conducted using a small wearable portable ABPM device (Apnea® ABP, CE certified, Meditech Ltd.), programmed to record BP every 15 minutes during daytime and every 30 minutes at night over 24 hours. The device was cross-checked with manual BP readings at the time of placement. Participants wore the ABPM device on their nondominant arm while following their usual activities. Diurnal BP rhythm was calculated using the following formula:

$$\text{Diurnal rhythm} = \frac{\text{Mean day time BP} - \text{Mean night times BP}}{\text{Mean day times BP}} \times 100$$

A diurnal rhythm of >10% classified a participant as a "dipper," while ≤10% indicated "nondipper" status.

Biochemical Measurements

Blood samples (5 mL) were collected from subjects after a 12-hour fasting interval. The samples were examined for Hs-CRP and lipid profiles utilizing the COBAS INTEGRA® 400 plus (Roche Diagnostics, Switzerland). Serum for Hs-CRP and lipids was prepared through centrifugation (3000 rpm for 5 minutes) and analyzed using immunonephelometry or turbidimetry. Additionally, urine samples were obtained in order to compute the UACR, which was determined using the following formula:

UACR = Urine albumin (mg/dL)/urine creatinine (gm/dL)

Data Collection

Demographic data, medical history, and lifestyle risk factors (including smoking and alcohol use) were collected from all participants. Physical measurements included height, weight, and body mass index (BMI). Cardiovascular risk variables, including lipid profile and fasting blood glucose, were documented for the study.

Statistical Analysis

GraphPad Prism (version 9.2.0) was employed to analyze all data. In the case of categorical variables, descriptive statistics comprised frequencies and means ± standard deviations for continuous variables. Categorical comparisons were conducted using the Chi-squared test or Fisher's exact test, while quantitative comparisons were conducted using the Student's *t*-test or one-way analysis of variance (ANOVA). Pearson's correlation coefficients assessed the relationships between BP parameters, UACR, and cardiovascular risk factors. Binary logistic regression identified variables associated with nondipper status and elevated cardiovascular risk. Statistical significance was defined with *p*-value of <0.05.

Ethical Considerations

Ethical approval for this work was secured from the Institutional Ethics Committee, ensuring adherence to ethical norms for research involving human beings. Prior to the inclusion of any participant in the study, written informed consent was taken from all of the participants, and absolute confidentiality was maintained for all of the data that were collected. Patient privacy was protected throughout all stages of analysis and reporting.

Results

Demographic and Baseline Characteristics

The study included 101 participants, 57.4% of whom were prehypertensive and 42.6% normotensive. In the prehypertensive cohort, 58.6% were female and 41.4% were male, with a mean age of 51.6 years. No statistically significant difference was found in the distribution of gender or age between normotensive and prehypertensive subjects ($p = 0.2276$ for gender; $p = 0.2603$ for age). The prevalence of alcohol and tobacco use was similar across the groups, with no significant differences noted ($p = 0.5516$ for smoking; $p = 0.4350$ for alcohol).

Blood Pressure Profiles

Prehypertensive individuals exhibited significantly elevated mean SBP and DBP in comparison to normotensive individuals over all time intervals (24-hour, daytime, and nighttime readings, $p < 0.001$ for each). During the 24-hour ABPM period, mean SBP was 130.1 ± 6.7 mm Hg and mean DBP was 83.0 ± 6.5 mm Hg in prehypertensive participants, compared to 116.9 ± 8.4 mm Hg (SBP) and 73.2 ± 7.9 mm Hg (DBP) in normotensive individuals. During daytime, SBP and DBP were similarly elevated in the prehypertensive group (133.8 ± 8.7 and 84.7 ± 6.0 mm Hg, respectively) compared to the normotensive group ($p < 0.001$).

Dipper vs Nondipper Status

In the prehypertensive cohort, 55.2% were categorized as "dippers" and 44.8% as "nondippers." Nondippers demonstrated significantly elevated nighttime SBP and DBP compared to dippers ($p < 0.001$), with mean nighttime SBP of 127.5 ± 6.2 mm Hg and DBP of 82.9 ± 6.3 mm Hg in nondippers, vs 118.8 ± 7.5 mm Hg (SBP) and 74.2 ± 6.9 mm Hg (DBP) in dippers. BP during the day was comparable for dippers and nondippers, but nondippers displayed a blunted circadian rhythm with <10% nocturnal BP reduction.

Urinary Albumin-to-Creatinine Ratio

The mean UACR was greater in prehypertensive participants compared to normotensive participants (26.4 ± 8.1 vs 23.8 ± 6.5 mg/gm), although the difference lacked statistical significance ($p = 0.0865$). In prehypertensive individuals, nondippers exhibited a greater mean UACR compared to dippers (27.4 ± 7.6 vs 25.9 ± 6.4 mg/gm). Nonetheless, this difference was statistically insignificant ($p = 0.4179$).

High-sensitivity C-reactive Protein Levels

High-sensitivity C-reactive protein levels were observed to be significantly elevated in prehypertensive participants compared to normotensive controls (4.71 ± 2.14 vs 1.96 ± 0.62 mg/L; $p < 0.001$). In prehypertensive individuals, nondippers demonstrated markedly elevated Hs-CRP levels compared to dippers (4.95 ± 0.94 vs 4.19 ± 1.57 mg/L; $p = 0.034$), indicating increased systemic inflammation in nondippers.

Cardiovascular Risk Factors

No significant differences were detected in cholesterol, triglyceride, or low-density lipoprotein (LDL) levels between normotensive and prehypertensive subjects. Hemoglobin levels were markedly elevated in the prehypertensive group ($p < 0.001$), but other indicators, including heart rate, respiration rate, total leukocyte count, and creatinine levels, exhibited insignificant differences.

Discussion

It is a well-established fact that hypertension is a significant risk factor for CVD. Prehypertensive states frequently precede hypertension and, if managed, can hasten the progression of hypertension. Over the past three decades, there have been concerns raised about the accuracy of traditional sphygmomanometers in measuring BP, which has prompted attempts to improve

measures using automated equipment. The use of ABPM in standard clinical practice is growing. ABPM may provide useful prognostic information, especially when it comes to evaluating nocturnal BP measurements. This has caused attention to shift away from relying just on discrete measures impacted by situational circumstances and toward measurement techniques that offer thorough profiles of BP. Hypertension is caused by various known risk factors, which emphasize the significance of early identification, ideally in the prehypertensive stage. Vascular inflammation may have some role in the onset as well as the progression of hypertension, according to mounting evidence.[6–9] Hypertensive individuals demonstrate increased concentrations of inflammatory markers, including CRP, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). Hs-CRP, an acute-phase reactant molecule, is produced primarily in hepatocytes stimulated by IL-6 and TNF, serving as a biomarker of systemic inflammation. Hs-CRP has been identified as a marker for assessing cardiovascular risk in individuals with high BP. However, the association between inflammatory markers and prehypertension or hypertension remains unclear.

The present study was designed as a cross-sectional observational study, with a total of 101 patients. Among these individuals, 42.6% were categorized as having normal BP, while 57.4% exhibited prehypertension. Similar prevalence rates were reported in prior studies; Jamalludin et al. reported 57.5% with normal BP and 42.5% with prehypertension, while Licitra et al. observed 40.2% prehypertensive and 59.8% normotensive subjects. Zare et al. documented a lower incidence of prehypertension at 42.03% compared to our findings.[10–12] Baseline parameters revealed nonsignificant differences in gender (p = 0.2276) or age (p = 0.2603) between normotensive and prehypertensive subjects (Table 1). The majority of individuals in the prehypertensive group were females (58.6%) compared to males (41.4%). Prehypertension was prevalent in 43.1% of individuals aged 30–50 years, with 56.9% of subjects falling within the fifth decade of life. Licitra et al., in contrast to our findings, found that males were more likely than females to have prehypertension (53.5%), and mean age of prehypertensive patients was 51 ± 11 years.[11] Furthermore, there were no discernible differences in alcohol or smoking across these groups ($p > 0.05$). These results were in line with those of Licitra et al.[11] who discovered an insignificant difference in smoking status between participants with normotension and those without (p = 0.09). In a similar line, Bharath and Manjula found an insignificant difference in the mean ages of prehypertensive and normotensive patients (26.15 ± 5.57 and 27.40 ± 5.89 years, respectively) (p = 0.332).[13] Furthermore, we found that prehypertensive participants had higher hemoglobin levels than normotensive subjects (Table 2). Other metrics, such as creatinine, UACR, cholesterol, lipid profiles, and total leukocyte count, did not, however, show significant differences between groups ($p > 0.05$). Bharath and Manjula, on the contrary, found that prehypertension was linked to noticeably greater levels of LDL and total cholesterol than in normal participants.[13] In a similar line, Licitra et al. discovered that prehypertensive participants had significantly ($p < 0.01$) higher cholesterol

Table 1: Baseline demographic and clinical characteristics of study participants

Parameter	*Normotensive (N = 43)*	*Prehypertensive (N = 58)*	*p-value*
Age (years)	Mean ± SD	Mean ± SD	0.2603
Gender (%)			0.2276
Male	53.5	41.4	
Female	46.5	58.6	
Smoking (%)			0.5516
Yes	34.9	29.3	
No	65.1	70.7	
Alcohol consumption (%)			0.4350
Yes	25.6	32.8	
No	74.4	67.2	

Table 2: Mean values of laboratory parameters in normotensive vs prehypertensive patients

Parameter	*Normotensive (N = 43)*	*Prehypertensive (N = 58)*	*p-value*
Hemoglobin (gm/dL)	12.3 ± 1.1	13.2 ± 0.8	<0.001
Total leukocyte count (/mm^3)	8800.6 ± 1767.7	8198.2 ± 1597.5	0.0764
Neutrophils (%)	55.8 ± 7.4	52.9 ± 9.6	0.1021
Lymphocytes (%)	34.2 ± 6.3	32.8 ± 8.4	0.3610
Platelet (lakh/mm^3)	2.62 ± 0.64	2.41 ± 0.58	0.0883
Fasting blood glucose (mg/dL)	95.2 ± 28.8	107.4 ± 32.1	0.0514
Cholesterol (mg/dL)	142.4 ± 38.5	153.0 ± 41.1	0.1911
Triglyceride (mg/dL)	214.6 ± 111.5	187. 9 ± 57.9	0.1212
VLDL (mg/dL)	47.9 ± 20.1	46.2 ± 19.1	0.6663
LDL (mg/dL)	65.4 ± 24.9	75.7 ± 30.5	0.0732
HDL (mg/dL)	36.0 ± 24.9	38.3 ± 12.5	0.5444
Creatinine (mg/dL)	0.9 ± 0.3	1.0 ± 0.4	0.1720

levels (218 ± 35 mg/dL) than normotensive subjects (196 ± 21 mg/dL).[11]

When comparing BP values between normotensive and prehypertensive individuals (Table 3), statistically significant differences were observed across all measurement periods ($p < 0.001$). Premeasurement readings for both SBP and DBP were notably higher in the prehypertensive group compared to normotensive individuals. Similarly, 24-hour monitoring data showed consistently elevated SBP and DBP values in prehypertensive individuals, indicating a persistent elevation in BP entire day. Daytime and nighttime measurements further reinforced these trends, with prehypertensive individuals exhibiting significantly higher SBP and DBP values compared to normotensive individuals during both periods. Licitra et al. also found significant differences in 24-hour ambulatory SBP between normotensive (119 ± 9 mm Hg) and prehypertensive (127 ± 9 mm Hg) subjects ($p < 0.001$), along with significant differences in DBP between groups ($p < 0.001$).[11] Normotensive and prehypertensive patients in the same study had significantly different SBP and DBP during the day ($p < 0.001$). Similarly, prehypertensive people had significantly higher SBP at night (107 ± 10 and 114 ± 10 mm Hg, respectively; $p = 0.001$) than normotensive people. Both prehypertensive and normotensive patients had considerably higher DBP ($p = 0.001$). Significant variations in SBP and DBP between prehypertensive and normotensive participants were found by Bharath and Manjula and Sinha et al. ($p < 0.001$).[13,14] Similarly, Farhan et al. noticed significant differences between mean 24-hour SBP and DBP measured *via* ABPM and those measured in an office setting ($p = 0.0001$).[15]

According to the circadian variation in BP, ABPM can categorize individuals into "dipper" and "nondipper" status. Dipper hypertension is defined physiologically by a nocturnal BP reduction exceeding 10% relative to daytime measurements. Conversely, if the nocturnal BP shows <10% decline from daytime values, it is classified as nondipper hypertension. Nondipping BP trends can indicate the severity of hypertension, particularly when correlated with additional risk factors and consequences. Daytime BP readings do not offer more predictive accuracy than overnight BP readings. The nondipping condition is frequently associated with the necessity for additional antihypertensive drugs for management, suggesting that a nondipping pattern may signify more severe pathology. Additionally, a nondipping pattern correlates with cardiovascular risk factors, end-organ damage, and subsequently an elevated risk of subsequent cerebrovascular incidents and secondary hypertension. Consequently, observing nocturnal BP variations can yield significant understanding of the management and prognosis of hypertension. In our study, we identified 55.2% of prehypertensive patients as dippers, demonstrating a nocturnal BP reduction over 10% relative to daytime readings, whereas the remaining 44.8% were classified as nondippers, indicating a reduction of 10% or less (Table 4). This corresponds with the results of Farhan et al., who documented analogous proportions of dippers (35.6%) and nondippers (64.4%).[15] In the present study, there were insignificant differences in premeasurement SBP and DBP values ($p = 0.0418$ and $p = 0.236$, respectively) or during day SBP and DBP values ($p = 0.5530$ and $p = 0.5271$, respectively) between dippers and nondippers. However, during daytime, both SBP ($p = 0.0197$) and DBP ($p = 0.0325$) were significantly higher in nondippers compared to dippers. The average SBP and DBP readings throughout the overnight period were notably reduced in the dipper group ($p < 0.001$). The findings align with those of Aksit et al. who similarly observed insignificant differences in mean SBP and DBP levels between groups during the day ($p = 0.802$, $p = 0.417$). However, the dipper group exhibited significantly lower mean SBP and DBP levels at night ($p = 0.001$, $p \leq 0.001$, respectively).[16] In comparison to the nondipper group, the dipper group experienced a significantly greater percentage change in both the SBP and DBPs ($p < 0.001$). The findings indicate that a dipper pattern in nocturnal BP is potentially linked to improved cardiovascular outcomes relative to a nondipper pattern.

C-reactive protein is an acute-phase protein that elevates in plasma during inflammatory responses. Hypertension correlates with low-grade systemic inflammation, resulting in elevated production of inflammatory substances such as CRP. Oxidative stress, recognized by an imbalance between reactive oxygen species (ROS) and antioxidant defenses, is frequently observed in individuals with hypertension. Oxidative stress can trigger inflammatory responses and contribute to elevated CRP levels. Activation of the renin–angiotensin–aldosterone system (RAAS), a key regulatory system in BP control, is implicated in hypertension.[17–19] Components of the RAAS, including angiotensin II, can provoke inflammation and lead to increased CRP levels. Multiple cross-sectional studies, as shown in Table 5, have consistently demonstrated elevated levels of Hs-CRP in hypertensive

Table 3: Mean blood pressure values in normotensive vs prehypertensive participants

BP measurement (mm Hg)	*Normotensive (N = 43)*	*Prehypertensive (N = 58)*	*p-value*
24-hour SBP	116.9 ± 8.4	130.1 ± 6.7	<0.001
24-hour DBP	73.2 ± 7.9	83.0 ± 6.5	<0.001
Daytime SBP	122.5 ± 8.2	133.8 ± 8.7	<0.001
Daytime DBP	75.3 ± 7.4	84.7 ± 6.0	<0.001
Nighttime SBP	118.1 ± 8.1	124.8 ± 8.1	<0.001
Nighttime DBP	72.9 ± 7.4	79.1 ± 7.8	<0.001

Table 4: Comparison of dipper and nondipper status in prehypertensive group

Parameter	*Dipper (N = 32)*	*Nondipper (N = 26)*	*p-value*
Nighttime SBP (mm Hg)	118.8 ± 7.5	127.5 ± 6.2	<0.001
Nighttime DBP (mm Hg)	74.2 ± 6.9	82.9 ± 6.3	<0.001
UACR (mg/gm)	25.9 ± 6.4	27.4 ± 7.6	0.4179
Hs-CRP (mg/L)	4.19 ± 1.57	4.95 ± 0.94	0.034

Table 5: Comparison of Hs-CRP values between normotensive and prehypertensive with other studies

Author	*Year*	*Sample size*	*Normotensive*	*Prehypertensive*
Saxena et al.[20]	2013	200	1.893 ± 0.74	5.93 ± 2.05
Bharat and Manjula[13]	2015	80	1.21 ± 0.19	1.49 ± 0.49
Sinha et al.[14]	2012	98	2.45 ± 1.35	7.89 ± 1.09
Present study	2023	101	1.96 ± 0.62	4.71 ± 2.14

Table 6: UACR and Hs-CRP levels in normotensive vs prehypertensive participants

Parameter	*Normotensive (N = 43)*	*Prehypertensive (N = 58)*	*p-value*
UACR (mg/gm)	23.8 ± 6.5	26.4 ± 8.1	0.0865
Hs-CRP (mg/L)	1.96 ± 0.62	4.71 ± 2.14	<0.001

individuals.[13,14,20] This relationship indicates that inflammation may be integral to the onset and advancement of hypertension. The observed differences in mean Hs-CRP levels between normotensive and prehypertensive individuals in our study support this notion. Specifically, the significantly lower mean Hs-CRP levels in normotensive individuals compared to prehypertensive individuals (1.96 ± 0.62 vs 4.71 ± 2.14, respectively; $p < 0.001$) suggest that inflammation may be more pronounced in individuals with prehypertension (Table 6).

The mean Hs-CRP level in dipper prehypertensive patients was 4.19 ± 1.57 mg/L, while in nondipper prehypertensive patients (Table 4), it was 4.95 ± 0.94 mg/L; and the difference was significant ($p = 0.034$). Turak et al. discovered that the serum levels of Hs-CRP in the nondipper group were markedly elevated compared to the other groups ($p < 0.001$).[21] In 2014, Tosu et al. examined the relationship between elevated levels of CRP, serum uric acid, and red blood cell distribution width (RDW) and nondipper hypertension. The authors observed that levels of CRP, RDW, and uric acid were markedly elevated in the nondipper hypertensive subjects when compared to both dipper hypertensive and the normotensive individuals ($p < 0.05$).[22]

The study by Cimen et al. also observed that nondippers had significantly raised levels of Hs-CRP than other groups ($p = 0.013$).[23] The reason for this significant difference could be related to the differing physiological profiles of dipper and nondipper prehypertensive patients. Nondippers tend to have less favorable cardiovascular profiles, including higher levels of inflammation, which could be reflected in their higher Hs-CRP levels compared to dippers. This finding could potentially suggest that nondippers are at an increased risk of CV events compared to dippers among prehypertensive patients, highlighting the importance of monitoring and managing inflammation in this population.

Clinical Implications

These findings highlight the potential utility of ABPM for the early detection of circadian BP abnormalities and their association with cardiovascular risk markers. Monitoring for dipper and nondipper status in prehypertensive patients could help stratify risk and guide early interventions. Given the association between nondipping patterns, inflammation, and renal stress, early lifestyle modifications or pharmacological interventions aimed at restoring normal BP circadian rhythms and reducing inflammation may benefit high-risk prehypertensive patients.

Limitations

The cross-sectional design and comparatively small sample size of this study restrict our capacity for establishing causation. Additionally, although we measured UACR and Hs-CRP as indicators of renal and inflammatory status, future studies with broader biomarkers may offer deeper insights. Longitudinal studies could further elucidate the progression from prehypertension to hypertension and associated cardiovascular risks.

Conclusion

This study emphasizes the importance of ABPM in prehypertensive patients, demonstrating that nondipping BP patterns are associated with elevated cardiovascular risk markers, including Hs-CRP and UACR. These findings underscore the potential of using circadian BP patterns as a tool to identify high-risk prehypertensive individuals for early intervention to prevent progression to hypertension and associated complications. Further research is warranted to explore targeted interventions for nondippers and the role of inflammation in cardiovascular risk progression.

References

1. Pannarale G, Moroni C, Acconcia MC, et al. The natural history of prehypertension. A 20-year follow-up. Eur Rev Med Pharmacol Sci 2017;21(6):1329–1334.
2. 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):2560–2571.
3. Hermida RC, Hermida RC. Ambulatory blood pressure monitoring in the prediction of cardiovascular events and effects of chronotherapy: rationale and design of the MAPEC study. Chronobiol Int 2007;24(4):749–775.
4. Gupta P, Nagaraju SP, Gupta A, et al. Prehypertension-time to act. Saudi J Kidney Dis Transpl 2012;23(2):223–233.
5. Izzedine H, Launay-Vacher V, Deray G. Abnormal blood pressure circadian rhythm: a target organ damage? Int J Cardiol 2006;107(3):343–349.
6. Bautista LE, Vera LM, Arenas IA, et al. Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF-α) and essential hypertension. J Hum Hypertens 2005;19(2):149–154.
7. Sun L, Gao YH, Tian DK, et al. Inflammation of different tissues in spontaneously hypertensive rats. Acta Physiol Sin 2006;58(4):318–323.
8. Tanito M, Nakamura H, Kwon YW, et al. Enhanced oxidative stress and impaired thioredoxin expression in spontaneously hypertensive rats. Antioxid Redox Signal 2004;6(1):89–97.
9. Vasan RS. Biomarkers of cardiovascular disease: molecular basis and practical considerations. Circulation 2006;113(19):2335–2362.
10. Jamalludin AR, Azarisman SM, Aidea NM, et al. High sensitivity C-reactive protein in pre-hypertensive young adults. Mater Today Proc 2019;16:2309–2312.
11. Licitra R, Acconcia MC, Puddu PE, et al. Ambulatory blood pressure monitoring in prehypertensive subjects. Cardiovasc Hematol Disord Drug Targets 2012;12(1):44–50.
12. Zare MG, Okati-Aliabad H, Ansari-Moghaddam A, et al. Prevalence and risk factors of pre-hypertension and hypertension among adults in Southeastern Iran: findings from the baseline survey of the Zahedan adult cohort study. PLoS One 2023;18(12):e0295270.
13. Bharath T, Manjula P. Lipid profile but not highly sensitive C-reactive protein helps distinguish prehypertensives from normal subjects. J Nat Sci Biol Med 2015;6(2):347.
14. Sinha MD, Gilg JA, Kerecuk L, et al. Progression to hypertension in non-hypertensive children following renal transplantation. Nephrol Dial Transplant 2012;27(7):2990–2996.
15. Farhan H, Al-Hasani M, Misbah M, et al. Comparative study of ambulatory blood pressure monitoring and clinic blood pressure measurement in the risk assessment and management of hypertension. Sultan Qaboos Univ Med J 2010;10(3):370.
16. Aksit E, Gursul E, Samsa M, et al. Non-dipper hypertension is associated with slow coronary flow among hypertensives with normal coronary angiogram. Cardiovasc J Afr 2017;28(1):14–18.
17. Shrivastava AK, Singh HV, Raizada A, et al. C-reactive protein, inflammation and coronary heart disease. Egypt Heart J 2015;67(2):89–97.

18. Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. Front Immunol 2018;9:754.
19. Vasanthii R, Kaarthikeyan G, Sasirekha G, et al. Prevalence of hs-CRP among Indians with hypertension. Bioinformation 2022;18(10):1041.
20. Saxena T, Agarwal BK, Sharma VK, et al. hs-CRP—a new risk assessment tool in prehypertensive subjects. Biosci Biotechnol Res Asia 2013;10: 921–924.
21. Turak O, Özcan F, Tok D, et al. Serum uric acid, inflammation, and nondipping circadian pattern in essential hypertension. J Clin Hypertens 2013;15(1): 7–13.
22. Tosu AR, Demir S, Selcuk M, et al. Comparison of inflammatory markers in non-dipper hypertension vs. dipper hypertension and in normotensive individuals: uric acid, C-reactive protein and red blood cell distribution width readings. Adv Interv Cardiol 2014;10(2):98–103.
23. Cimen T, Bilgin M, Akyel A, et al. Endocan and non-dipping circadian pattern in newly diagnosed essential hypertension. Korean Circ J 2016;46(6): 827–833.

ORIGINAL ARTICLE

Influence of Problem-based Learning Method on Learning Outcomes in Medical Curriculum

Saara Banu EPM[1], Yazhini Karuppiah[2*], Bhuvaneswari K[3]

Received: 18 February 2025; *Accepted:* 21 March 2025

Abstract

Introduction: Problem-based learning (PBL) is a student-centered learning approach in which students learn through analyzing and solving problems.

Justification: Traditional teaching program is in the form of a dictated lecture and is teacher-centered. A larger number of topics can be covered without active student participation. In PBL, which promotes deep learning, students learn to justify their knowledge with the help of cognitive skills and complex thinking.

Methods: This retrospective study was done after obtaining Institutional Human Ethics Committee (IHEC) approval. Data collected from three internal assessment examinations (IAEs) written between the period of January 2017 and August 2017 by 151 students pursuing second-year MBBS training in the Department of Pharmacology. Examination papers for second-year MBBS students contain questions such as short notes, ultrashort, and PBL.

Results: Wilcoxon Mann–Whitney test analysis of IAE-1 with IAE-2 and IAE-1 with IAE-3 in SPSS software gave *p*-value—0.393 and 0.020, respectively. Using analysis of variance (ANOVA), IAE-2 with PBL and IAE-3 with PBL showed *p*-value 0.001, which was statistically significant. There was an increase in the pass percentage [number of students who scored 40 and above in IAE-3 (with PBL) when compared to IAE-1 (without PBL)].

Conclusion: This audit showed definite knowledge improvement by the students using PBL as a tool along with a traditional teaching program.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1079

Introduction

Problem-based learning (PBL) is a learning program which promotes self-regulated learning, improves knowledge, and develops complex thinking.[1] PBL was first introduced in 1969 at McMaster University, Canada.[2] The two scholars, Howard Barrows and Robyn Tamblyn,[3] were the first to publish a book on PBL: "Problem-based learning: An approach to medical education" in 1980.

Problem-based learning is a student-centered learning approach in which students learn through analyzing and solving problems. PBL replaces teacher-centered traditional teaching programs, enhances students' critical thinking, and promotes knowledge retention for a much longer period due to a deep understanding of the subject. In a traditional teaching program, the ideas are transferred directly from the minds of the tutor to students, as depicted in Figure 1, whereas in PBL, which promotes deep learning, students learn to justify the knowledge applied with the help of cognitive skills,[4] as depicted in Figure 2.

In traditional lecture-based learning, students passively listen to the lecturer which does not promote complex learning, and they fail to connect ideas with the facts. PBL helps students gain immense knowledge and promotes self-directed learning. PBL promotes constructive learning and improves cognitive skills.

This study aims to evaluate the percentage of knowledge gained through PBL method in the second-year MBBS students' learning program and to compare the percentage of marks obtained through PBL and traditional teaching assessment.

Materials and Methods

- Ethical clearance: Institutional Human Ethics Committee has exempted this study from Ethical Review, EC letter no. 17/333; dated October 27, 2017.
- Study population: Second-year MBBS students, 2015 batch.
- Place: Department of Pharmacology, PSG IMSR.
- Sample size: 151.
- Duration: 6 months.

Methods

Problem-based learning methods were implemented through class activities by small-group teaching. The students were randomly sorted into small groups under a facilitator. They were provided with a clinical scenario with structured questions. Students were encouraged to actively participate in group discussion; they analyze, interpret, and identify what is known and how to apply it to bring about a solution. Internal assessment examination (IEA) papers of the 2015 batch second-year MBBS which includes theory papers (recall type of questions having short notes, very short answers, and PBL (structured questions) were used to analyze the performance and outcome. IAE-1 with only the recall type of questions without PBL was used to compare the mean scores of the other two IAE papers (IAE-2 and IAE-3) with PBL, as shown in Table 1.

The audit focused on:

- Assessing the knowledge of students based on problem-based learning.
- PBL and its impact on students' performance.

Statistical Analysis

One-way analysis of variance (ANOVA) was used to compare students' performance between groups, Mann–Whitney *U* test was applied to compare students' performance within the groups, and the International Organization for Standardization (ISO) grading system was used to grade the students' scores.

Results

The scores obtained by the students in the IAE-1–3 are shown in Table 2.

Normal distribution pattern of the students' scores in the three IAEs is shown in Figure 3. The blue curve represents IAE-1 score of 151 students; the red curve on the

[1]Assistant Professor, Department of Pharmacology, Government Medical College & Hospital, The Nilgiris, Ooty; [2]Associate Professor, Department of Microbiology, Saveetha Medical College and Hospital, SIMATS University, Thandalam; [3]Professor and HOD, Department of Pharmacology, PSG Institute of Medical Sciences & Research, Coimbatore, Tamil Nadu, India; *Corresponding Author

How to cite this article: EPM SB, Karuppiah Y, Bhuvaneswari K. Influence of Problem-based Learning Method on Learning Outcomes in Medical Curriculum. J Assoc Physicians India 2025;73(8):32–34.

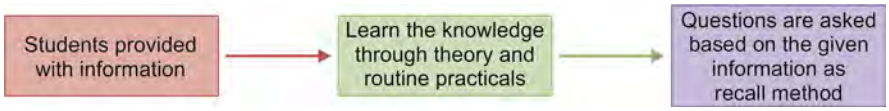


Fig. 1: Traditional teaching program

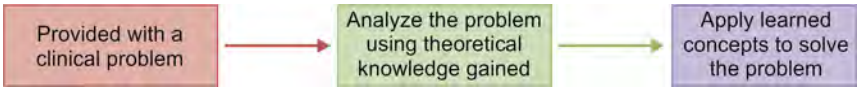


Fig. 2: Problem-based learning

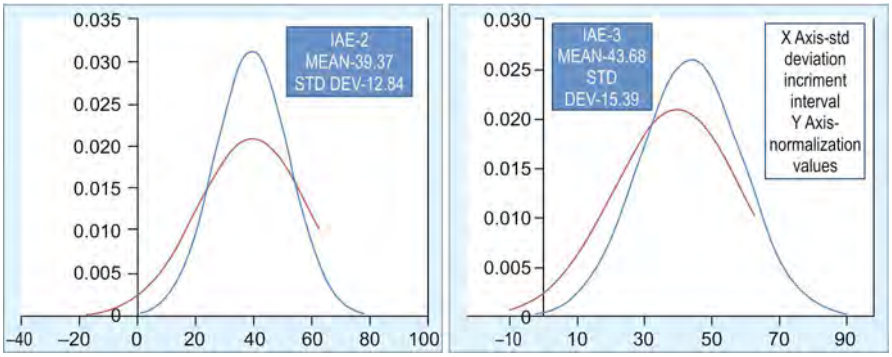


Fig. 3: Normal distribution pattern of the students' score in the three IAE.

left represents IAE-2, and on the right, that of IAE-3.

Analyzing IAE-1 and IAE-2 by comparing the mean values using Mann–Whitney *U* test in SPSS software gives a *U* value—11,047.5 and *Z* score—0.26625 with *p*-value—0.39358 (*p*-value >0.05). Analyzing IAE-1 with IAE-3 by comparing the mean scores using Mann–Whitney *U* test in SPSS software gives U value—9513 and Z score—2.30903 with *p*-value—0.02088 (statistically significant). Statistical analysis reports are shown in Tables 3 and 4. Using one-way ANOVA, IAE-2 with PBL and IAE-3 with PBL gives *p*-value 0.001 (statistically significant), as shown in Table 5.

It was noticed that there was a significant improvement in students' performance in IAEs with PBL, and the percentage of students below a score of 34 had been reduced. There was an increase in students' number in the score group of 50–74 in IAE-2 and IAE-3 with PBL, as depicted in Figures 4 and 5.

Table 1: Scores of recall type questions vs PBL

Sr. no.	*IAE-1 (recall type questions)*	*IAE-2/PBL-2*	*IAE-3/PBL-3*

Table 2: Scores obtained by the students in the internal assessment examinations

Sr. no.	*IAE-1*	*IAE-2*	*IAE-3*
1. Sum	5,865.5	5,984.5	6,596.5
2. Mean	39.63176	39.37171	43.68543
3. Median	37.75	38.5	42
4. Mode	43	38.5	40.5
5. Standard deviation	±19.09269	±15.39604	±12.84703

Table 3: Descriptive statistics tests of within-subjects effects SPSS version 19

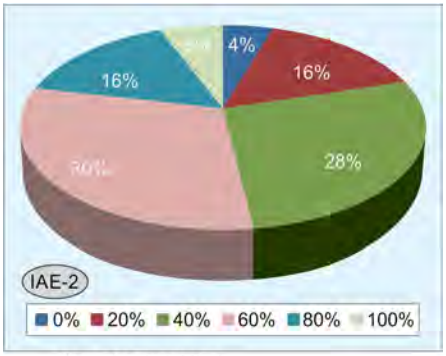
	N	*Minimum*	*Maximum*	*Mean*	*Standard deviation*	*Skewness*	
	Statistic	*Statistic*	*Statistic*	*Statistic*	*Statistic*	*Statistic*	*Standard error*
IAE-3	151	15.00	81.00	43.6854	12.84703	0.165	0.197
IAE-2	151	4.0	81.0	39.298	15.4204	0.207	0.197
IAE-1	151	0.00	85.50	38.3974	19.92478	0.253	0.197

Table 4: Paired samples statistics

		Mean	*N*	*Standard deviation*	*Standard error mean*
Pair 1	PBL-2	9.8675	151	8.03050	0.65351
	PBL-3 (out of 30)	8.715	151	5.5918	0.4551

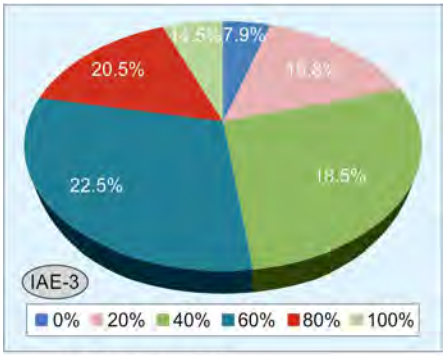
Table 5: One-way ANOVA, *p*-value 0.001 (statistically significant)

		Sum of squares	*Degrees of freedom (df)*	*Mean square*	*F*	*Significance*
IAE-2	Between groups	28,594.944	97	294.793	2.212	0.001
	Within groups	7,197.804	54	133.293		
	Total	35,792.748	151			
IAE-3	Between groups	21,500.680	97	221.656	2.323	0.003
	Within groups	5,152.115	54	95.410		
	Total	26,652.794	151			



0% - Not attempted
20% - **1** question correctly answer
40% - **2** questions correctly answered
60% - **3** questions correctly answered
80% - **4** questions correctly answered
100% - **5** questions correctly answered

Fig. 4: Number of PBL questions correctly answered by the students in IAE-2



0% - Not attempted
20% - **1** question correctly answer
40% - **2** questions correctly answered
60% - **3** questions correctly answered
80% - **4** questions correctly answered
100% - **5** questions correctly answered

Fig. 5: Number of PBL questions correctly answered by the students in IAE-3

Discussion

In lecture-based traditional teaching programs, face-to-face interaction between the students and teacher is possible. It is usually of mixed type, i.e., didactic and interactive.[4] A larger number of topics can be covered. But learning is an active process which requires active student participation. In case of lecture-based learning, students' active participation is less. Attention is not the same throughout the lecture. On many occasions, students take a passive role because traditional teaching methods are usually teacher-centered.

Problem-based learning methods are used most frequently in medical schools as an educational tool. Students are provided with a clinical scenario. The effectiveness of PBL can be achieved based on the nature of the clinical scenario. PBL method promotes in-depth learning and better retention[4] and helps students confidently face their examinations. PBL is student-centered and self-directed learning. Active group discussions through small-group teaching programs help students develop communication skills. It helps students to take the initiative in learning. Prior knowledge is essential in solving PBL questions, as it helps students to recall basic facts. PBL activities promote critical thinking.[5]

Problem-based learning activities are time-consuming. Only a limited number of topics can be covered. They require manpower to support the needs of the students. They require proper preparation of the scenario, time, and planning.[6]

Though PBL is an effective teaching program implemented in many teaching institutes across the countries, our audit focuses only on the 20% improvement in the class pass percentage using PBL when compared with theory-based examination without PBL (IAE-1) based on a study by Ahlam and Gaber[7] titled "Impact of problem-based learning on students critical thinking disposition, knowledge acquisition and retention" done in Mansoura University, Egypt. On statistical analysis, there were significant improvements in students' thinking capacity in the post-PBL group when compared with preintervention group. This study showed a 20% improvement in the mean value of students' performance in the post-PBL group. Since PBL is not the recommended teaching program as per our university guidelines, a 20% improvement in the class pass percentage when compared with a lecture-based learning program is used as the standard. One-way ANOVA showed improvement in individual students' performance (p-value –0.001). The estimated mean value of students' scores had also improved successively.

Improvement in the PBL scores in the second and third IAEs was associated with a corresponding improvement in theory marks as well. The number of students in the score group below 34 had decreased. The number of students in the score group between 35 and 49 had increased. The number of students in the score group between 50 and 70 had increased. There was successive improvement in the overall pass percentage of students in IAE-2 (with PBL) and IAE-3 (with PBL) when compared to IAE-1 without PBL.

Conclusion

Problem-based learning has a significant role in enhancing the academic performance of second-year MBBS students. This audit compares students' performance (marks) of traditional lecture-based teaching in the IAE-1 (without PBL) with that of IAE-2 and IAE-3 (with PBL), showing statistically significant results and definite knowledge acquisition by the students using the PBL teaching program, comparable to international studies.

Limitations of the Study

- This audit was based on the performance of only a single batch of second-year MBBS students.
- Students' interest is one of the important factors in gaining knowledge through learning pharmacology and applying pharmacological principles.

Orcid

Saara Banu EPM https://orcid.org/0000-0002-1802-0646
Yazhini Karuppiah https://orcid.org/0000-0001-5592-0013

References

1. Khan IA, Al-Swailmi FK. Perceptions of faculty and students regarding problem based learning: a mixed methods study. J Pak Med Assoc 2015;65(12):1334–1338.
2. Smits PB, Verbeek JH, De Buisonje CD. Problem based learning in continuing medical education: a review of controlled evaluation studies. BMJ 2002;324(7330):153–156.
3. Barrows HS, Tamblyn R. Problem-based learning: an approach to medical education. New York: Springer Pub Co, 1980.
4. Balagué Mola N. The use of ISO 9001 quality standard in higher education institution libraries. Lib Serv 2007;11(3):66–78.
5. Davis D, O'Brien MA, Freemantle N, et al. Impact of formal continuing medical education: do conferences, workshops, rounds, and other traditional continuing education activities change physician behaviour or health care outcomes? JAMA 1999;282:867–874.
6. McParland M, Noble LM, Livingston G. The effectiveness of problem-based learning compared to traditional teaching in undergraduate psychiatry. Med Educ 2004;38(8):859–867.
7. Ahlam ES, Gaber H. Impact of problem-based learning on students critical thinking dispositions, knowledge acquisition and retention. J Educ Pract 2014;5(14):74–83.

ORIGINAL ARTICLE

Incidence and Pattern of Transfusion Reactions and its Association with Blood and its Components in a Tertiary Care Hospital

Sonia Gupta[1*], Rajesh Kumar[2], Shruti Kakkar[3]

Received: 01 February 2024; *Revised:* 03 March 2025; *Accepted:* 26 March 2025

Abstract

Objectives: Transfusion medicine has made substantial progress in research, and blood transfusions are now safer than ever before. Still, the inherent risk of transfusion reactions (TRs) continues with transfusion of blood and blood components. The study was designed to analyze the incidence and nature of TRs reported in the blood center.

Materials and methods: A retrospective review of all TRs reported to the blood center was retrieved from incident reporting forms from January 2020 to December 2022. All acute transfusion reactions (ATRs) were tabulated and analyzed by the blood transfusion officer and classified according to National Blood Transfusion guidelines. Data were described in terms of range, mean ± standard deviation (± SD), median (IQR), frequencies (number of cases), and relative frequencies (percentages), as appropriate.

Results: A total of 1,65,121 blood and blood components were issued, and ATRs reported were 296 (0.18%). The median (IQR) age of the patient was 45–60, with M:F of 1.3:1. Febrile nonhemolytic transfusion reactions (FNHTR) 151 (51%) were the most common ATRs, followed by allergic TRs 111 (37.5%). The estimated risk of transfusion reaction per 1,000 units was highest with whole blood (WB) 3.84 ($p = 0.038$), followed by packed red blood cells (PRBCs) 2.85 ($p = 0.001$), and single donor platelet (SDP) 1.47 ($p = 0.571$). The most common symptoms observed were fever 31.8%, followed by chills 28.7%, and rashes 27.4%. FNHTR (27/151) 17.8% were reported most frequently from gastroenterology, allergic (26/111) 23.4% from emergency, and delayed hemolytic transfusion reactions (DHTR) (9/9) 100% from thalassemia day care center ($p = 0.001$).

Conclusion: The overall incidence of TRs was 0.18%. The incidence of actual TRs remains underestimated due to lack of awareness regarding TRs among healthcare professionals.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1081

Introduction

Transfusion reactions (TR) are defined as adverse events associated with the transfusion of whole blood (WB) or one of its components. These may range in severity from minor to life-threatening. The estimated frequency of these adverse TR ranges from 0.2 to 10%, and their mortality is approximately 1 in 2,50,000.[1] The TRs can occur during the transfusion (acute TR) or days to weeks later (delayed TR) and may be immune or nonimmune depending upon the pathophysiology.[2] Hemovigilance is a systematic surveillance of adverse TR, and the primary objective of the program is to track adverse events associated with transfusion of blood and blood products. The lack of robust hemovigilance systems across the country makes it challenging to assess the true and actual incidence of these reactions.

Materials and Methods

A retrospective observational study was carried out in a tertiary care hospital from January 2020 to December 2022. This study was approved by the Ethics and Research Committee of Dayanand Medical College and Hospital in accordance with the World Medical Association Declaration of Helsinki, vide no. DMCH/IEC/2023/221 dated July 18th, 2023. All the reactions were analyzed as per the algorithm as shown in Figure 1.

The following work-up was performed after receiving the residual blood bag along with the blood transfusion set and the patient posttransfusion blood sample:

- Clerical check for identification error.
- Visual check of posttransfusion plasma for hemolysis.
- Comparing patient pre- and posttransfusion sample for proper identification.
- Performing ABO and Rh grouping and direct antiglobulin test (DAT) on posttransfusion sample and compare with pretransfusion samples.
- Bacteriological testing was done by sending the blood from blood bag for culture.
- Urine routine for examination of color/microscopic RBCs.

The purpose of the present study is to estimate the incidence and pattern of transfusion related events in our center.

Statistical Analysis

Data were described in terms of range; mean ± standard deviation (± SD), median (IQR), frequencies (number of cases), and relative frequencies (percentages), as appropriate. To compare categorical data, the Chi-squared (χ^2) test was performed. All statistical calculations were done using Statistical Package for the Social Sciences (SPSS) for Microsoft Windows 10 Pro.

Results

A total of 1,65,121 blood and its components were issued over a period of 3 years. These comprised 1,821 (1.10%) WB, 69,710 (42.2%) packed red blood cells (PRBCs), 69,200 (41.9%) fresh frozen plasma (FFP), 49 (0.02%) single donor plasma, 1,747 (1.06%) cryoprecipitate (CRYO), 17,161 (10.4%) random donor platelet (RDP), and 5,433 (3.3%) single donor platelet (SDP). The TRs were observed in 296 (0.18%) recipients.

The median (IQR) age of the patients was 45 years (31–60), with an M:F ratio of 1.3:1. The TRs were most frequent in the age-group >60 years (23.3%), followed by the age-group 41–50 years (20.6%), with 11.8% TRs in patients <21 years of age. B positive Rh blood group (37.2%) showed maximum TRs, followed by O Rh positive blood group (31.8%). PRBC transfusion (67.2%) showed a higher incidence of TRs, followed by FFP (24.3%). No reaction was observed with CRYO or single donor plasma. It was also observed

[1]Associate Professor; [2]Professor, Department of Immunohematology and Blood Transfusion; [3]Associate Professor, Department of Pediatrics, Dayanand Medical College and Hospital, Ludhiana, Punjab, India; *Corresponding Author

How to cite this article: Gupta S, Kumar R, Kakkar S. Incidence and Pattern of Transfusion Reactions and its Association with Blood and its Components in a Tertiary Care Hospital. J Assoc Physicians India 2025;73(8):35–39.

that TRs were more in patients receiving multiple transfusions ($p = 0.010$), with a mean of 2.19 ± 2.57.

Transfusion reactions were observed most frequently within 30–60 minutes (33.4%) of starting transfusion, with a mean of 6.59 ± 42.18 minutes ($p = 0.010$). Nearly one-third of TRs were observed with as little as 20–60 mL of product transfused, with a mean of 113 ± 69.02 mL. Most TRs were reported in the department of gastroenterology ($n = 48$; 16.2%), followed by emergency ($n = 46$; 15.5%). The estimated risk of TRs per 1,000 units was maximum with WB 3.84 ($p = 0.038$), followed by PRBC 2.85 ($p = 0.001$), and minimum with RDP 0.58 ($p = 0.001$), as shown in Table 1.

The most common immune-mediated reactions encountered in our study were febrile nonhemolytic transfusion reaction (51%), followed by allergic transfusion reaction (37.8%), anaphylactic reaction (1.4%), hemolytic transfusion reaction (0.7%), and transfusion-related acute lung injury (TRALI) (0.3%). The nonimmune-mediated reactions recorded were transfusion-associated circulatory overload (TACO) (1%) and transfusion-associated hypotension (TAH) (2.4%). Delayed hemolytic transfusion reactions (DHTR) were seen in 3% of cases. All the recipients were multitransfused, transfusion-dependent thalassemia.

The common symptoms and signs observed during TRs are shown in Figure 2A. PRBC transfusions were associated with TR in 199 recipients (0.3%), the most common being febrile nonhemolytic transfusion reactions (FNHTR) ($n = 142$; 94%), as shown in Table 2. TRs were observed in 72 FFP transfusion recipients (0.1%), allergic reaction being the most frequent ($n = 64$; 57.1%). SDP and RDP transfusions were associated with only allergic reactions in 8/5,433 (0.14%) and 10/17,161 (0.05%) recipients, respectively. It was seen that in recipients younger than 21 years of age, FNHTR (57.1%), followed by DHTR (20%) and allergic (20%), were most common, whereas in older recipients, FNHTR (50.2%) and allergic (40.2%) were common ($p = 0.001$). FNHTR (27/151) was reported most frequently from the department of gastroenterology, allergic (26/112) from emergency, and DHTR (9/9) from thalassemia day care center ($p = 0.001$), as shown in Figure 2B. The year-wise risk of transfusion reaction per 1,000 units is shown in Figure 2C.

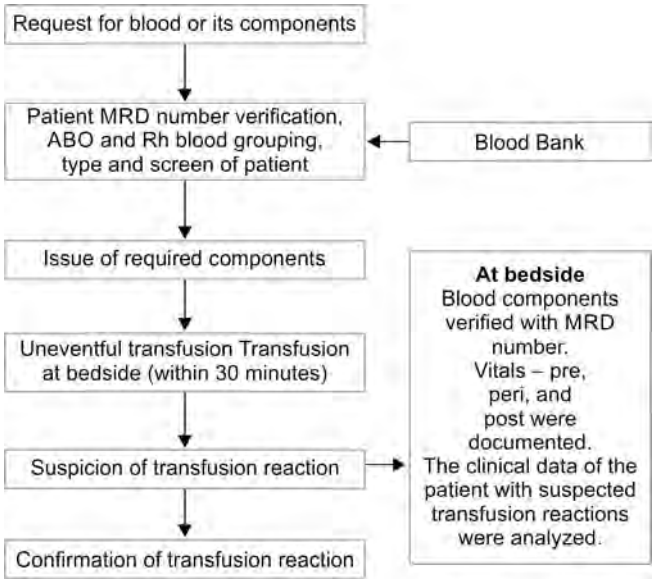


Fig. 1: Algorithm for work-up of issuing of blood and its components

Discussion

The safe transfusion of blood and its components requires strict adherence in maintaining the blood cold chain. The "blood cold chain" is the system for storing and transporting blood and its components so that they are kept at the correct temperature at all times from collection to transfusion. Any break in the blood cold chain increases the risk of a small number of contaminating bacteria growing in lethal numbers, especially platelets, which are kept at room temperature at 22–24°C, posing a threat of transfusion reaction. The blood and the blood components should be transfused within 30 minutes after issue from the blood bank.

The incidence of TRs observed in our study was 0.18%. Table 3 shows the frequency of TRs reported in various national and international studies, ranging from 0.73 to 9.45%.[3–11] The frequency of TRs in females was lower than in males (43.6 vs 56.4%), as shown in a similar study by Kumar et al. (45.7/54.3%).[3] The majority of TR occurred due to PRBCs (67.2%), as found in a similar study by Prakash et al. (42.8%).[12] Most of the TRs in our study were nonhemolytic, out of which the commonest was FNHTR, 51%, followed by allergic, 37.8%. In the study by Pahuja et al.[10] the frequency of FNHTR and allergic was 54.7/41.4%.

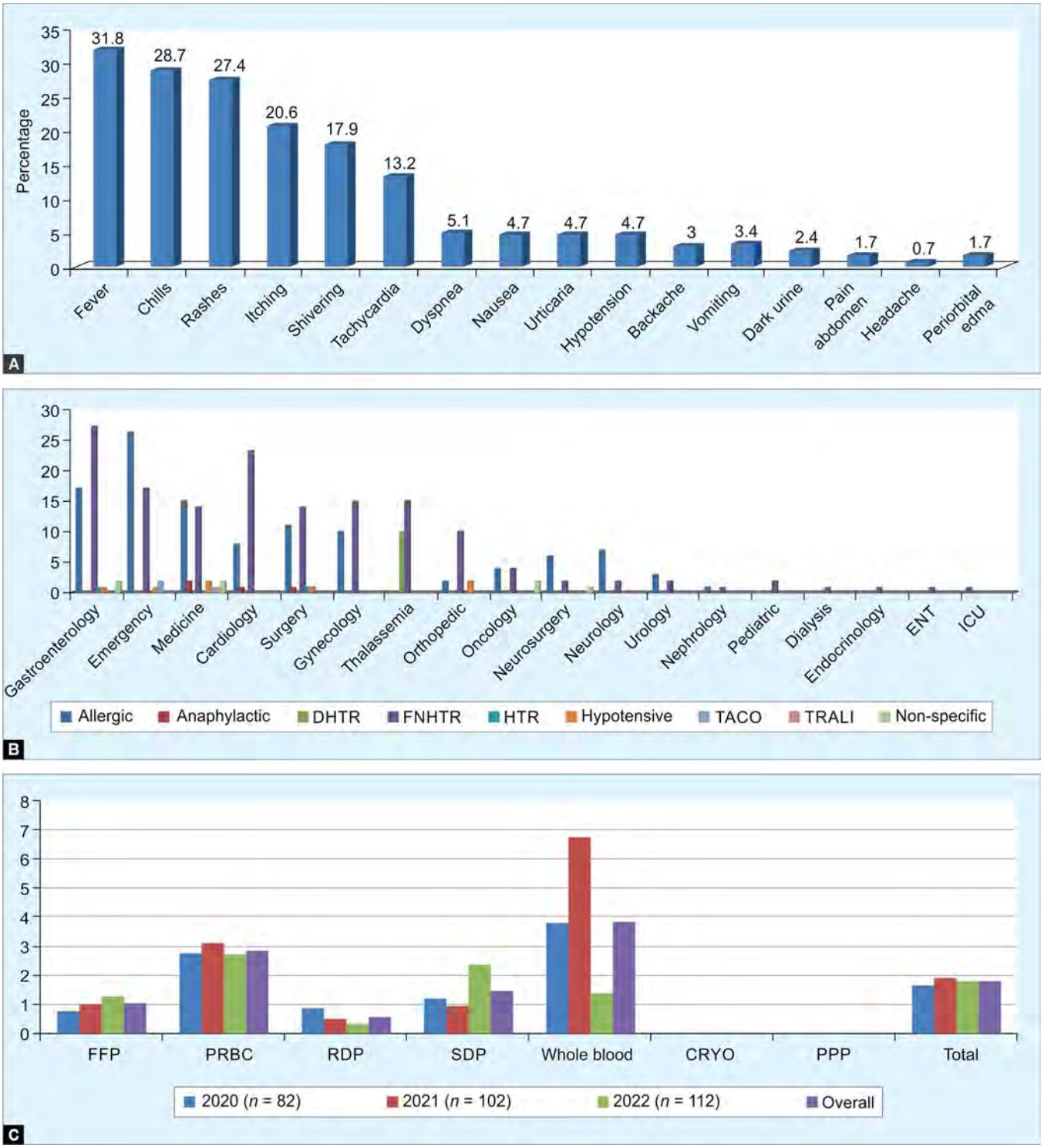
The most common TR observed in our study was FNHTR, 51%, as shown by Khalid et al., who reported 41.9%.[13] Ramanathan reported 51.4%.[14] It was observed with 94.0% PRBC, followed by 3.97% FFP and 1.98% WB in a similar study by Sidhu et al.[15] The most common presenting symptoms were fever, chills, and shivering. Nausea and headache were also seen in a few cases.

Human leukocyte antigen (HLA), granulocyte, and platelet-specific antibodies have been implicated in the pathogenesis of FNHTR. The recipient's antibodies react with

Table 1: The total supply and estimated risk of TR per thousand units of blood and blood components

	Total supply	*Total supply per 1,000*	*Reaction*	*Per 1,000 reaction*	*Chi-square value*	*p-value*
FFP	69200	41.9%	72	1.04	37.535	0.0001
PRBC	69710	42.2%	199	2.85	75.754	0.001
RDP	17161	10.4%	10	0.58	15.628	0.001
SDP	5433	3.3%	8	1.47	0.321	0.571
WB	1821	1.1%	7	3.84	4.306	0.038
CRYO	1747	1.1%	0	0.00	3.165	0.078
PPP	49	0.0%	0	0.00	0.008	0.767
Total	165121	100.0%	296	1.79		

$p < 0.05$ significant



Figs 2A to C: (A) Signs and symptoms of TRs; (B) TRs with respect to different clinical departments; (C) Year-wise risk of TR per thousand units of blood and blood components transfused

transfused antigens, leading to activation of the complement system and release of cytokines (IL-1), which is capable of causing fever. The most effective way to prevent FNHTR is prestorage leukocyte depletion, causing removal of WBC before the release of cytokines, by Heddle.[16]

Febrile nonhemolytic transfusion reactions was defined by the International Society of Blood Transfusion and the International Hemovigilance Network (IHN) as the presence of fever (body temperature ≥38°C, or an increase of >1°C from the pretransfusion temperature) during or within 4 hours after transfusion, or with fear of cold, chills, headache, nausea, and other symptoms, to the exclusion of hemolytic TR, bacterial contamination, and other potential factors.[17]

The patients were managed by immediately stopping the transfusion and giving antipyretics. The relatively high risk of FNHTR in our study could be because

Table 2: Number of TRs with respect to blood and its components

Type of reaction	*Component*										*Total*
	FFP		*PRBC*		*RDP*		*SDP*		*WB*		
FNHTR	6	3.97%	142	94.0%	0	0.0%	0	0.0%	3	1.98%	151
Allergic	64	57.1%	28	25.0%	10	8.9%	8	7.1%	2	1.78%	112
DHTR	0	0.0%	9	100%	0	0.0%	0	0.0%	0	0.0%	9
Hypotensive	1	14.2%	5	71.4%	0	0.0%	0	0.0%	1	14.2%	7
Anaphylactic	0	0.0%	4	100%	0	0.0%	0	0.0%	0	0.0%	4
TACO	0	0.0%	2	66.6%	0	0.0%	0	0.0%	1	33.3%	3
HTR	0	0.0%	2	100%	0	0.0%	0	0.0%	0	0.0%	2
TRALI	0	0.0%	1	0.5%	0	0.0%	0	0.0%	0	0.0%	1
Nonspecific	1	14.2%	6	85.7%	0	0.0%	0	0.0%	0	0.0%	7
Total	72		199		10		8		7		296

Table 3: Comparative studies of incidence of TRs

Name of the study	*Allergic reaction (%)*	*Anaphylactoid reaction (%)*	*FNHTR (%)*	*HTR (%)*	*Hypotensive reaction (%)*	*TACO (%)*	*TRALI (%)*	*Other (%)*	*Incidence (per 1,000 components)*
Kumar et al.[3]	51.1	5.1	35.7	2.6	–	0.5	0.5	2.5	0.5
Shajil et al.[4]	53.2	–	36.3	1.2	1.3	–	–	7.8	0.4
Payandeh et al.[5]	49.2	–	37.2	–	6.8	–	–	6.8	9.45
Mafirakureva et al.[6]	34	1.4	58.5	5.2	0.4	0.25	0.25	–	0.46
Bassi et al.[7]	24	–	73	1	1	–	–	1	3.98
Sharma et al.[8]	65.6	3.12	28.1	–	–	–	–	3.18	9.26
Philip et al.[9]	40.14	0.70	51.40	4.22	–	0.70	–	2.81	0.73
Pahuja et al.[10]	41.4	1.27	54.7	1.27	–	0.955	0.31	–	1.95
Saha et al.[11]	49.2	1	25.47	3	5.22	4	3	1.49	1.39
Present study	37.5	1.4	51	0.7	2.4	1	0.3	2.4	1.80

of the lack of universal leukoreduction of the components in our blood center. We have shifted to 80% leukoreduction, so most of the reactions reported are due to nonleukoreduced blood and its components. Leukoreduced PRBC and filters are being exclusively used for hemato-oncology patients in our hospital. The average time lapse from blood components issue to bedside transfusion of the components is within 30 minutes, thereby decreasing the possibility of TR.

Allergic reaction was the second commonest TR (37.8%) as shown in similar studies by Sidhu et al.[15] (41.5%) and Joy et al. (39.4%).[18] SDP and RDP transfusions were associated with only allergic reactions. The allergic reactions in SDP were probably due to sensitization to plasma constituents that cannot be filtered out. Majority of patients presented with rash, itching, and urticaria. Fever and periorbital edema were also seen in a few cases. FFP (64/112; 57.1%) was the most common component ordered by the physician for patients with deranged coagulation profile and thawed in a plasma water bath at 37°C. Allergic reactions are commonly due to transfusion of allergens (e.g., donor-ingested food and medications) and polymorphic serum proteins like haptoglobins, C3, C4, transferrin, albumin, etc., which react with IgE antibody bound to basophils or mast cells in the recipient's blood. This interaction results in release of C3a, C5a, histamine, prostaglandins D_2, leukotrienes C and D_4, causing increased vascular permeability. Histamine release causes rashes, itching, and edema.

Anaphylactic reactions were seen in 4/1,65,121 (0.002%) patients with transfusion of PRBCs. Patients presented with rashes, itching, and hypotension in a similar study by Salmani et al.[19] It is due to IgA deficiency of the recipient and subsequent formation of anti-IgA by Sandler et al.[20] These reactions can be reduced by giving washed leukodepleted PRBCs.

A single case of TRALI was reported in our study in a female patient, with an incidence of 0.0006%. TRALI reported in various studies in Western literature ranges from 0.014 to 0.08%.[21] It was seen with PRBC transfusion. Patient presented with fever, dyspnea, and tachycardia, as shown in a similar study by Joy et al.[18] X-ray of the patient showed bilateral infiltrates. The donor sample could not be evaluated for antineutrophilic antibodies. TRALI is rare but an important mortality associated with transfusion. It is a great mimicker of a variety of clinical conditions and is often underdiagnosed. It can be reduced by careful selection of donors, using plasma from male donors, and screening female donors for HLA and human neutrophilic antibodies, which are strong risk factors.

Acute hemolytic transfusion reaction was seen in 0.001% of all transfusions. One reaction was due to ABO mismatch, as B positive blood was transfused to an A positive patient by human error. Baele et al.[22] reported bedside transfusion error in 12.4 per thousand transfusions. In order to reduce the chances of human error, our hospital policy recommends a trained and competent healthcare worker to collect blood from the blood center with appropriate documentation using patient identifier, and final check to be conducted next to the patient at bedside by a trained staff who administered the product using the same identifier. The other case was due to alloimmunization. The antibody was present in low titer and could not be detected during routine crossmatching, as shown in a similar study by Shajil et al.[4] who reported an incidence of 1.29%. HTR was seen with only PRBC transfusion, and patients presented with

fever, chills, abdominal pain, and dark-colored urine in our study.

Among the nonimmune-mediated TR, TAH and TACO were also seen in our study. TAH is defined as a drop in systolic BP ≥30 mm Hg and a systolic BP ≤80 mm Hg. TAH was seen in 2.4% in our study. It was seen with 71.4% of PRBC, 14.2% of WB, and 14.2% of FFP transfusions in our study. The reported incidence of TAH varied in literature, as shown by Shajil et al.[4] (1.3%) and Saha et al.[11] (6.4%). TAH was observed as isolated findings with no underlying cause and responded to supportive treatment.

Transfusion-associated circulatory overload was seen in three (0.002%) recipients, two of whom had underlying diabetes, hypertension, history of myocardial infarction, and reduced ejection fraction. Patient presented with dyspnea and decreased oxygen saturation levels (dropped to 60% on room air) after PRBC transfusion. Brain natriuretic peptide (BNP) levels were 286 pg/mL posttransfusion in two cases. Another case was an elderly female who came for orthopedic surgery and developed TACO post-WB transfusion. Joy et al.[18] reported incidence of 0.008%.

Delayed hemolytic transfusion reactions was seen in 0.005% recipients. It was seen with 100% of PRBCs. The most common presenting symptoms and signs were back pain, nausea, abdominal pain, and mild hematuria, as shown in a similar study by Sidhu et al.[15] All patients had underlying thalassemia and were on regular transfusion. DHTR is a side effect of blood transfusion due to recipient RBC autoantibodies and alloantibodies. This can be reduced by giving extended phenotype-matched leukodepleted blood. There was no incidence of transfusion-associated graft-vs-host disease (TAGVHD) in our study.

Nonspecific reactions were 7/1,65,121 (0.004%) of transfusions. These could not be categorized into any TR and were probably because of underlying medical conditions of the patient. Safe blood transfusion forms an indispensable part of quality parameter in transfusion services. Continuous hemovigilance is aimed at identifying the adverse events related to transfusion, which in turn guides in setting up measures to mitigate the frequency of such events. Our blood center is also a part of the Hemovigilance Program of India.

Conclusion

The overall incidence of TR in our study was 0.18%. The risk of reaction per 1,000 components transfused was maximum with WB 3.84 and PRBC 2.85, and minimum with RDP 0.58. Though consumption of WB is reduced, it is still used in patients who need all the components of blood, such as in significant blood loss due to trauma/surgery and cardiovascular surgeries. Nowadays, reconstituted-WB is used, also known as reconstituted red blood cells. This is a combination of red blood cells and plasma to achieve a specific volume of a targeted hematocrit. It is immunologically safer and better than using WB. DHTRs are often missed, as the temporal relationship with transfusion is overlooked. Every hospital should have a hospital transfusion committee who has the overarching responsibility to maintain safe hospital transfusion practices by investigating transfusion events and developing strategies for reduction and improvement. Our main aim is to improve the reporting of transfusion reaction and data collection, followed by evidence-based improvement in blood transfusion practices.

References

1. Kuriyan M, Carson JL. Blood transfusion risks in the intensive care unit. Crit Care Clin 2004;20(2):237–253.
2. Suddock JT, Crookston KP. Transfusion Reactions. In: Stat Pearls. Treasure Island (FL): Stat Pearls Publishing; 2024.
3. Kumar P, Thapliyal R, Coshic P, et al. Retrospective evaluation of adverse transfusion reactions following blood product transfusion from a tertiary care hospital: a preliminary step towards hemovigilance. Asian J Transfus Sci 2013;7:109–115.
4. Shajil S, Adiga DSA, Saha D, et al. A study of frequency and pattern of adverse transfusion reactions at a blood bank in a tertiary care hospital: towards haemovigilance. Ann Pathol Lab Med 2020;7:576–581.
5. Payandeh M, Zare ME, Kansestani AN, et al. Descriptions of acute transfusion reactions in the teaching hospitals of Kermanshah university of medical sciences, Iran. Int J Hematol Oncol Stem Cell Res 2013;7:11–16.
6. Mafirakureva N, Khoza S, Mvere DA, et al. Incidence and pattern of 12 years of reported transfusion adverse events in Zimbabwe: a retrospective analysis. Blood Transfus 2014;12:362–367.
7. Bassi R, Aggarwal S, Bhardwaj K, et al. Patterns of adverse transfusion reactions in a tertiary care center of North India: a step towards hemovigilance. Indian J Hematol Blood Transfus 2017;33:248–253.
8. Sharma DK, Datta S, Gupta A. Study of acute transfusion reactions in a teaching hospital of Sikkim: a hemovigilance initiative. Indian J Pharmacol 2015;47:370–374.
9. Philip J, Pawar A, Chatterjee T, et al. Non infectious complications related to blood transfusion: an 11 year retrospective analysis in a tertiary care hospital. Indian J Hematol Blood Transfus 2016;32:292–298.
10. Pahuja S, Puri V, Mahajan G, et al. Reporting adverse transfusion reactions: a retrospective study from tertiary care hospital from New Delhi, India. Asian J Transfus Sci 2017;11:6–12.
11. Saha S, Krishna D, Prasath R, et al. Incidence and analysis of 7 years adverse transfusion reaction: a retrospective analysis. Indian J Hematol Blood Transfus 2020;36:149–155.
12. Prakash P, Basavaraj V, Kumar RB. Recipient hemovigilance study in a university teaching hospital of South India: an institutional report for the year 2014–2015. Glob J Transfus Med 2017;2:124–129.
13. Khalid S, Usman M, Khurshid M. Acute transfusion reactions encountered in patients at a tertiary care center. J Pak Med Assoc 2010;60:832–836.
14. Ramanathan T, Meena D, Sushama D. Reporting adverse transfusion reactions in a tertiary care center, Kerala, India. Natl J Lab Med 2019;8:8–10.
15. Sidhu M, Meenia R, Yasmeen I, et al. A study of transfusion related adverse events at a tertiary care center in North India: an initiative towards haemovigilance. Int J Adv Med 2015;2:206–210.
16. Heddle NM. Pathophysiology of febrile nonhemolytic transfusion reactions. Curr Opin Hematol 1999;6:420–426.
17. Wood EM, Ang AL, Bisht A, et al. International haemovigilance: what have we learned and what do we need to do next? Transfus Med 2019;29:221–230.
18. Joy A, Sahoo D, Abhishekh B, et al. Incidence of adverse transfusion reaction and practices for its prevention. Haematol Int J 2021;5(1):00183.
19. Salmani A, Bhardwaj A, Ahmed S, et al. A clinicohaematological profile of adverse transfusion reactions and its association with blood components. Era J Med Res 2022;9:1–7.
20. Sandler SG, Mallory D, Malamut D, et al. IgA anaphylactic transfusion reactions. Transfus Med Rev 1995;9:1–8.
21. Webert KE, Blajchman MA. Transfusion-related acute lung injury. Transfus Med Rev 2003;17:252–262.
22. Baele PL, De Bruyere M, Deneys V, et al. Bedside transfusion errors. A prospective survey by the Belgium SAnGUIS Group. Vox Sang 1994;66:117–121.

ORIGINAL ARTICLE

Decoding "Ghabrahat": A Cross-sectional KAP Study of Healthcare Professionals' Understanding and Management of a Complex South Asian Medical Term

Rahul Garg[1*], Anmol Thakre[2]

Received: 11 February 2025; *Accepted:* 05 April 2025

Abstract

Background: In South Asian healthcare settings, certain symptoms described in local languages create unique challenges in medical practice. "Ghabrahat" is a commonly used term that lacks standardization in medical terminology and presents difficulties in translation and interpretation. This study aimed to comprehensively assess the knowledge, attitudes, and practices (KAP) regarding "ghabrahat" among healthcare professionals.

Materials and methods: A cross-sectional study was conducted among 107 healthcare professionals, including faculty members and postgraduate trainees, across multiple tertiary care centers. A structured questionnaire was used to evaluate their understanding, perceptions, and clinical approaches regarding "ghabrahat" as a medical term.

Results: Of the 107 participants, 105 (98.1%) had encountered the term during their medical practice. The majority (77.6%) believed that "ghabrahat" requires further medical investigation, and 94.4% considered it treatable/manageable. Significant associations were found with cardiovascular (86%) and psychological (73.8%) systems. Gender differences in perception were noted by 67.2% of participants, while 88.8% believed that comorbidities influence its presentation. Notably, 54.2% of participants reported encountering mortalities directly attributed to "ghabrahat."

Conclusion: While "ghabrahat" is widely recognized among healthcare professionals, there exists substantial variation in its interpretation, perceived severity, and management approaches. This study highlights the urgent need for standardization in understanding and approaching this commonly reported symptom in South Asian medical practice.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1076

Introduction

In South Asian healthcare settings, particularly where English serves as the primary medium of medical education, certain symptoms described in local languages pose unique challenges in translation and interpretation. "Ghabrahat" is one such term that, despite its frequent usage in clinical practice, lacks a direct equivalent in standard medical terminology. This linguistic complexity creates significant challenges in diagnosis, treatment planning, and effective patient–provider communication.

This medically unexplained symptom (MUS) and its perceived associations with multiple body systems pose difficulty for diagnosis and treatment.[1,2]

The term "ghabrahat" generally encompasses various symptoms, including anxiety, palpitations, restlessness, and discomfort, making it difficult to attribute to a single system or disease.[3–5] In primary healthcare, patients often present with physical and mental symptoms that are challenging to classify according to standardized classification systems.[3] Previous studies have shown that in 21% of primary healthcare cases, symptoms or complaints are used for diagnosis rather than specific disease entities.[2]

The complexity of ghabrahat is evident in how it has been used in different studies. For instance, in research conducted in Zimbabwe on depression in developing countries, the author used ghabrahat to describe symptoms of anxiety and depression.[6] In contrast, another study employed this term specifically for palpitations.[7]

The significance of studying "ghabrahat" lies in its prevalence and impact on healthcare delivery in South Asian contexts. The term's ambiguity can lead to diagnostic uncertainty, potentially resulting in either overinvestigation or underdiagnosis of serious conditions. Understanding healthcare providers' perceptions and approaches to this symptom is crucial for improving patient care and developing standardized management protocols.

Materials and Methods

Study Design and Setting

A cross-sectional survey was conducted using a structured questionnaire to evaluate healthcare professionals' knowledge, attitudes, and practices (KAP) regarding "ghabrahat" as a medical term. The study was designed to capture comprehensive data about the understanding and management of this commonly encountered symptom.

Participants

The study included 107 healthcare professionals, comprising 48 (45%) faculty members and 59 (55%) postgraduate trainees. The gender distribution showed 77 (72%) males and 30 (28%) females, with a mean age of 43.04 ± 12.76 years (Table 1). Participants were recruited from multiple tertiary care centers to ensure diverse perspectives and experiences.

Data Collection Tool

A comprehensive questionnaire was developed addressing the following five key areas:

- Demographics and professional background.
- Knowledge and awareness of "ghabrahat."
- Clinical perceptions and attitudes.
- Management practices and approaches.
- Opinions on further investigation and research are needed.

Table 1: Demography of the study participants

Characteristic	*Value*
Total participants	107
Males	77 (72%)
Females	30 (28%)
Faculty	48 (45%)
Postgraduates	59 (55%)
Mean age (years)	43.04 ± 12.76

[1]Associate Professor; [2]PG Resident, Department of Medicine, FH Medical College, Agra, Uttar Pradesh, India; *Corresponding Author

How to cite this article: Garg R, Thakre A. Decoding "Ghabrahat": A Cross-sectional KAP Study of Healthcare Professionals' Understanding and Management of a Complex South Asian Medical Term. J Assoc Physicians India 2025;73(8):40–42.

Statistical Analysis

Data were analyzed using MS Excel. Frequencies and percentages were calculated for categorical variables. Results were organized to highlight patterns in understanding and management approaches among healthcare professionals.

Results

Knowledge and Awareness

The study revealed extensive exposure to "ghabrahat" among healthcare professionals, with 105 (98.1%) participants having encountered the term during their medical training or practice (Table 2) with 61% of them encountering it frequently (Fig. 1). This high percentage underscores the term's prevalence in South Asian healthcare settings. When asked about their understanding of the symptom, participants provided varied interpretations, demonstrating the term's complex nature, with 9.3% having an excellent understanding of the term, 36.4% having a good understanding, 38.3% having a fair understanding, while 15.9% having a poor understanding of this term. The majority associated "ghabrahat" with multiple body systems, with cardiovascular (86%) and psychological (73.8%) systems being the most frequently cited (Fig. 2). Other significant associations included drug side effects (31%), endocrine disorders (23.4%), gynecological issues (5.2%), and various other conditions, including respiratory diseases, anemia, and dehydration (3.4%).

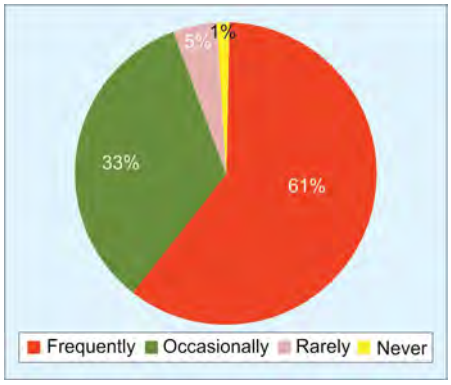


Fig. 1: Frequency of encountering patients with ghabrahat

Perceptions and Attitudes

The study revealed significant variations in how healthcare professionals perceive "ghabrahat" and its clinical significance (Fig. 3). A substantial majority (77.6%) believed that the condition requires further medical investigation, indicating recognition of its potential clinical importance (Table 2). Gender-based differences in perception were noted by 67.2% of participants, suggesting that patient gender influences how the symptom is interpreted and managed (Table 2). An even larger proportion (88.8%) believed that comorbidities and risk factors significantly affect the presentation and interpretation of "ghabrahat" (Table 2).

A particularly noteworthy finding was that 54.2% of participants reported encountering mortalities directly attributed to "ghabrahat," highlighting the potential severity of conditions presenting with this symptom (Table 2). This finding contradicts any assumption that "ghabrahat" is always a benign presentation and emphasizes the need for careful evaluation of patients presenting with this symptom.

Clinical Practice and Management

The study revealed diverse approaches to managing patients presenting with "ghabrahat." An overwhelming majority (94.4%) of participants considered it a treatable or manageable condition (Table 2), with 71.7% specifically believing in the success of medical treatment (Fig. 4). The management strategies employed by healthcare professionals varied considerably, reflecting the complex nature of the symptom. Different interpretations of "ghabrahat" led to various diagnostic (Fig. 5) and treatment approaches, with participants reporting success with both pharmacological and nonpharmacological interventions (Fig. 4).

When asked about specific symptom interpretations, healthcare providers associated "ghabrahat" with multiple manifestations:

- Anxiety or nervousness (79.3%).
- Palpitations (59.8%).
- Restlessness (53%).
- Breathing difficulty (42.5%).
- Pain or discomfort (28.9%).
- Depression (17.7%).
- Irritability (15.9%).
- Fear of impending disaster (14.5%).

System-wise Association

The multisystem association of "ghabrahat" emerged as a significant finding, with participants linking it to various physiological and psychological conditions. The predominant association with cardiovascular and psychological systems suggests a possible psychosomatic component, requiring a holistic approach to diagnosis and treatment. The diverse system associations reported by participants highlight the challenge in developing standardized treatment protocols.

Discussion

This comprehensive study of healthcare professionals' KAP regarding "ghabrahat" reveals several important findings that have significant implications for clinical practice. The near-universal recognition of the term (98.1%) among participants confirms its prevalence in South Asian healthcare settings and underscores the importance of understanding its various interpretations and implications.

Table 2: Perception of the participants regarding the term "ghabrahat"

Question number	*Question*	*Yes n (%)*	*No n (%)*
1	Have you encountered the term "ghabrahat" during your medical training or practice?	105 (98.1%)	2 (1.9%)
2	Do you think the perception of "ghabrahat" varies based on the patient's sex?	72 (67.2%)	35 (32.8%)
3	Do you think the perception of "ghabrahat" varies based on the patient's comorbidities or risk factors?	95 (88.8%)	12 (11.2%)
4	In your experience, have you encountered any mortalities directly attributed to "ghabrahat"?	58 (54.2%)	49 (45.8%)
5	In your opinion, is "ghabrahat" a condition that requires further medical investigation?	83 (77.6%)	24 (22.4%)
6	Do you believe that "ghabrahat" is a treatable/manageable condition?	101 (94.4%)	6 (5.6%)

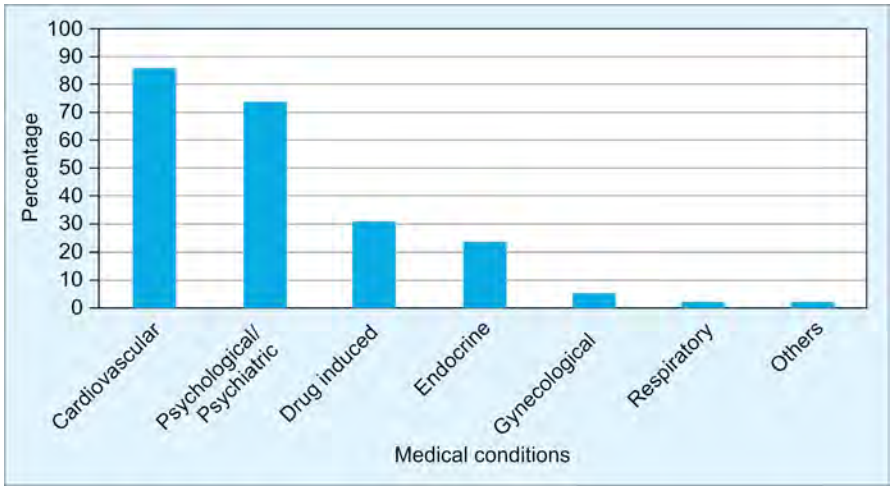


Fig. 2: Medical conditions associated with ghabrahat

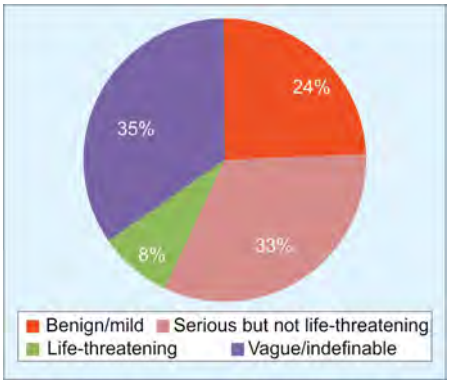


Fig. 3: Perception of ghabrahat as a medical symptom

Fig. 4: Management strategies for ghabrahat

The study highlights three key challenges in dealing with "ghabrahat" as a medical term. First, the wide variety of symptoms associated with the term makes it difficult to establish standardized diagnostic criteria. Second, the significant variation in healthcare providers' interpretations and management approaches suggests a need for more structured guidelines. Third, the high percentage of participants reporting mortality cases associated with "ghabrahat" (54.2%) indicates that this symptom should not be dismissed as merely a manifestation of anxiety or mild distress.

The strong association with both cardiovascular and psychological systems (86 and 73.8%, respectively) suggests that "ghabrahat" might represent a complex psychosomatic manifestation requiring a multidisciplinary approach to diagnosis and treatment. This finding aligns with previous research indicating the challenges of classifying such symptoms within conventional medical frameworks.[3,5–7]

The influence of patient demographics and comorbidities on the perception and presentation of "ghabrahat" adds another layer of complexity to its clinical management. The high percentage of participants (88.8%) noting the impact of comorbidities suggests the need for individualized assessment and treatment approaches.

Limitations of the Study

The study's limitations include its cross-sectional nature, which prevents the assessment of temporal changes in understanding and management approaches. Additionally, the focus on tertiary care centers might not fully represent the perspectives of healthcare providers in primary care settings.

Conclusion

This study provides comprehensive insights into healthcare professionals' understanding and management of "ghabrahat" in South Asian medical practice. While the term is widely recognized, there is significant variation in its interpretation and management. These results emphasize the urgent need for standardized guidelines, enhanced medical education regarding culturally specific symptoms, and the development of evidence-based protocols. Further research is warranted to better understand the relationship between "ghabrahat" and serious medical conditions, ultimately improving patient care in South Asian healthcare settings.

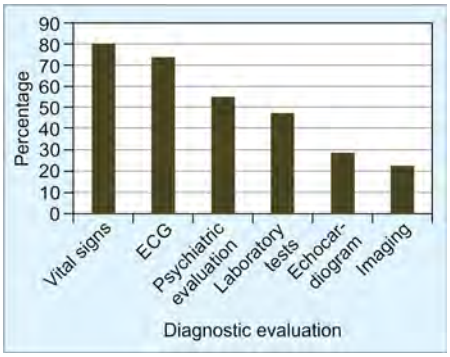


Fig. 5: Diagnostic evaluation of ghabrahat

Orcid

Rahul Garg https://orcid.org/0009-0008-5219-806X
Anmol Thakre https://orcid.org/0009-0005-4370-0773

References

1. Woivalin T, Krantz G, Mantyranta T, et al. Medically unexplained symptoms: perceptions of physicians in primary health care. Fam Pract 2004;21:199–203.
2. Ringsberg KC, Krantz G. Coping with patients with medically unexplained symptoms work-related strategies of physicians in primary health care. J Health Psychol 2006;11:107–116.
3. Irfan SS, Ahmed Z, Farooq MZ, et al. Evaluation of "Ghabrahat" as a medical term: a survey of healthcare professionals. J Pak Med Assoc 2016;66(1):122–124.
4. Sidana A, Sharma RP, Chavan BS, et al. Psychiatric profile of patients attending general emergency room services—a prospective study. J Mental Health Human Behav 2009;14:80–83.
5. Khan MS, Jafary FH, Faruqui AM, et al. High prevalence of lack of knowledge of symptoms of acute myocardial infarction in Pakistan and its contribution to delayed presentation to the hospital. BMC Public Health 2007;7:284.
6. Patel V, Abas M, Broadhead J, et al. Depression in developing countries: lessons from Zimbabwe. BMJ 2001;322:482–484.
7. Shakoor A, Shafqat F, Mehmud TeH, et al. Frequency of depression and somatic symptoms in patients on interferon alpha/ribavirin for chronic hepatitis C. J Ayub Med Coll Abbottabad 2010;22:6–9.

ORIGINAL ARTICLE

Prevalence of Hypertension in Young Adults in Punjab

Manpreet Singh Brar[1], Meghna Gupta[2*], Vitull K Gupta[3], Keshav Garg[4]

Received: 30 January 2025; *Accepted:* 05 April 2025

Abstract

Introduction: India has shown dramatic increase in noncommunicable diseases (NCDs), so much so that about 70% of the overall mortality is estimated to be because of NCDs. Young adults <35 years of age constitute 65%, a significant section of Indian population, but there is paucity of studies exploring prevalence of HTN among young adults in India, especially in Punjab. So, the present study was conducted to know the prevalence of HTN among young adults in Punjab.

Materials and methods: This observational study was conducted as part of a global blood pressure (BP) screening program, after approval from Institutional Ethics Committee. Subjects of 18–80 years were included after verbal informed consent. Data obtained was analyzed as per the standard statistical method, and Chi-squared test was applied.

Results: A total of 24,685 participants completed the study including 43.5% young adults. The prevalence of HTN in young adults was 9.2 and 18.8% in older adults. About 71.8% hypertensive young adults were overweight or obese. Males demonstrated 16.7% prevalence of HTN as compared to 12.3% in females, whereas in young adults 28.4% females had HTN as compared to 26.6% males.

Conclusion: Present study documents increase in prevalence of HTN among young adults and its association with overweight and obesity necessitating initiation of HTN prevention and control strategies, especially focused on young adults.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1065

Introduction

Over decades, India has shown progressive decline in the prevalence of communicable diseases (CDs) and dramatic increase in noncommunicable diseases (NCDs), such as diabetes mellitus (DM), hypertension (HTN), cardiovascular diseases (CVDs), and cancers, so much so that presently about 70% of the overall mortality is estimated to be because of NCDs.[1] In 2023, India surpassed China to become the most populous country in the world with an estimated population of over 1.4 billion people with 50% of the population under the age of 25 years; about 65% of the population was under 35 years of age, and 6.9% were over 65 years of age.[2,3] Population of Punjab is about 3.17 crores, and the youth constitutes 46.5% of the population.[4] A report by the Technical Group of the National Commission suggested that 33.7% population is between 20 and 39 years of age, and 29.1% population is between the age-group of 40 and 79 years in Punjab.[5] In India, states and regions differ widely in ethnic and religious composition, socioeconomic development, and dietary habits. The overall prevalence of NCDs in various regions of India also varies, thereby making documentation of regional data an utmost important subject in order to plan and implement NCDs prevention and management programs.[6]

Recent data suggests 35.5% overall weighted prevalence of HTN in India with a state-wise prevalence ranging from the lowest 24.3% in Meghalaya to the highest 51.8% in Punjab.[1,6]

The Fifth National Family Health Survey (NFHS-5) presented the most representative and comprehensive data on HTN epidemiology. It documented significant state-wise differences in the prevalence of HTN with the highest prevalence among females in Sikkim (34.5%) and Punjab (31.2%) and also among men in Sikkim (41.6%) and Punjab (37.7%). In India, higher prevalence of HTN at young age than North and South America and Europe has been documented.[7] A study documented 11.2% prevalence of HTN among the young adults; prevalence was more in men than women (20.5 vs 7.5%; $p < 0.001$), and no gender difference was observed in older adults.[8]

Young adults constitute a significant section of Indian population, but there is paucity of studies exploring the prevalence of HTN among young adults in India, especially in Punjab, a state with one of the highest prevalence of HTN. We report the prevalence of HTN among young adults who participated in a global blood pressure (BP) screening program, the May Measurement Month (MMM), an initiative of the International Society of Hypertension in year 2017–2019, 2021, and 2024. The May Measurement Month had to be deferred in 2020 due to the COVID-19.

Aims and Objectives

To study the prevalence of HTN among young adults in Punjab.

Materials and Methods

Study Design and Participants

This observational study was conducted as part of a global BP screening program; the MMM, an initiative of International Society of Hypertension and the Indian Society of Hypertension. Our center was a part of this initiative in year 2017–2019, 2021, and 2024, conducted hospital-based screening, and organized screening camps. The campaign was conducted from May 1 to May 31 every year and sometimes extended to the month of June and July also. Institutional Ethics Committee approved the project vide letter number: 3/2017/3.4.2017. All subjects between the ages of 18 and 80 years were included in the study after verbal informed consent approved by the Institutional Ethics Committee. Those who did not give verbal informed consent were not included in the study. Subjects were recruited through convenience sampling.

Blood Pressure Measurement

Measurement of BP was done, according to the standard protocol, preferably from the left arm, in comfortably seated position with a back rest, uncrossed legs with feet touching the ground, and after a 5-minute rest. Three readings of BP were taken, 1 minute apart, the mean of second and third BP measurement was considered for the study. OMRON BP monitors were used for the screening campaign.

[1]PG Resident, Department of ENT; [2]Assistant Professor, Department of Psychiatry, Krishna Mohan Medical College & Hospital, Mathura, Uttar Pradesh; [3]Consultant, Department of Medicine, Kishori Ram Hospital and Diabetes Care Centre, Bathinda, Punjab; [4]Doctor, Department of Medicine, Government Medical College & Hospital, Chandigarh, India; *Corresponding Author

How to cite this article: Brar MS, Gupta M, Gupta VK, *et al.* Prevalence of Hypertension in Young Adults in Punjab. J Assoc Physicians India 2025;73(8):44–49.

Definition of Hypertension

Hypertension was defined, according to the Indian Hypertension Guidelines as BP of ≥140/90 mm Hg, isolated systolic HTN as BP of ≥140 mm Hg and isolated diastolic HTN as BP of ≥90 mm Hg.[9,10]

Definition of Young Adults

The American College of Cardiology (ACC) and the American Heart Association (AHA) often classify 18–39 years as a distinct age-group for studies on HTN and early identification of cardiovascular (CV) risk.[11,12] In Indian context, public health studies and studies on HTN generally defined young adults as 20–40 years or 18–40 years of age-group.[8]

Hypertension in young has been defined as presence of HTN in patients <40 years of age.[13] So, in our study we have considered 18–40 years age-group to study prevalence of HTN in young adults.

Body Mass Index

Weight was measured in kilograms using standard weighing machine; height was measured using standard measuring scale, and body mass index (BMI) was calculated by using the formula = weight (kg)/height (m^2).

The World Health Organization and several other guidelines categorize BMI in Asian population with a BMI of <18.5 kg/m^2 as underweight, 18.5–22.9 kg/m^2 as normal weight, 23.0–27.5 kg/m^2 as overweight, and ≥27.5 kg/m^2 as obese. In the present study for convenience, BMI was categorized in three categories of underweight as BMI of <18.5 kg/m^2, normal weight as BMI of 18.5–22.9 kg/m^2, and overweight and obese as BMI of >23.0 kg/m^2.[14,15]

Heart Rate

The AHA, all guidelines, and textbooks define normal sinus heart rate (HR) as between 60 and 100 beats per minute (bpm) and bradycardia if HR is <60 bpm and tachycardia if HR is >100 bpm.[16,17]

Statistical Analysis

The prevalence of HTN, according to Indian Hypertension Guidelines, was calculated for the study population, and prevalence was compared. Data obtained was analyzed as per the standard statistical method. Frequency and percentages were calculated, and Chi-squared test was applied to find out their association and significance.

Results

Baseline Characteristics of Study Population

Among the total study population of 24,685 participants, young adults (18–40 years) constituted 43.5%. Females constituted a slightly higher proportion of the young adult group (53.0%) compared to males (47.0%), in contrast with the older age-group (41–80 years), where males constituted a higher proportion (Table 1).

Young adults had a statistically significant higher prevalence of normal BMI (30.9%) compared to older adults (21.7%). However, the majority of young adults (59.7%) were overweight or obese (BMI ≥23 kg/m^2), indicating a significant burden of overweight or obesity even in younger population cohort. Heart rate measurements were predominantly within the normal range (60–100 bpm) in young adults (94.0%).

Prevalence of Hypertension in Young Adults

The prevalence of HTN in young adults was 9.2%, significantly lower than the 18.8% in older adults (Table 2). Among hypertensive young adults, males accounted for 58.4% of cases, while females accounted for 41.6%, though this gender difference was not statistically significant. A significant proportion of hypertensive young adults (71.8%) were overweight or obese (BMI >23 kg/m^2), underscoring the strong association between excess weight and HTN in this age-group ($p < 0.0001$). Normal BMI (18.5–22.9 kg/m^2) subjects accounted for 22.2% of HTN cases among young adults, indicating that HTN is not exclusively confined to those with higher BMI levels (Table 2). In hypertensive young adults, HR was predominantly normal (86.6%; Table 2), while a minority of young hypertensive patients had tachycardia (12.8%). Similar pattern was seen in the older hypertensive patients showing 90.0% subjects had normal HR, and 9% had tachycardia.

Prevalence of Hypertension among Gender Groups

Table 3 highlights gender-specific differences in the prevalence of HTN. Overall, males demonstrated a statistically significant higher prevalence of HTN (16.7%) as compared to females (12.3%, $p = 0.0003$). Among young adults (18–40 years), females had a marginally higher prevalence of HTN (28.4%) than males (26.6%, $p = 0.5322$). Conversely, in older adults (41–80 years), males exhibited a slightly higher prevalence (73.4%) compared to females (71.6%, $p = 0.3121$). These findings suggest insignificant gender differences in young adults but a trend toward statistically significant higher prevalence of HTN in older males. In overweight or obese BMI group (>23 kg/m^2), the prevalence of HTN was more in total study population (77.2%), males (77.9%) as well as females (76.2%) as compared to normal/underweight weight population.

Systolic and Diastolic Hypertension in Young Adults

Systolic HTN [systolic blood pressure (SBP) ≥140 mm Hg] was observed in 15.8% of young adults, compared to 32.0% in older adults ($p < 0.0001$; Table 4). Diastolic HTN [diastolic blood pressure (DBP) ≥90 mm Hg] was

Table 1: Baseline characteristics of study population, according to gender, BMI, and HR among age-groups [% (*n*)]

Characteristic factors		*Age-groups*			*95% CI*	*p*
		18–80 years	*18–40 years*	*41–80 years*		
Study population		24,685	43.5 (10,732)	56.5 (13,953)	11.7497–14.2444%	<0.0001 S
Gender	Male	52.6 (12,996)	47.0 (5,043)	57.0 (7,953)	8.2413–11.7509%	<0.0001 S
	Females	47.4 (11,689)	53.0 (5,689)	43.0 (6,000)	8.1929–11.7980%	<0.0001 S
BMI, kg/m^2	<18.5	6.2 (1,516)	9.6 (1,031)	3.5 (485)	3.4794–8.4469%	<0.0001 S
	18.5–22.9	25.6 (6,324)	30.9 (3,296)	21.7 (3,028)	6.8395–11.1444%	<0.0001 S
	≥23	68.2 (16,845)	59.7 (6,405)	74.8 (10,440)	13.6382–16.5610%	<0.0001 S
HR/mts	<60	0.7 (181)	0.7 (75)	0.7 (106)	−5.4612 to 4.0965%	= 1.0000 NS
	60–100	94.1 (23,230)	94.0 (10,089)	94.2 (13,141)	−0.4083 to 0.8168%	= 0.5209 NS
	>100	5.2 (1,274)	5.3 (570)	5.1 (704)	−2.3593 to 2.6443%	= 0.8732 NS

BMI, body mass index; CI, confidence interval; HR/mts, heart rate/minute; NS, statistically not significant *p*-value; S, statistically significant *p*-value

Table 2: Prevalence of HTN (≥140/90 mm Hg) in study population, according to gender, BMI, and HR among age-groups [% (*n*)]

Characteristic factors		*Age-groups*			*95% CI*	*p*
		18–80 years	*18–40 years*	*41–80 years*		
Study population		24,685	43.5 (10,732)	56.5 (13,953)	11.7497–14.2444%	<0.0001 S
Total ≥140/90 mm Hg		14.6 (3,611)	9.2 (986)	18.8 (2,625)	7.1581–11.8563%	<0.0001 S
Gender	Male	60.1 (2,169)	58.4 (576)	60.7 (1,593)	−2.3388 to 7.0079%	= 0.3342 NS
	Females	39.9 (1,442)	41.6 (410)	39.3 (1,032)	−3.2596 to 7.9496%	= 0.4213 NS
BMI, kg/m^2	<18.5	3.5 (127)	6.0 (59)	2.6 (68)	−4.5525 to 12.7503%	= 0.3415 NS
	18.5–22.9	19.3 (697)	22.2 (219)	18.2 (478)	−2.2235 to 10.7623%	= 0.2159 NS
	≥23	77.2 (2,787)	71.8 (708)	79.2 (2,079)	3.7383–11.2195%	<0.0001 S
HR/mts	<60	0.8 (31)	0.6 (6)	1.0 (25)	−38.7708 to 14.4077%	= 0.9279 NS
	60–100	89.1 (3,217)	86.6 (854)	90.0 (2,363)	0.9246–6.1040%	= 0.0063 S
	>100	10.1 (363)	12.8 (126)	9.0 (237)	−2.6256 to 11.3788%	= 0.2579 NS

BMI, body mass index; CI, confidence interval; HR/mts, heart rate/minute; NS, statistically not significant *p*-value; S, statistically significant *p*-value

Table 3: Prevalence of HTN (≥140/90 mm Hg), according to age groups, BMI, and HR among gender groups in study population [% (*n*)]

Characteristic factors		*Gender groups*			*95% CI*	*p*
		Total	*Male*	*Females*		
Study population		24,685	52.6 (12,996)	47.4 (11,689)	3.9515–6.4462%	<0.0001 S
Total ≥140/90 mm Hg		14.6 (3,611)	16.7 (2,169)	12.3 (1,442)	2.0532–6.6798%	= 0.0003 S
Age-groups	18–40 years	27.3 (986)	26.6 (576)	28.4 (410)	−3.7956 to 7.5067%	= 0.5322 NS
	41–80 years	72.7 (2,625)	73.4 (1,593)	71.6 (1,032)	−1.6729 to 5.3289%	= 0.3121 NS
BMI, kg/m^2	<18.5	3.5 (127)	3.5 (76)	3.5 (51)	−7.3235 to 9.4150%	= 1.0000 NS
	18.5–22.9	19.3 (697)	18.6 (404)	20.3 (293)	−4.1634 to 7.7793%	= 0.5749 NS
	>23	77.2 (2,787)	77.9 (1,689)	76.2 (1,098)	−1.4694 to 4.9347%	= 0.2958 NS
HR/mts	<60	0.8 (31)	0.9 (19)	0.8 (12)	24.5575–17.4959%	= 0.9770 NS
	60–100	89.1 (3,217)	88.8 (1,927)	89.5 (1,290)	−1.5324 to 2.8524%	= 0.5328 NS
	>100	10.1 (363)	10.3 (223)	9.7 (140)	−6.2942 to 6.6818%	= 0.8535 NS

BMI, body mass index; CI, confidence interval; HR/mts, heart rate/minute; NS, statistically not significant *p*-value; S, statistically significant *p*-value

present in 16.7% of young adults, compared to 26.7% in older adults ($p < 0.0001$). These findings suggest that isolated systolic HTN is less common than diastolic HTN in young adults, whereas in older age-groups systolic HTN was more common than diastolic HTN. Prevalence of systolic HTN was higher (71.9%) than diastolic HTN (70.2%) in overweight or obese BMI group among young adults, whereas prevalence of diastolic HTN (79.1%) was relatively high as compared to systolic HTN (77.9%) in overweight and obese BMI group in older adults.

Prevalence of systolic HTN was higher in young males (58.3%) as compared to young females (41.7%). Prevalence of diastolic HTN followed a similar trend with higher prevalence in young males (56.8%) as compared to young females (43.2%).

Prevalence of Hypertension according to Heart Rate among Young Adults

Normal HR (60–100 bpm) was observed in 84.5% of systolic hypertensive young adults and 91.9% systolic hypertensive older adults, and the difference was statistically significant. Tachycardia (HR >100 bpm) was present in 14.4% of systolic hypertensive young adults, which was statistically and significantly higher than older systolic hypertensive adults (6.8%, $p = 0.0035$; Table 4). Bradycardia (HR <60 bpm) was uncommon in both young and old adults with HTN and showed no significant association with age or gender groups.

In diastolic hypertensive patients, normal HR (60–100 bpm) was observed in 85.4% of young adults, statistically and significantly less as compared to 93.6% in older adults ($p < 0.0001$), while the trend reversed as it was seen in 14.1% of young adults, and 5.6% older adults showed tachycardia.

Systolic and Diastolic Hypertension across Gender Groups

The analysis of HTN across gender groups is shown in Table 5. Among males, the prevalence of systolic HTN (SBP ≥140 mm Hg) was 28.4%, significantly higher than the 21.1% observed in females ($p < 0.0001$). Similarly, diastolic HTN (DBP ≥90 mm Hg) was more prevalent in males (24.9%) than females (19.2%; $p < 0.0001$).

Discussion

Hypertension in Young Adults: A Growing Concern

Present study underlines a substantial burden of HTN (≥140/90 mm Hg) in 9.2% of young adults (18–40 years) with notable links to overweight and obesity. Young adults had lower HTN prevalence rates than older adults, but the findings stress the importance of screening procedures and interventions at early stages to prevent long-term consequences on CV health.[18,19]

Present study shows that among the young hypertensive population, 71.8% were either overweight or obese, suggesting overweight/obesity as one of the important risk factors for high BP in young hypertensive population. In addition, this cohort had slightly more prevalence of diastolic HTN (16.7%) than systolic HTN (15.8%) which is contrary to older adults who had a higher level of systolic HTN. These findings of increased prevalence of HTN in young adults corroborates with the findings of several international and Indian studies so far which have reported the increasing prevalence of

Table 4: Prevalence of systolic HTN (≥140 mm Hg) and diastolic HTN (≥90 mm Hg) in study population, according to gender, BMI, and HR groups among age-groups [% (*n*)]

BP		*Systolic HTN ≥140 mm Hg*			*Diastolic HTN ≥90 mm Hg*		
Age-groups		18–40 years	41–80 years	95% CI/*p*	18–40 years	41–80 years	95% CI/*p*
Study population		10,732	13,953		10,732	13,953	
Total		15.8 (1,696)	32.0 (4,462)	13.9380–18.3598% <0.0001 S	16.7 (1,762)	26.7 (3,721)	7.7108–12.2073% <0.0001 S
Gender groups	Males	58.3 (989)	60.6 (2,706)	−1.2569 to 5.8966% = 0.2065 NS	56.8 (1,000)	60.0 (2,234)	−0.4636 to 6.8880% = 0.0873 NS
	Females	41.7 (707)	39.4 (1,756)	−1.9586 to 6.6098% = 0.2921 NS	43.2 (762)	40.0 (1,487)	−1.0877 to 7.5136% = 0.1444 NS
BMI, kg/m^2	<18.5	5.8 (98)	3.5 (157)	−2.9296 to 9.0863% = 0.3838 NS	6.9 (121)	2.6 (98)	−2.0001 to 10.5264% = 0.1466 NS
	18.5–22.9	22.3 (378)	18.6 (830)	−1.0997 to 8.8157% = 0.1344 NS	22.9 (404)	18.3 (680)	−0.3164 to 9.7259% = 0.0673 NS
	≥23	71.9 (1,220)	77.9 (3,475)	3.1729–8.9181% <0.0001 S	70.2 (1,237)	79.1 (2,943)	5.9957–11.8748% < 0.0001 S
HR/mts	<60	1.1 (19)	1.3 (56)	−17.3295 to 7.6439% = 0.9463 NS	0.5 (9)	0.8 (28)	−29.8192 to 12.9391% = 0.9276 NS
	60–100	84.5 (1,433)	91.9 (4,101)	5.4155–9.5210% <0.0001 S	85.4 (1,504)	93.6 (3,483)	6.2990–10.2251% <0.0001 S
	>100	14.4 (244)	6.8 (305)	2.4634–13.0740% = 0.0035 S	14.1 (249)	5.6 (210)	3.0113–13.9226% = 0.0028 S

BP, blood pressure; BMI, body mass index; CI, confidence interval; HR/mts, heart rate/minute; NS, statistically not significant *p*-value; S, statistically significant *p*-value

Table 5: Prevalence of systolic HTN (≥140 mm Hg) and diastolic HTN (≥90 mm Hg) in study population according to age-groups, BMI, and HR groups among gender groups [% (*n*)]

BP		*Systolic HTN ≥140 mm Hg*			*Diastolic HTN ≥90 mm Hg*		
Gender groups		Males	Females	95% CI/*p*	Males	Females	95% CI/*p*
Study population		12,996	11,689		12,996	11,689	
Total		28.4 (3,695)	21.1 (2,463)	5.1116–9.4517% *p* < 0.0001S	24.9 (3,234)	19.2 (2,249)	3.4744–7.8884% *p* < 0.0001 S
Age-groups	18–40 years	26.8 (989)	28.1 (693)	−2.9967 to 5.6686% *p* = 0.5561 NS	30.9 (1,000)	33.9 (762)	−1.3944 to 7.4224% *p* = 0.1819 NS
	41–80 years	73.2 (2,706)	71.9 (1,770)	−1.3598 to 3.9929% *p* = 0.3399 NS	69.1 (2,234)	66.1 (1,487)	−0.0612 to 6.0852% *p* = 0.0549 NS
BMI, kg/m^2	<18.5	3.9 (143)	4.5 (112)	−4.6291 to 6.5743% *p* = 0.8122 NS	3.9 (126)	4.1 (93)	−5.3692 to 6.7617% *p* = 0.9405 NS
	18.5–22.9	19.0 (701)	20.6 (507)	−2.9021 to 6.2277% *p* = 0.4901 NS	18.3 (592)	21.9 (492)	−1.1700 to 8.4357% *p* = 0.1398 NS
	≥23	77.1 (2,851)	74.9 (1,844)	−0.2899 to 4.7267% *p* = 0.0837 NS	77.8 (2,516)	74.0 (1,664)	1.1582–6.4776% *p* = 0.0047 S
HR/mts	<60	1.5 (54)	0.9 (21)	−15.4955 to 8.3619% *p* = 0.8398 NS	0.7 (22)	0.7 (15)	−15.3465 to 20.7957% *p* = 1.0000 NS
	60–100	89.8 (3,320)	89.9 (2,214)	−1.5504 to 1.7019% *p* = 0.9040 NS	90.8 (2,938)	91.1 (2,049)	−1.3444 to 1.8960% *p* = 0.7168 NS
	>100	8.7 (321)	9.2 (228)	−4.2481 to 5.6679% *p* = 0.8395 NS	8.5 (274)	8.2 (185)	−5.2821 to 5.3180% *p* = 0.9095 NS

BP, blood pressure; BMI, body mass index; CI, confidence interval; HR/mts, heart rate/minute; NS, statistically not significant *p*-value; S, statistically significant *p*-value

HTN among the younger populations because of lifestyle changes and urbanization.[12,20]

Hypertension has always been thought be associated with older age; however, presently it is becoming far more prevalent in younger populations which is a cause for concern. In the present study, young adults had a high prevalence of diastolic HTN (16.7%) and a significant burden of systolic HTN (15.8%), thus suggesting the advantage of early screening for prevention and management of HTN in the young adult demographic. The data also

revealed that diastolic HTN was more prevalent among the younger population as compared to the older age-group, where higher prevalence of systolic HTN was documented. These findings of more prevalence of diastolic HTN in young adults can be explained on the basis of vascular physiological variations in younger people as compared to older people, who have increased arterial toughening as well as systemic inflammation leading to increased prevalence of systolic HTN. While, in young individuals, a raised diastolic pressure could open a new set of complications as it would be the early sign of deterioration of vascular physiological system.[9,21,22]

Increasing prevalence of HTN including isolated systolic as well as isolated diastolic HTN in young adults poses specific challenges, such as paucity of healthcare services, lesser awareness about HTN, its risk factors, complications, and beliefs about their nonvulnerability to NCDs or chronic diseases which can lead to poor prevention, management, and control of HTN, exposing the young adult population to greater risk of CVD morbidity and mortality. Results of the present study suggest a focused need for public health interventions in this group, and the interventions should focus on education, lifestyle change, and routine monitoring of BP to fill these gaps.[12,22]

Gender Differences in Hypertension

Statistically insignificant [$p = 0.5322$; not significant (NS)] difference was observed in gender comparison in the prevalence of HTN among young adults, with 26.6% prevalence of HTN among males and 28.4% among females. Systolic HTN appeared slightly higher (28.1%) among females than males (26.8%), while diastolic HTN showed an opposite trend, being more common among females (33.9%) than males (30.9%). Such an observation while not very significant, still accounts for the gender factors depending on generalized physiological and hormonal relations with BP mechanisms. Estrogen as a protective factor among women may turn out to be a contributor of these patterns.[23,24]

The gender gap was more apparent in elderly people, where males had a significantly higher rate of both systolic and diastolic HTN compared to females. This might be due to the postmenopausal hormonal changes in women and greater exposure to behavioral risk factors, such as smoking and alcohol consumption in men.[25,26]

Body Mass Index and Hypertension in Young Adults

In the present study, overweight/obesity group showed a significant association with prevalence of HTN, with prevalence of HTN of 71.8% in overweight/obese (>23 kg/m^2) young adults as compared to normal BMI young adults who showed significantly higher prevalence of systolic (23.2%), and diastolic (21.9%) HTN. Overweight/obesity triggers several pathophysiological alterations, such as sympathetic activity, insulin resistance, and vascular dysfunction, all of which together lead to increased BP.[27] Since, HTN is also present in young adults with normal BMI (22.2%), this suggests contribution of other risk factors, such as genetic predisposition, stress, and diet.[28–30]

These findings emphasize the dire need for focused public health interventions, such as diet-related, physical activity-based weight management programs with behavior modifications. Weight management, along with control of obesity-induced HTN in young adults, is an important intervention for preventing long-term CV complications.[31,32]

Heart Rate and Hypertension

The link between high HRs and HTN in young adults was another significant observation. Tachycardia (HR >100 bpm) occurred in 14.4% of systolic hypertensive and 14.1% of diastolic hypertensive young adults, which was substantially higher than older adults. High HRs may serve as a marker of additional CV stress, underlining the necessity for comprehensive HR evaluations in HTN management.[33]

Comparisons with Existing Data

Results of the present study compare well with results of studies from the United States and China showing increasing prevalence of HTN, especially in young adult group.[34,35] Prevalence of HTN in young adults aged 18–44 years was documented by a US study from the year 2019 to 2022 to be 7.4, 6.9, 6.7, and 7.2%, respectively.[36] A study from an urban slum of Mumbai, Maharashtra, documented 12.2% of prevalence of HTN in young adults aged 20–40 years.[37] A study documented 17.7% prevalence of HTN in young adults aged 18–40 years including 18.8% among men and 15.2% among women from the North India.[38] Hypertension among young people is common, affecting one in eight adults aged between 20 and 40 years.[39] The prevalence of HTN was high even among young age individuals as observed in the HTN epidemiological study conducted in India.[21] The trends were attributed to common risk factors, such as dietary transitions, reduced physical activity, and increased urbanization.[40,41] For India, the high prevalence of HTN in young adults, along with resource constraints, underlines the need for tailored strategies that balance early diagnosis with healthcare system capacity.

Public Health and Clinical Implications

The results of the present study will have considerable significance for health as well as the practice in India. India should initiate futuristic-targeted HTN prevention as well as control programs focusing on the young adults. This is important to arrest the rising trends of HTN and its complications. Such an initiative focusing on young adults would prevent increased prevalence of HTN in the future. Lifestyle modifications stressing on dietary control, physical workout, stress reduction, and other risk factor control should be included in the prevention and control programs. Young adults can also be involved in the technology-based solutions, such as mobile health applications that would provide more uptake and adherence to these interventions.[42] Monitoring HR in young adults might give useful information for HTN evaluation and detection efforts in clinical settings. Efforts should be made at the community level to serve marginalized regions in terms of access to care as well as treatment outcomes.

Generally, guidelines do not address the issues of HTN in young which is presently a growing concern in India as substantiated by the results of the present study. Given the high prevalence of HTN in young in the present study, India must focus on early and effective intervention for prevention, detection, and control of HTN to harvest immense benefits of reduction of morbidity and mortality in young adults. In the absence of quality studies and guidelines, doctors are leading the fight against HTN in young adults based only on clinical experience.[43]

Limitations

The present study in spite of having surveyed a large number of subjects has several limitations. Firstly, the cross-sectional study design may show causal association between gender, overweight/obesity, and HTN. Secondly, convenience sampling method used in the present study may lead to selection bias and limit the generalizability of the results which is considered an important limitation. Third, limitation is the consideration of single-point BP measurement. In the present study, mean of second and third BP measurement was considered, but guidelines do not recommend diagnosis of HTN based on single-point BP measurement and that could result in increased or decreased prevalence of HTN by including transient HTN.[12] Future studies should consider the above-discussed

limitations through conducting longitudinal studies and including larger, randomized samples.

Conclusion

Present study documents the increase in prevalence of HTN among young adults and its association with overweight and obesity. Prevalence of diastolic HTN in young population was observed as compared to increased prevalence of systolic HTN in older adults which signify age-related factors contributing to differences in the pathophysiology of HTN. Differences in HTN patterns among gender underscore the impact of hormonal and behavioral determinants.

The present study may suggest additional opportunities to curb increasing prevalence of HTN in young adults by improvement in the design and implementation of universal public health programs, such as routine screening and lifestyle modifications, including diet and exercise focusing on high-risk groups.

The present study suggests increasing HTN-related health concern among the young adults. Further studies must be done with more focus on longitudinal studies in order to fully understand HTN in young adults, its risk factors, possible prevention and management issues using modern technology to combat HTN, especially in young adults.

Orcid

Vitull K Gupta https://orcid.org/0009-0005-3146-0098

References

1. Mohan V, Anjana RM, Tandon N. Lessons learnt from the ICMR–INDIAB study. Natl Med J India 2023;36(3):137–139.
2. O'Neill A. Age Distribution in India 2013 to 2023; 2025.
3. United Nations. Department of Economic and Social Affairs, Population Division. World Population Prospects 2024: Demographic Indicators by Region, Subregion and Country, Annually for 1950-2100 (XSLX) ("Total Population, as of 1 July (thousands)"); 2025.
4. Randhawa G. Guest Column: It's High Time to Engage Youth Productively; 2023.
5. Statistics Times. Population of Punjab: 2011-36-Report of The Technical Group on Population Projections; 2024.
6. Anjana RM, Unnikrishnan R, Deepa M, et al. Metabolic non-communicable disease health report of India: the ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). Lancet Diabetes Endocrinol 2023;11(7):474–489.
7. Gupta R, Gaur K, Sharma SC, et al. District level variation in hypertension epidemiology in India and influence of social determinants: National Family Health Survey-5. medRxiv 2023.
8. Geevar Z, Krishnan MN, Venugopal K, et al. Prevalence, awareness, treatment, and control of hypertension in young adults (20–39 years) in Kerala, South India. Front Cardiovasc Med 2022:9:765442.
9. Shah SN, Munjal YP, Kamath SA, et al. Indian guidelines on hypertension-IV (2019). J Hum Hypertens 2020;34(11):745–758.
10. Gupta R, Maheshwari A, Verma N, et al. InSH consensus guideline for the management of hypertension, 2023. Hypertension J 2023;9(3):57–132.
11. Yano Y, Reis JP, Colangelo LA, et al. Association of blood pressure classification in young adults using the 2017 American College of Cardiology/American Heart Association blood pressure guideline with cardiovascular events later in life. JAMA 2018;320(17):1774–1782.
12. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018;71(6):1269–1324.
13. Sukor N. Clinical approach to young hypertension. Brunei Int Med J 2013;9(2):81–92.
14. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363(9403):157–163.
15. Misra A, Chowbey P, Makkar BM. Consensus statement for diagnosis of obesity, abdominal obesity and the metabolic syndrome for Asian Indians and recommendations for physical activity, medical and surgical management. J Assoc Physicians India 2009;57:163–170.
16. Mason JW, Ramesh DJ, Chanter DO, et al. Electrocardiographic reference ranges derived from 79,743 ambulatory subjects. J Electrocardiol 2007;40(3):228–234.
17. Sapra A, Malik A, Bhandari P. Vital Sign Assessment. StatPearls; 2023.
18. Kawabe H, Azegami T, Takeda A, et al. Features of and preventive measures against HTN in the young. Hypertens Res 2019;42(7):935–948.
19. Leeson P. Hypertension and cardiovascular risk in young adult life: insights from CAVI. Eur Heart J Suppl 2017;19(suppl_B):B24–B29.
20. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311(5):507–520.
21. Gupta R, Gaur K, Ram CVS. Emerging trends in hypertension epidemiology in India. J Hum Hypertens 2019;33(8):575–587.
22. Chopra HK, Ram CVS. Recent guidelines for hypertension. Circ Res 2019;124(7):984–986.
23. Khera R, Lu Y, Lu J, et al. Impact of 2017 ACC/AHA guidelines on prevalence of HTN and eligibility for antihypertensive treatment in United States and China: nationally representative cross sectional study. BMJ 2018;362:k2357.
24. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. J Am Coll Cardiol 2020;76(25):2982–3021.
25. Li Y, Lu Y, Hurwitz EL, et al. Gender disparities of heart disease and the association with smoking and drinking behavior among middle-aged and older adults, a cross-sectional study of data from the US health and retirement study and the China health and retirement longitudinal study. Int J Environ Res Public Health 2022;19(4):2188.
26. Ramirez LA, Sullivan JC. Sex differences in hypertension: where we have been and where we are going. Am J Hypertens 2018;31(12):1247–1254.
27. Kotsis V, Stabouli S, Papakatsika S, et al. Mechanisms of obesity-induced hypertension. Hypertens Res 2010;33(5):386–393.
28. Prabhakaran D, Jeemon P, Roy A. Cardiovascular diseases in India: current epidemiology and future directions. Circulation 2016;133(16):1605–1620.
29. Muntner P, Carey RM, Gidding S, et al. Potential US population impact of the 2017 ACC/AHA high blood pressure guideline. Circulation 2018;137(2):109–118.
30. Kornitzer M, Dramaix M, De Backer G. Epidemiology of risk factors for hypertension: implications for prevention and therapy. Drugs 1999;57(5):695–712.
31. Boakye K, Bovbjerg M, Schuna J Jr, et al. Urbanization and physical activity in the global prospective urban and rural epidemiology study. Sci Rep 2023;13(1):290.
32. Baoum S, Alamri M, Bana R, et al. Hypertension in young adults: causes, management and lifestyle modification. J Healthc Sci 2023;3(7):202–209.
33. Seravalle G, Grassi G. Heart rate as marker of cardiovascular risk. Postgrad Med 2020;132(4):358–367.
34. Ahmad MM. Hypertension: the silent killer. Int J Sci Res 2020;9(9):65–66.
35. Gao Y, Chen G, Tian H, et al. Prevalence of hypertension in China: a cross-sectional study. PLoS One 2013;8(6):e65938.
36. Khalid N, Haider S, Hasnat M, et al. Trends and disparities in prevalence of diagnosed hypertension among U.S. adults from 2019 to 2022. Curr Probl Cardiol 2024;49(10):102750.
37. Tadvi AY, Bandi JR. Study of prevalence of hypertension in young adult population of age group 20 to 40 years in an urban slum of Mumbai, Maharashtra, India. Int J Comm Med Pub Health 2016;3(12):3325–3331.
38. Zafar KS, Ram VS, Kumar M, et al. The prevalence of hypertension among young adults in a rural population of North India. Int J Res Med Sci 2017:5(11):4869–4872.
39. Hinton TC, Adams ZH, Baker RP, et al. Investigation and treatment of high blood pressure in young people: too much medicine or appropriate risk reduction? Hypertension 2020;75(1):16–22.
40. Gupta K, Ramakrishnan S, Zachariah G, et al. Impact of the 2017 ACC/AHA guidelines on the prevalence of HTN among Indian adults: results from a cross-sectional survey. Int J Cardiol Hypertens 2020;7:100055.
41. International Institute for Population Sciences (IIPS), ICF. National Family Health Survey (NFHS-5), 2019-21: India Report. Mumbai: IIPS; 2021.
42. Kaur P, Kunwar A, Sharma M, et al. The India hypertension control initiative—early outcomes in 26 districts across five states of India, 2018–2020. J Hum Hypertens 2023;37(7):560–567.
43. Jadhav U, Tiwaskar M, Khan A, et al. Hypertension in young adults in India: perspectives and therapeutic options amongst clinician's in a cross sectional observational study. J Assoc Physicians India 2021:69(11):11–12.

ORIGINAL ARTICLE

Viva Voce Examination Using Unstructured Impromptu Questions and Structured *Viva Voce* Cards: A Comparative Study among Final Year MBBS Students in the Subject of Internal Medicine

Abraham M Ittyachen[1*], Binitha Baby[2], Meera B John[3], Neha M Baby[4], Sarath C Mathew[5]

Received: 06 January 2025; *Accepted:* 23 May 2025

Abstract

Background: In the medical curriculum, *viva voce* is a crucial component of formative and summative assessment. However, despite many advantages, it also has some pitfalls. The primary objective of this study is to ascertain whether there is a significant difference in assessment between *viva voce* conducted using extempore questions and *viva voce* conducted using structured *viva voce* cards.

Methods: This prospective observational study took place over a period of 3 months. *Viva voce* was conducted by four examiners in internal medicine among final-year students pursuing MBBS, initially in an unstructured manner using extempore questions, and later using structured questions of increasing difficulty in the form of printed cards. A theory examination was conducted before the *viva voce*. In addition, a feedback survey using a Likert scale questionnaire was conducted among the students and examiners to assess their perception.

Results: Students scored the best in unstructured *viva*, followed by theory and structured *viva*. There was a moderately positive correlation between unstructured and structured *viva* and theory scores. There was a poor correlation between *viva* and perception scores for both unstructured and structured *viva*. The examiners had a slightly more positive perception toward the unstructured *viva* method than the structured method.

Conclusion: Unlike most studies in preclinical and paraclinical subjects, this study is a contradiction, with students scoring better in the unstructured method and faculty also showing a preference for the same. Further research is required on the effectiveness of both unstructured and structured *viva* in clinical settings.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1083

Introduction

"*Viva Voce*" (Medieval Latin) or examination "by word of mouth," "orally," and "by the living voice," was the earliest form of formal assessment of medical and other apprentices, dating back to premedieval times.[1] Currently also, *viva voce* forms an important part of formative and summative evaluation in medical courses. It allows the examiner to test the scope of knowledge of the subject[2] and probe the limits of knowledge in both borderline and exceptional students.[3] However, the method has been an area of contention because of excessive subjectivity and being swayed by academic and nonacademic factors associated with students and teachers.[3] Low validity and low reliability are the other disadvantages of the traditional *viva*.[4]

Research Question

Is there a significant difference in the assessment between *viva voce* conducted using extempore questions and in a structured manner using *viva voce* cards?

Objectives

- To estimate whether there was a significant difference in assessment between *viva voce* conducted using extempore questions and in a structured manner using *viva voce* cards.
- To compare the marks, the examinee (student) obtained in the two *viva voce* methods with those obtained in the traditional theory paper.
- To conduct a postsurvey study using a Likert scale questionnaire among students and examiners to assess their perception of the study.

Review of Literature

Viva voce, or conventional oral examination, is an important instrument for evaluation in medical education. However, common drawbacks are that it is affected by both academic and nonacademic factors that pertain to students and teachers, which led to the criticism for being too subjective.[3]

The test environment and the candidate's level of anxiety may affect scores in the traditional form of *viva voce*.[5] The examination scores were also correlated with personality scores.[6] The system-related factors described are central tendency, leniency, "Halo effect," and error of contrast.[7]

One important drawback of the conventional oral examination is examiner "fatigue." Students who are initially examined may be asked many questions, but as the examination proceeds, students toward the end tend to be asked fewer questions for the same duration. This contributes to subjective variation in the assessment of candidates. In addition to the high subjectivity of the examiner,[3,8–10] *viva voce* may also be taken casually. Studies have shown that scores are directly proportional to the number of words spoken by the examiners and the time taken by them.[11]

Overall, conventional oral examinations are more time consuming and much less cost-effective than other methods of examination.[12,13]

Examiners may be prejudiced by their knowledge of the subject, their choice areas of interest, and momentary environmental distractions.[14–16] The standard of the questions asked, the self-esteem of the examiner, and the order in which the questions are asked, sometimes the students felt dissatisfied and disgraced. In some cases, the event is felt as intimidating and threatening, which at times gives way to confrontation.[15–17]

[1]Professor of Medicine and Consultant in Critical Care; [2–5]Assistant Professor, Department of General Medicine, Malankara Orthodox Syrian Church Medical College Hospital, Ernakulam, Kerala, India; *Corresponding Author

How to cite this article: Ittyachen AM, Baby B, John MB, *et al. Viva Voce* Examination Using Unstructured Impromptu Questions and Structured *Viva Voce* Cards: A Comparative Study among Final Year MBBS Students in the Subject of Internal Medicine. J Assoc Physicians India 2025;73(8):50–54.

Examiners may discriminate on the basis of economic status, gender, ethnic status, or minority status. They may even be influenced by personality, clothing, and verbal style of the candidate, in *viva voce*.[15]

Methodology

This prospective observational study (cohort study) was conducted in the Department of Medicine of Malankara Orthodox Syrian Church Medical College Hospital, Ernakulam, Kerala, India. The study period was 3 months (from April 1 to June 30, 2024), and the study subjects were final-year MBBS students.

Inclusion Criteria

All final-year MBBS students (2020 batch) participated in the second sessional exam and were ready to participate in the study.

Exclusion Criteria

Final-year MBBS students (2020 batch) participated in the second sessional exam and were not willing to be part of the study.

After securing informed consent, the study objectives were explained to the participating students. On the 1st day, four examiners assessed the students using *viva voce* in an unstructured manner by asking questions; each examiner was restricted to one subject. The next day, the same four examiners asked four questions using structured cards, each of graded difficulty (one to four marks, one for the easiest question among the four, and four for the most difficult), and marks were awarded based on the number of questions answered correctly. Each examiner was restricted to one participant. The questions were arranged in a manner that progressively increased in difficulty, in accordance with Bloom's taxonomy of educational objectives of the cognitive domain, and were collectively endorsed by the examiners. Theory examination was conducted before the *viva voce*. The topics covered in the theory and *viva* were the same. Care was taken to ensure that questions on the printed cards were not asked during the unstructured *viva voce*. In addition, a feedback survey using a Likert scale questionnaire was conducted among the students and examiners to assess their perception toward the two methods of *viva* (Fig. 1). A questionnaire was developed specifically for this study. The study protocol was approved by the Institutional Ethics Committee (IEC): (MOSC/IEC/127/2024).

Statistical Analysis

Descriptive statistics were used to detail students' performance across the two examination formats. The Wilcoxon signed-rank test was conducted to compare structured and unstructured *viva* scores, and in the same way for structured and unstructured *viva* scores with theory scores. The association between student gender, with two defined categories, and examination scores was also explored. If the data within each sex category followed a normal distribution, independent *t*-tests were used to compare the mean scores between male and female. For nonnormally distributed data, the Mann–Whitney *U* test was used. Correlation analysis was used to examine the relationship between continuous variables, such as the marks obtained in the two examination formats, and between marks and sex. The Pearson correlation coefficient was computed for data that followed a normal distribution, while Spearman's rank correlation was applied to data that did not conform to normality. A statistical significance threshold of $p < 0.05$ was established. The statistical analyses were conducted utilizing IBM Statistical Package for the Social Sciences (SPSS) version 22.

The rationale behind testing the correlation between perception and *viva* scores was to ascertain if a statistical relationship existed between how students perceived their understanding of the subject and their actual performance in *viva* (oral examination). A strong correlation suggests that student's perceptions accurately reflect their knowledge, whereas a weak correlation indicates a mismatch between perception and actual performance.

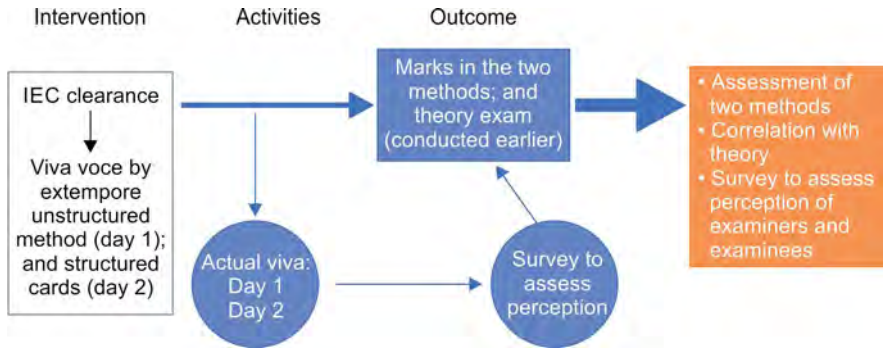


Fig. 1: Schematic representation of the research methodology

Results

Collectively, 83 students were part of the study, of whom 15 (18.1%) were male and 68 (81.9%) were female. Average age of the study participants was 22.5 ± 0.75 (min: 21, max: 24).

A statistically significant difference was observed in the average scores of students (subject-wise) when comparing unstructured and structured *viva* voices, with students scoring better in unstructured *viva* (Table 1).

When comparisons were made between unstructured *viva* scores (subject-wise) and theory marks, a statistically significant difference in the scores of students was noted, with students scoring better in unstructured *viva* (Table 2A). However, a comparison between the structured *viva* scores (subject-wise) and theory indicated that students scored better in theory (Table 2B).

When the subjects were taken together, there was a statistically significant difference in the average score of the students, with students scoring better in the unstructured *viva* than structured *viva* (Fig. 2).

Spearman rank correlation showed a moderate positive correlation between structured *viva* scores and theory scores ($r = 0.483$, p-value < 0.001) and unstructured viva scores with theory scores ($r = 0.496$, p-value < 0.001).

Among males, there was a moderate positive correlation between the structured *viva* and theory scores, but this did not

Table 1: Comparison of unstructured *viva* scores with structured *viva* scores

Subjects	*Unstructured viva score median (Q1, Q3)*	*Structured viva score median (Q1, Q3)*	*Test statistic value*	*p-value*
Cardiovascular system (CVS)	4.5 (4.0, 5.0)	2.0 (1.0, 3.5)	6.73	<0.001*
Respiratory system (RS)	6.0 (4.0, 7.0)	2.0 (1.5, 3.0)	7.73	<0.001*
Nephrology	5.0 (5.0, 6.0)	3.0 (1.0, 4.0)	7.44	<0.001*
Gastrointestinal tract (GIT)	6.0 (5.0, 7.0)	2.0 (1.0, 4.0)	7.67	<0.001*

*Statistically significant at $p < 0.05$

Table 2: Comparison of *viva* scores (subject-wise) with theory scores

Subjects	*Unstructured viva score median (Q1, Q3)*	*Theory marks median (Q1, Q3)*	*Test statistic value*	*p-value*
(A) Unstructured				
Cardiovascular system (CVS)	4.5 (4.0, 5.0)	3.5 (2.6, 4.5)	5.42	<0.001*
Respiratory system (RS)	6.0 (4.0, 7.0)	3.5 (2.6, 4.5)	7.42	<0.001*
Nephrology	5.0 (5.0, 6.0)	3.5 (2.6, 4.5)	6.90	<0.001*
Gastrointestinal tract (GIT)	6.0 (5.0, 7.0)	3.5 (2.6, 4.5)	7.53	<0.001*
Subjects	*Structured viva score median (Q1, Q3)*	*Theory marks median (Q1, Q3)*	*Test statistic value*	*p-value*
(B) Structured				
CVS	2.0 (1.0, 3.5)	3.5 (2.6, 4.5)	4.78	<0.001*
RS	2.0 (1.5, 3.0)	3.5 (2.6, 4.5)	5.40	<0.001*
Nephrology	3.0 (1.0, 4.0)	3.5 (2.6, 4.5)	4.29	<0.001*
GIT	2.0 (1.0, 4.0)	3.5 (2.6, 4.5)	4.89	<0.001*

*Statistically significant at $p < 0.05$

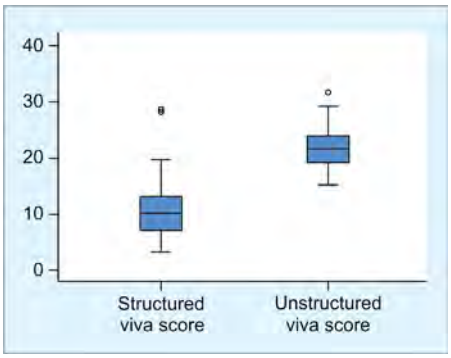


Fig. 2: Comparison of total score (total of all subjects) of structured and unstructured *viva*

reach statistical significance ($r = 0.401$, p-value = 0.139). Conversely, a moderate positive correlation was identified between the unstructured *viva* and theory scores which was statistically significant ($r = 0.604$, p-value = 0.017). Among females, a statistically significant moderate positive correlation existed between the structured *viva* scores ($r = 0.467$, p-value < 0.001), unstructured *viva* scores ($r = 0.487$, p-value < 0.001), and theory scores.

The Mann–Whitney *U* test revealed no statistically significant difference in structured [11.5 (6, 12.5) vs 10 (7, 13), p-value = 0.873] and unstructured *viva* scores [21.50 (18, 23) vs 21.25 (19, 24), p-value = 0.785] between males and females.

In the questionnaire to assess the perception of students with regards to the structured *viva voce* method, there were eight questions rated on a Likert scale, with a lowest possible score of eight and a highest possible score of 40. The median score was 27 (23, 29). Questionnaire reliability was assessed using Cronbach's alpha. The alpha value was 0.760, which is good and acceptable. The Spearman's correlation coefficient revealed a poor correlation ($r = 0.017$) between the structured *viva voce* and perception scores. The Mann–Whitney *U* test was used to compare the perception score between genders, with a median (Q1, Q3) score of 27 (23, 29.75) for females and 26 (26, 28) for males, which was statistically insignificant (p-value = 0.565).

In the questionnaire used to assess the perception of students toward the unstructured *viva voce* method, there were six questions on a Likert scale, with a minimum score of six and a maximum score of 30. The median score was 21 (19, 23). Questionnaire reliability was assessed using Cronbach's alpha. The alpha value was 0.639, which was acceptable. The Spearman's correlation coefficient revealed a poor correlation ($r = 0.181$) between the unstructured *viva voce* and perception scores. The Mann–Whitney *U* test was used to compare the perception scores between genders, with median (Q1, Q3) scores of 21 (19, 23) for females and 21 (20, 23) for males, which was not statistically significant (p-value = 0.374).

The feedback survey using a Likert scale among the four examiners to assess their perceptions toward structured *viva voce* and unstructured *viva voce* methods consisted of 10 questions, with a minimum score of 10 and a maximum score of 50. The median perception score of examiners regarding their structured *viva voce* method was 31 (30, 33.5), whereas for unstructured *viva voce* method it was 33.5 (30.75, 34.75).

Discussion

The *viva voce* method of examination forms an important part of assessment in the medical education. In this study, an attempt was made to determine whether there is a significant difference in the assessment between *viva voce* conducted using extempore questions and *viva voce* conducted in a structured manner using *viva voce* cards in the subject of internal medicine. Most studies available in the literature have compared unstructured and structured *viva voce* examinations involving pre- and paraclinical subjects. This study involved a clinical discipline (internal medicine) and, therefore, may be considered rare.

When comparison was made in this study between unstructured and structured *viva voce*, a statistically significant difference in the average score of students was noted, with students scoring better in unstructured *viva*. This was true when the analysis was conducted subject-wise and when done with the subjects taken together. In a study by Khilnani et al.,[2] *viva voce* was conducted with both conventional and structured methods among undergraduate students in pharmacology; structured *viva* yielded significantly lower marks compared to conventional *viva*. However, this was not true for all subjects. When a similar study was conducted among undergraduate anatomy students, no major difference was found in mean scores between the two methods.[17] Across specialties, when the academic performance of undergraduate dental students was compared using structured and unstructured oral examinations, there was no major difference in mean scores achieved.[18] Since no single method, structured or unstructured, can be considered superior across the spectrum of undergraduate medical subjects, further studies should be conducted on this topic. In a systematic review and meta-analysis by Anbarasi et al.,[19] 18 peer-reviewed articles on conventional and structured oral examinations for medical students were reviewed. The analysis indicated that there was no difference in the mean marks obtained by the conventional *viva* or structured method.

The cognitive domain is the most important of all domains. Psychomotor and affective domains are inextricably linked to the cognitive domain. Without appropriate intelligence/knowledge of the subject, it is unlikely that the student will demonstrate exceptional skills or conduct. In medical courses, the cognitive domain is primarily expressed in the theory paper.[20]

In this study, when comparing unstructured *viva* scores (subject-wise) and theory marks, there was a statistically significant difference in the scores of students, with students scoring better on the unstructured *viva*. If theory is considered the gold standard in the assessment of the cognitive domain, a higher score in unstructured *viva* indicates a poor correlation between the two, and unstructured *viva* is a poor marker of the cognitive domain.

When comparison was made between structured *viva* scores (subject-wise) and theory marks in this study, there was a statistically significant difference in the scores of students, with students scoring better in theory. Studies have shown a better correlation between theory and structured *viva* than unstructured *viva*.[21,22] A properly designed structured *viva* has multiple advantages in that it has wide coverage; it promotes disinhibition, encourages better expression, and reduces anxiety and shyness in the student, in contrast to an unstructured *viva* that is stained with high subjectivity, lack of a format and uniformity,[9] and unreliability.[15,23] An unstructured *viva* also heightens apprehension among students (strenuous level of questions, emphasis on problem-solving, and direct and immediate feedback) and hesitation among faculty members (structured *viva* demands comprehensive planning, prevalidated well-structured questions, scoring criteria, and adequate resources and manpower) in terms of execution.[24]

The Spearman rank correlation showed a moderate positive correlation between unstructured and structured *viva* and theory scores in this study. However, when comparisons were made (as explained above) between the scores obtained by the two *viva* methods (unstructured and structured) and theory, there was a statistically significant difference in the score with students scoring better in unstructured *viva*. However, this was not the case for structured with students scoring better in theory.

There was no statistically significant difference in structured and unstructured *viva* scores between males and females in this study. However, studies involving the traditional (unstructured) *viva voce* have highlighted the presence of possible gender bias. Lack of standardization leading to variability in questioning and assessment can inadvertently introduce gender bias. By implementing a standardized set of questions and evaluation criteria, structured *viva* can provide a uniform platform for all candidates thereby reducing the scope to gender bias.

When the questionnaire assessing the perception of students toward unstructured *viva voce* was analyzed, there was a poor correlation between *viva* and perception scores. So was the conclusion with structured *viva*.

When the feedback survey from the examiners to assess their perception toward the two types of *viva* was analyzed, the median scores and the ranges provided suggested that the examiners had a slightly more positive perception toward the unstructured *viva* method. This information could be useful in understanding the examiner's preferences and perceptions toward the two different *viva voce* methods, which could in turn decide the choice of assessment method or the need for further studies.

Conclusion

Students scored best in unstructured *viva voce* setting, followed by theory and structured *viva*. There was a moderately positive correlation between unstructured and structured *viva* and theory scores. There was a poor correlation between the *viva* scores and the perception (toward *viva*) scores of students. Examiners had a slightly more positive perception toward the unstructured *viva* method. Most of the studies showing the acceptability of structured *viva* have dealt with pre- and paraclinical subjects, whereas studies on clinical subjects in which the two *viva* methods are compared are rare. Unlike studies involving pre- and paraclinical subjects that have shown acceptability for structured *viva*, this study revealed an opposite trend, with students scoring better in the unstructured method and faculty also showing a preference for the same. Further research is required to assess the efficacy of both unstructured and structured *viva voce* examination in clinical subjects to assess learning progress.

Another option would be to modify the traditional *viva voce* methods to bring out the best of the two methods studied here. Combining the structured and unstructured elements (hybrid approach) can offer a balanced assessment. For instance, starting with standardized questions to ensure core competencies are covered, followed by open-ended questions that allow exploration of the student's clinical reasoning and problem-solving abilities.

Limitations

This study has some limitations. The sample size was small because only students from one institution participated in the study. Moreover, this was a single-center study and may not represent a wider population of medical students. This study involved a clinical discipline and, as already mentioned, similar studies involving a clinical subject are rare; hence, further research involving other clinical disciplines is needed. Additionally, methodological limitations include variables that could affect student's performance, such as prior knowledge or test anxiety, which may not have been controlled for. The presence of potential confounders, and effect modifiers is also a limitation.

As a study this could have potential confounders and effect modifiers. First, the examiner bias where the results of the assessment may be affected by the prejudgments or preferences of individual examiners for particular *viva voce* techniques. Experienced examiners might handle impromptu questioning more proficiently, while less experienced ones might rely heavily on structured formats. This discrepancy can affect the consistency and fairness of assessments. Second, student's readiness representing differences in student's preparedness or familiarity with the various *viva voce* forms may have a direct bearing on the outcome. For instance, those familiar with structured questions might excel in that format but struggle with impromptu questions, leading to performance differences unrelated to actual knowledge or skills.

Prolonged assessment periods can lead to examiner fatigue, potentially affecting their concentration and judgment. Examiners' personal biases and personality traits can introduce variability in student's assessments. The interplay of examiner fatigue, biases, and personality can create an inconsistent assessment environment, potentially disadvantaging students.

Finally, the examination room environment, such as comfort, noise level, distractions, and overall atmosphere can influence student's outcomes.

Acknowledgments

The authors wish to express their gratitude to the students of the 2020 MBBS batch of Malankara Orthodox Syrian Church Medical College Hospital, Ernakulam, who participated in the study; the staff of the Department of Medicine, Malankara Orthodox Syrian Church Medical College Hospital, Ernakulam; Mrs Anjaly S Nair, lecturer and biostatistician in Malankara Orthodox Syrian Church Medical College Hospital, Ernakulam; and the Faculty of National Medical Commission (NMC) Nodal Center for Faculty Development, Government Medical College, Kottayam, India.

Orcid

Abraham M Ittyachen https://orcid.org/0000-0001-7918-5500
Neha M Baby https://orcid.org/0009-0000-1392-0277

References

1. Bode C, Ugwu B, Donkor P. *Viva voce* in postgraduate surgical examinations in anglophone West Africa. J West Afr Coll Surg 2011;1(1):40–52.
2. Khilnani AK, Charan J, Thaddanee R, et al. Structured oral examination in pharmacology for undergraduate medical students: factors influencing its implementation. Indian J Pharmacol 2015;47(5):546–550.
3. Torke S, Abraham R, Komattil R, et al. The impact of *viva voce* examination on students' performance in theory component of final summative evaluation in physiology. J Physiol Pathophysiol 2010;1:10–12.
4. Abuzied AIH, Nabag WOM. Structured viva validity, reliability, and acceptability as an assessment tool in health professions education: a systematic review and meta-analysis. BMC Med Educ 2023;23(1):531.
5. Iqbal IZ, Naqvi S, Abeysundara L, et al. The value of oral assessments: a review. Ann R Coll Surg Engl 2010;92:1–6.
6. Memon MA, Joughin GR, Memon B. Oral assessment and postgraduate medical examinations: establishing conditions for validity, reliability and fairness. Adv Health Sci Educ Theory Pract 2010;15(2):277–289.
7. Evans LR, Ingersoll RW, Smith EJ. The reliability, validity, and taxonomic structure of the oral examination. J Med Educ 1966;41(7):651–657.
8. Ray MK, Ray S, Ray U. Technology enabled assessment of *viva voce*: a new challenge. J Adv Res Biol Sci 2013;5:238–242.
9. Ghosh A, Mandal A, Das N, et al. Student's performance in written and viva-voce components of final summative pharmacology examination in MBBS curriculum: a critical insight. Indian J Pharmacol 2012;44(2):274–275.
10. Verma A, Mahajan N, Jasani K. Evaluation & comparison of results: conventional viva vs. structured viva. Glob Res Anal 2013;2(5):188–189.
11. Holloway PJ, Hardwick JL, Morris J, et al. The validity of essay and viva-voce examining techniques. Br Dent J 1967;123(5):227–232.
12. Oakley B, Hencken C. Oral examination assessment practices: effectiveness and change with a first year undergraduate cohort. J Hosp Leis Sport Tourism Educ 2005;4(1):3–14.
13. Schuwirth LWT, van der Vleuten CPM. Changing education, changing assessment, changing research? Med Educ 2004;38(8):805–812.
14. Singel TC, Shah C, Dixit D. Small group structured oral examination: an innovation in oral examination. Natl J Integr Res Med 2014;5(1):141–145.
15. Davis MH, Karunathilake I. The place of the oral examination in today's assessment systems. Med Teach 2005;27(4):294–297.
16. Haque M, Yousuf R, Abu Bakar SM, et al. Assessment in undergraduate medical education: Bangladesh perspectives. Bangladesh J Med Sci 2013;12(4):357–363.
17. Shaikh ST. Objective structured viva examination versus traditional viva examination of medical students. Anat Physiol 2015;5(3):175.
18. Lakshminarayan N, Usha GV. Comparison of undergraduate dental students' academic performance using structured and unstructured oral examinations. Int J Acad Med 2022;8(3):131–136.
19. Anbarasi K, Karunakaran JV, Ravichandran L, et al. Effectiveness of the structured and conventional methods of viva examination in medical education: a systematic review and meta-analysis. J Clin Diagn Res 2022;16(9):JE01–JE07.
20. Shukla S, Acharya S, Acharya N, et al. Quality theory paper writing for medical examinations. J Clin Diagn Res 2014;8(4):XC01–XC04.
21. Dhasmana DC, Bala S, Sharma R, et al. Introducing structured *viva voce* examination in medical undergraduate pharmacology: a pilot study. Indian J Pharmacol 2016;48(Suppl 1):S52–S56.
22. Ahsan M, Mallick AK. A study to assess the reliability of structured viva examination over traditional viva examination among 2nd-year pharmacology students. J Datta Meghe Inst Med Sci Univ 2022;17(3):589–594.
23. Muzzin LR, Hart L. Oral examinations. In: Neufeld VR, Norman GR, editors. Assessing Clinical Competence. New York: Springer Publishing Company; 1985. pp. 71–93.
24. Rahman G. Appropriateness of using oral examination as an assessment method in medical or dental education. J Educ Ethics Dent 2011;1(2):46.

ORIGINAL ARTICLE

Correlation of Glycemic Status with Angiographic Severity of Coronary Artery Disease in Acute Coronary Syndrome

Varsha Rakshitha Prakash[1*], Mohammed Omar Shariff[2], Vadagenalli Sathyanarayanarao Prakash[3]

Received: 01 February 2025; *Accepted:* 17 March 2025

Abstract

Background: Cardiovascular disease (CVD) remains the leading cause of illness and death worldwide, placing a significant strain on healthcare systems. Its development is influenced by multiple factors, with major risk contributors including hypertension, dyslipidemia, diabetes mellitus (DM), and lifestyle-related behaviors. Among these, DM notably increases the risk of coronary artery disease (CAD), particularly acute coronary syndrome (ACS). Chronic hyperglycemia in DM accelerates atherosclerosis, thereby heightening the risk of vascular complications.

Given the intricate relationship between diabetes and CVD, assessing the influence of glycemic status on CAD severity is essential.

This study aims to evaluate the severity of CAD in diabetic, prediabetic, and nondiabetic patients presenting with ACS using the Gensini score, a validated angiographic tool for measuring disease severity.

Aim: To assess the severity of CAD in patients with ACS using the Gensini score, comparing disease severity among prediabetic, diabetic, and nondiabetic individuals.

Materials and methods: A 6-month hospital-based cross-sectional study was conducted at a tertiary care center from July to December 2023, involving 150 patients diagnosed with ACS who underwent coronary angiography (CAG). Data collection was carried out retrospectively (July to September 2023) from inpatient records and prospectively (October to December 2023) from patients meeting the inclusion criteria. Clinical parameters, including patient history, comorbid conditions, cardiac biomarkers, HbA1c levels, electrocardiography (ECG), echocardiography (ECHO), and angiographic findings, were analyzed. The severity of CAD was assessed using the Gensini score.

Statistical analysis: Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 22. Categorical variables were expressed as frequencies and percentages, with statistical significance determined using the Chi-square or Fisher's exact test. Continuous variables were represented as mean ± standard deviation (SD) and compared using analysis of variance (ANOVA). Pearson's correlation was employed to examine associations between variables. Multivariate regression analysis was conducted to identify predictors of CAD severity (based on the Gensini score), adjusting for potential confounders such as diabetes duration (HbA1c ≥6.5%), age, and other cardiovascular risk factors. A *p*-value of <0.05 was considered statistically significant. Graphs were generated using Microsoft Excel and Word.

Results: The study analyzed 150 patients with ACS who underwent CAG, comprising 114 diabetic, 20 prediabetic, and 16 nondiabetic individuals. A male predominance was observed, with 100 male participants.

Diabetic patients exhibited the highest severity of CAD, with a mean Gensini score of 49.08 ± 39.67, followed by prediabetic patients with a mean score of 24.48 ± 41.42. Nondiabetic patients had the least severe CAD, with a mean Gensini score of 0.94 ± 2.56. Additionally, triple-vessel disease was more prevalent among diabetic individuals.

A significant positive correlation was observed between diabetes duration and CAD severity, indicating that prolonged diabetes exposure is associated with more extensive coronary artery involvement.

Conclusion: This study confirms that diabetes significantly exacerbates the severity of CAD, with diabetic patients exhibiting more severe CAD than prediabetic and nondiabetic individuals. Additionally, the findings demonstrate a direct correlation between diabetes duration and increased CAD severity.

The results emphasize the heightened risk of triple-vessel disease in diabetic patients, underscoring the necessity for targeted cardiovascular and diabetes management strategies to mitigate disease progression and improve patient outcomes.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1034

Introduction

Cardiovascular disease (CVD) is the foremost contributor to both illness and mortality on a global scale.

Affecting >523 million individuals, atherosclerotic conditions, notably ischemic heart disease and stroke, are the primary drivers of the CVD burden. Ischemic heart disease alone is linked to about half of all CVD-related deaths, while ischemic stroke accounts for roughly another quarter.[1]

Diabetes mellitus (DM) is a major risk factor for cardiovascular conditions, including acute coronary syndrome (ACS). The link between these diseases is well established, as diabetes not only contributes to the onset of ACS but also exacerbates its outcomes. Individuals with diabetes face a two to four times greater risk of experiencing ACS events—such as non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI)—primarily due to the accelerated development of atherosclerosis, endothelial dysfunction, and a prothrombotic state that result from chronic hyperglycemia and insulin resistance.

From a pathophysiological perspective, diabetes tends to induce a more aggressive form of coronary artery disease (CAD), frequently affecting multiple vessels and leading to increased complications in ACS patients. Moreover, diabetics often have altered platelet function, which heightens their risk for thrombotic events. The presence of autonomic neuropathy in many of these patients can lead to "silent ischemia," delaying both diagnosis and treatment. This delay is associated with poorer outcomes, including higher mortality rates, recurrent myocardial infarctions, and an increased incidence of heart failure.

On a global scale, diabetes represents a significant public health challenge. Currently, around 537 million adults between the ages of 20 and 79 years are living with the condition. According to projections by the International Diabetes Federation, by 2045 approximately 783 million adults—or one in eight—will be affected by diabetes.

[1]Assistant Professor; [2]Senior Resident; [3]Professor, Head of the Department, Department of Cardiology, Ramaiah Medical College, Bengaluru, Karnataka, India; *Corresponding Author

How to cite this article: Prakash VR, Shariff MO, Prakash VS. Correlation of Glycemic Status with Angiographic Severity of Coronary Artery Disease in Acute Coronary Syndrome. J Assoc Physicians India 2025;73(8):60–66.

Diabetes creates a significant economic strain around the globe, with developing nations bearing the brunt of its impact. Approximately 75% of adults with diabetes live in low- and middle-income countries, which exacerbates the financial challenges these regions face.[2]

National Cholesterol Education Program's Adult Treatment Panel III guidelines[3] equate having diabetes with having CAD.

Diabetes damages the endothelium of blood vessels and leads to the formation of harmful glycation products, accelerating atherosclerosis. Compared to individuals without diabetes, those with the condition face an elevated risk of vascular complications that can affect major organs.[4]

The aging population globally is contributing to the increasing prevalence of CVDs. As individuals age, the risk of developing CVD significantly increases due to factors such as arterial stiffness, hypertension, and lifestyle changes. By 2050, it is estimated that nearly one in six people worldwide will be over the age of 65, exacerbating the global burden of CVD.[5]

Cardiovascular disease stands as the foremost contributor to both morbidity and mortality in individuals with diabetes.[6,7]

Among individuals with diabetes, major risk factors for CVD include high blood pressure, elevated cholesterol levels, hyperglycemia, and obesity.

Several studies have shown a direct link between chronic high blood sugar levels and cardiovascular complications in people with diabetes.[8,9]

Lifestyle choices that are within our control—such as consuming an unhealthy diet, remaining physically inactive, smoking, and drinking excessive amounts of alcohol—play a major role in the onset of CVDs. According to estimates from the World Health Organization, these behavioral risk factors are responsible for nearly 80% of cases of coronary heart disease and cerebrovascular disease.[10]

Cardiovascular diseases place a heavy burden on healthcare systems worldwide and also carry considerable economic consequences. In 2015, the global expenditure associated with CVD was estimated at around $863 billion. This cost is projected to increase to approximately $1 trillion per year by 2030, driven by rising healthcare expenses, reduced productivity, and the growing demands for long-term care.[11]

Women with diabetes experience a loss of the inherent protective advantage they usually have against developing CAD, making them more susceptible to the condition compared to women without diabetes.[12] The Organization to Assess Strategies for Ischemic Syndromes study found that diabetic patients without any prior history of CVD experience long-term morbidity and mortality rates similar to those of nondiabetic patients who already have established CVD following hospitalization for unstable CAD.[13]

Diabetic patients experience a high mortality rate following their first myocardial infarction, with a significant number of these deaths occurring outside of hospital settings.[14]

These findings, along with the results of the INTERHEART study,[15] further reinforce the connection between diabetes and CAD. Despite extensive research, gaps remain in understanding how varying degrees of glycemic dysregulation (i.e., nondiabetic, prediabetic, and diabetic states) correlate with the angiographic severity of CAD in ACS patients. The Organization to Assess Strategies for Ischemic Syndromes (OASIS) study revealed that diabetic patients have similar cardiovascular outcomes as nondiabetics with a history of CVD, yet the specific differences in CAD severity between prediabetic and diabetic patients remain less explored. Furthermore, while studies such as INTERHEART have highlighted the global impact of diabetes on myocardial infarction, a more detailed analysis of angiographic severity based on glycemic status is needed. This study aims to fill these gaps by quantitatively evaluating CAD severity using the Gensini score,[16] an angiographic severity index, and analyzing how CAD severity differs between nondiabetic, prediabetic, and diabetic ACS patients. Through this analysis, we aim to offer new insights into the relationship between glycemic status and CAD, potentially guiding more tailored management strategies in clinical practice.

Aim

The aim is to evaluate the severity of CAD in ACS patients by applying the Gensini score, and to compare the findings across prediabetic, diabetic, and nondiabetic groups.

Objectives

- To assess CAD severity in ACS patients across prediabetic, diabetic, and nondiabetic groups by analyzing coronary angiography (CAG) results, utilizing the Gensini score and HbA1c levels.
- To determine the correlation between glycemic control and CAD severity.
- To analyze the relationship between diabetes duration and CAD severity in diabetic patients.

Materials and Methods

The study was conducted at Ramaiah Medical College and Hospital in Bengaluru, Karnataka, India. Data were collected over 6 months, from July to December 2023, using both retrospective and prospective methods. During the retrospective phase, patient records for those admitted with ACS who had CAG between July and September 2023 were examined. In the prospective phase, information was gathered from ACS patients who had CAG between October and December 2023.

Study Population

A total of 150 patients over the age of 18 years who were diagnosed with ACS participated in the study. Based on their HbA1c levels, these patients were classified into three distinct glycemic groups:

- Diabetic: HbA1c ≥6.5%.
- Prediabetic: HbA1c 5.7–6.4%.
- Nondiabetic: HbA1c <5.7%.

Exclusion Criteria

Patients presenting any of the following conditions were not included in the study:

- Prior diagnosis of CAD.
- Severe anemia.
- Renal failure.
- Chronic obstructive pulmonary disease (COPD).
- Malignancies.

Clinical and Laboratory Assessments

All patients underwent comprehensive clinical evaluations, including:

- Physical examination.
- Cardiac biomarker analysis.
- Electrocardiography (ECG).
- Echocardiography (ECHO).

Diagnosis of ACS was based on ECG findings and biomarker analysis, classifying patients into the following subgroups:

- Unstable angina.
- NSTEMI.
- STEMI.

Gensini Score Calculation and Coronary Angiography

Coronary angiograms were analyzed, and the extent of CAD was evaluated using the Gensini score,[16] which assigns severity points based on the degree of stenosis in various coronary artery segments. The Gensini score was derived by assigning a severity rating to each lesion according to the degree of luminal narrowing and then multiplying that rating by

a factor based on the lesion's location within the coronary arterial system.

Overall Gensini score was obtained by summing the individual lesion scores. A total score ranging from 1 to 40 signified mild atherosclerosis, while scores above 40 indicated severe atherosclerosis.[17]

The steps to calculate the Gensini score are as follows:

- Step 1: Each coronary lesion is given a severity score that reflects the extent of its luminal narrowing, with additional adjustments made for total occlusions or lesions with 99% obstruction that are supplied by collateral circulation (Table 1).
- Step 2: Each lesion's score is adjusted by a multiplier that reflects its position within the coronary arterial system (Table 2).
- Step 3: (1) Gensini score for each lesion is calculated by multiplying the severity score of the stenosis with the location's weight factor. (2) Gensini score is calculated as the sum of the severity scores of all the lesions.

The Gensini score serves as a comprehensive measure of CAD severity, with higher scores indicating a more advanced level of disease.

Sample Size

The sample size was determined using the correlation coefficient between the Gensini score and HbA1c, which was reported as 0.31 (i.e., $r = -0.31$) in the study by Muhammad et al.[18] Using a 95% confidence level and 90% power in the calculation, the minimum required sample size was found to be 105. When accounting for a 10% nonresponse rate, the adjusted sample size became 116 (105 + 10.5). Nevertheless, 150 subjects who met the inclusion criteria were ultimately enrolled and analyzed during the study period.

Total sample size = $N = [(Z_\alpha + Z_\beta)/C]^2 + 3$

The standard normal deviate for $\alpha = Z_\alpha = 1.960$

The standard normal deviation for $\beta = Z_\beta = 1.28$

r = correlation coefficient = −0.31

$C = 0.5 \times \ln [(1 + r)/(1 - r)] = 0.3205$

$N = 105$

Statistical Analysis

Data were entered into Microsoft Excel, and statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) version 22 (IBM SPSS Statistics, Somers, NY, USA).

Categorical Data Analysis

- Categorical variables were summarized by calculating frequencies and proportions.
- To assess statistical significance for qualitative data, either the Chi-squared test or Fisher's exact test (for 2 × 2 contingency tables) was used.

Continuous Data Analysis

- Continuous variables were presented as mean values along with standard deviations (SDs).
- For comparing the means across more than two groups, analysis of variance (ANOVA) was employed.
- The Pearson correlation coefficient was applied to investigate the relationships between continuous variables.

Graphical Representation

Various charts and graphs were created using Microsoft Excel and MS Word to visually represent the data.

Statistical Significance

A p-value of <0.05 was regarded as statistically significant, in line with the assumptions underlying the statistical tests used.

Multivariate Regression Analysis

A multivariate regression model was developed to assess the relationship between diabetes duration (HbA1c ≥6.5%) and various clinical and demographic predictors.

Variables included in the model are as follows:

- Dependent variable: Duration of diabetes (years).
- Independent variables:
  - Gensini score.
  - Age.
  - Gender.
  - Diagnosis.

Table 2: Calculation of the Gensini score. Step 2: a multiplying factor is applied to each lesion score based upon its location in the coronary tree

Segment	*Right dominance*	*Left dominance*
RCA proximal	1	1
RCA mid	1	1
RCA distal	1	1
PDA	1	1
PLB	0.5	0.5
Left main	5	5
LAD proximal	2.5	2.5
LAD mid	1.5	1.5
LAD apical	1	1
First diagonal	1	1
Second diagonal	0.5	0.5
LCx proximal	2.5	3.5
LCx mid	1	2
LCx distal	1	1
Obtuse marginal	1	1

Table 1: Calculation of the Gensini score. Step 1: a severity score is assigned to each coronary lesion based on the degree of luminal narrowing and adjustment for total occlusions or 99% obstructive lesions receiving collaterals

Degree of stenosis (%)	*Receiving collaterals*	*Adjustment for collaterals*	*Severity score*
1–25	–	0	1
26–50	–	0	2
51–75	–	0	4
76–90	–	0	8
91–99	No	0	16
99	Yes	–8	8
100	No	0	32
100	Yes and normal source vessel	–16	16
100	Yes and 25% stenosis source vessel	–12	20
100	Yes and 50% stenosis source vessel	–8	24
100	Yes and 75% stenosis source vessel	–4	28
100	Yes and 90% stenosis source vessel	–2	30

- CAG findings.
- HbA1c levels.
- Hypertension.
- Smoking status.
- Obesity.

The regression model aimed to identify significant predictors while adjusting for potential confounders. The following statistical parameters were computed:

- Unstandardized and standardized regression coefficients.
- *T*-values and corresponding *p*-values were calculated for every independent variable.
- % confidence intervals (CIs) for estimated coefficients.

Statistical analyses were carried out using SPSS version 22, ensuring the robustness and reliability of the results.

Table 3: Distribution of subjects according to HbA1c

	Frequency	*Percentage (%)*
Nondiabetic	16	10.7
Prediabetic	20	13.3
Diabetic	114	76.0
Total	150	100.0

HbA1c level of 6.5% or higher indicated diabetes; 5.7–6.4% indicated prediabetes; and below 5.7% indicated nondiabetes

Table 4: Distribution of subjects according to sex

	Frequency	*Percentage (%)*
Female	50	33.3
Male	100	66.7
Total	150	100.0

Results

The study included 150 patients. Of them, 114 were diabetic, 16 were nondiabetic, and 20 were prediabetic (Table 3).

Out of the 150 patients enrolled in the study, 50 were female and 100 were male (Table 4).

Overall, male participants were more prevalent in the study. This trend was especially pronounced in the diabetic group, where males constituted 71.1% of the participants (Table 5).

Single-vessel disease occurred more frequently in diabetics (34.2%) than in prediabetics (25%). Additionally, triple-vessel disease was significantly more prevalent in the diabetic group compared to the nondiabetic group ($p < 0.001$) (Table 5).

The majority of patients in the study were between the age-group of 61 and 70 years—30% (Table 6).

In this study, most patients diagnosed with ACS exhibited symptoms of unstable angina (Table 7).

The average age at presentation was higher in the diabetic and prediabetic groups, at 62.76 and 60.6 years, respectively (Table 8).

The diabetic group exhibited markedly more severe CAD, as reflected by a significantly higher average score.

The Gensini score of 49.083, compared to prediabetics 24.475 and nondiabetics 0.938.

Table 6: Distribution of subjects according to age-group

Years	*Frequency*	*Percentage (%)*
<40	7	4.7
41–50	22	14.7
51–60	43	28.7
61–70	45	30.0
>70	33	22.0
Total	150	100.0

The observed differences reached statistical significance, with a *p*-value of 0.001 (Table 9).

The longer a person has diabetes, the more severe their CAD tends to be (Fig. 1).

		Duration of diabetes
Gensini score	Pearson correlation	0.790**
	p-value	<0.001

**Indicates significance

Among diabetic patients, the extent of CAD was significantly linked to the duration of their diabetes ($p < 0.001$).

Table 7: Distribution of subjects according to diagnosis

	Frequency	*Percentage (%)*
STEMI	55	36.7
NSTEMI	23	15.3
Unstable angina	72	48.0
Total	150	100.0

ACS, acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction

Table 8: Comparison of mean age according to HbA1c

		Age
Nondiabetic	Mean	53.13
	SD	11.165
Prediabetic	Mean	60.60
	SD	9.511
Diabetic	Mean	62.76
	SD	12.353
Total	Mean	61.45
	SD	12.193

p-value = 0.011; Statistical test utilized: ANOVA

Table 5: Comparison of sex and CAG findings according to HbA1c

	Normal		*Pre-DM*		*DM*		*p-value*
	N	*%*	*N*	*%*	*N*	*%*	
Sex							
Female	6	37.5	11	55.0	33	28.9	0.069
Male	10	62.5	9	45.0	81	71.1	
CAG findings							
Double vessel disease	0	0.0	2	10.0	45	39.5	<0.001
Minor CAD	2	12.5	9	45.0	6	5.3	
Normal	14	87.5	2	10.0	0	0.0	
Single vessel disease	0	0.0	5	25.0	39	34.2	
Triple vessel disease	0	0.0	2	10.0	24	21.1	

N represents the total number of observations; Statistical test utilized: Chi-squared test of independence

Majority of patients had double vessel disease 31.3% (Table 10).

Multivariate Regression Analysis

Table 11 presents a summary of the findings from the multivariate regression analysis.

The dependent variable was the duration of diabetes years, defined as HbA1c ≥6.5. The independent variables included the Gensini score, age, gender, diagnosis, CAG findings, HbA1c%, hypertension, smoking, and obesity. The table provides unstandardized and standardized coefficients (β), *t*-statistics, significance (*p*-values), and 95% CIs.

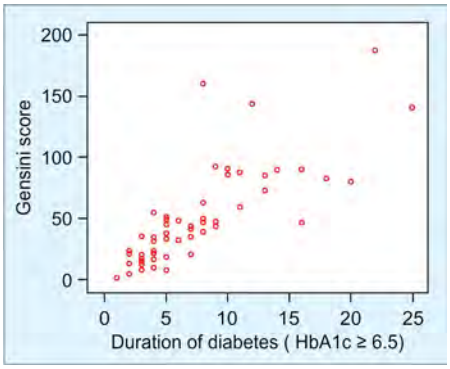


Fig. 1: Comparison of the duration of diabetes in years and the Gensini score

Table 9: Comparison of mean Gensini score according to HbA1c

		Gensini score
Nondiabetic	Mean	0.938
	SD	2.5617
Prediabetic	Mean	24.475
	SD	41.4213
Diabetic	Mean	49.083
	SD	39.6651
Total	Mean	40.667
	SD	40.8842

p-value = 0.001; Statistical test utilized: ANOVA

Key Findings

- The Gensini score demonstrated a robust and statistically significant relationship with the duration of diabetes ($B = 0.106, \beta = 0.803, p < 0.001$), suggesting a meaningful relationship between CAD severity and diabetes duration.
- Age also demonstrated a significant positive relationship ($B = 0.115, \beta = 0.274, p < 0.001$). This finding suggests that increased age is correlated with a longer history of diabetes.
- Other variables, including gender, diagnosis, CAG findings, HbA1c, and hypertension, did not show significant associations ($p > 0.05$).
- Smoking and obesity were not statistically significant predictors, with *p*-values of 0.171 and 0.283, respectively.

Table 11 highlights the importance of the Gensini score and age as key factors influencing the duration of diabetes. Although other variables did not reach statistical significance, the findings support the hypothesis that the severity of CAD, as measured by the Gensini score, is correlated with long-standing diabetes.

Table 10: Distribution of subjects according to vessel involved

	Frequency	*Percentage (%)*
Normal	16	10.7
DVD	47	31.3
Minor CAD	17	11.3
SVD	44	29.3
TVD	26	17.3
Total	150	100.0

Distribution of subjects according to vessel involved: DVD, double vessel disease; SVD, single vessel disease; TVD, triple vessel disease

Discussion

The study encompassed 150 patients with ACS who underwent CAG, including 114 diabetic, 16 nondiabetic, and 20 prediabetic individuals.

Consistent with other studies, diabetics comprised the majority of the study population. Our study revealed a preponderance of males among the study subjects. This finding aligns with previous research, such as that conducted by Roth et al.[19] and Maas and Appelman,[20] indicating a higher incidence of CVD in men compared to women.[21,22]

This study compared the mean age, sex, and type of ACS across each group. The study explored the correlation between glycemic status, measured by HbA1c, and the severity of CAD, evaluated employing Gensini score. The GUSTO-118 trial,[21] noted that diabetic patients were generally older than nondiabetic patients—a trend that our study similarly reflected.

The Gensini score, utilized in this study, provides a more detailed assessment of CAD by accounting for even minor lesions. Using the Gensini score to assess CAD severity, diabetic patients exhibited the highest mean score of 49.083, while prediabetic patients had a mean score of 24.475.

Coronary artery disease was least severe in people without diabetes, with an average score of 0.938. A study by Kumar et al.[22] found that diabetic patients experienced a higher degree of CAD severity than their nondiabetic counterparts. Additionally, their

Table 11: Multivariate regression analysis

Coefficients[a]							
Model	*Unstandardized coefficients*		*Standardized coefficients*	*t*	*Sig.*	*95.0% CI for B*	
	B	*Standard error*	β			*Lower bound*	*Upper bound*
1 Constant	−5.715	2.315		−2.468	0.015	−10.307	−1.124
Gensini score	0.106	0.008	0.803	12.797	0.000	0.090	0.122
Age	0.115	0.021	0.274	5.392	0.000	0.073	0.157
Gender	0.154	0.581	0.013	0.264	0.792	−0.998	1.306
Diagnosis	0.064	0.341	0.011	0.189	0.850	−0.612	0.741
CAG findings	0.567	0.329	0.091	1.724	0.088	−0.085	1.219
HbA1c%	−0.240	0.131	−0.094	−1.827	0.071	−0.500	0.020
Hypertension	−0.766	0.556	−0.072	−1.377	0.171	−1.869	0.337
Smoking	1.178	0.666	0.093	1.767	0.080	−0.144	2.499
Obesity	0.608	0.563	0.058	1.080	0.283	−0.508	1.723

[a]Dependent variable: duration of diabetes (years) (HbA1c ≥6.5)

findings revealed that the longer a patient had diabetes, the more severe their CAD became—an observation that concurs with the results of our study. The study by Sliema et al.[23] identified that longer durations of diabetes were associated with more extensive CAD, consistent with the findings of this study. A strong positive linear link was found between diabetes duration and the extent of CAD, as reflected by a Pearson correlation coefficient of 0.791 and a p-value < 0.001. In a similar study by Saleem et al.,[24] a direct linear correlation was identified between the duration of diabetes and the severity of CAD. A positive correlation between diabetes duration and CAD severity emphasizes the cumulative detrimental effect of long-term hyperglycemia on cardiovascular health. Chronic exposure to high glucose levels leads to increased atherosclerotic plaque formation, reduced arterial compliance, and heightened inflammatory responses, which contribute to more severe CAD over time.[25,26] HbA1c is a marker of long-term glycemic control but may not directly reflect acute plaque burden or coronary lesion characteristics.[27] For individuals with diabetes, intensive treatment approaches—including strict blood sugar regulation and the administration of medications such as sodium–glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists—have been found to lower the risk of cardiovascular events. Recent evidence further indicates that these treatments not only manage blood glucose effectively but also provide additional protection to the heart.[28,29] Recent clinical trials, such as EMPA-REG OUTCOME trial[28] and CANVAS program,[30] demonstrated that SGLT2 inhibitors (e.g., empagliflozin, canagliflozin) decrease major cardiovascular events, including myocardial infarction, in diabetic patients. Similarly, trials like LEADER[29] and REWIND[31] revealed that GLP-1 receptor agonists not only improve glycemic control but also reduce cardiovascular death and nonfatal myocardial infarction in high-risk patients. Given the study's findings of more severe CAD in diabetic patients, incorporating these novel agents into routine clinical practice could lead to significant improvements in long-term cardiovascular outcomes. These drugs not only address glycemic control but also act on mechanisms such as reducing oxidative stress, ameliorating endothelial dysfunction, and promoting favorable hemodynamic changes, all of which are crucial in slowing CAD progression.

Although medications are crucial for managing CAD in diabetic patients, lifestyle changes—such as improving diet, increasing physical activity, and quitting smoking—remain fundamental for reducing cardiovascular risk. Lifestyle interventions can lower blood pressure, improve lipid profiles, enhance insulin sensitivity, and reduce inflammation, which collectively contributes to a slower progression of CAD.[32,33] Given the heightened risk of CAD in diabetic patients, early detection through regular cardiovascular screening is essential. Studies suggest that noninvasive tests such as coronary artery calcium scoring and carotid intima-media thickness measurements can identify subclinical atherosclerosis, enabling earlier intervention and more aggressive risk management.[34,35] Recent research is focusing on novel biomarkers, such as adiponectin, leptin, and advanced glycation end (AGE)-products, which may offer additional predictive power for CAD severity in diabetic patients. These biomarkers reflect the metabolic and inflammatory changes that drive both insulin resistance and atherosclerosis and may improve the risk stratification of diabetic individuals.[36,37] Beyond traditional cardiovascular risk factors, psychosocial factors such as depression, anxiety, and social isolation have been linked to worse outcomes in diabetic patients with CAD. Addressing mental health issues in these patients is crucial for enhancing treatment adherence and improving overall cardiovascular health.[38,39]

Limitations of the Study

Single-center Study

This research was performed at a single medical center, which may limit the generalizability of its findings to other populations. Factors such as regional differences, varying demographics, and distinct healthcare settings might affect how applicable the results are in different contexts.

Reliance on HbA1c

The study measured glycemic status using HbA1c, which reflects long-term glucose control. However, HbA1c may not capture short-term fluctuations in blood glucose levels, which could also influence CAD severity.

Future research that addresses these limitations could significantly strengthen the validity and broader applicability of the findings.

Conclusion

The study demonstrates that diabetes has a significant effect on CAD severity, with diabetic individuals showing more pronounced CAD than both prediabetic and nondiabetic groups. The findings also indicate that the duration of diabetes correlates with increased CAD severity. These findings underscore the importance of integrated cardiovascular and diabetes care to reduce the elevated risk of adverse cardiac events in diabetics.

Acknowledgment

I would like to express my deepest gratitude to my esteemed teachers, Dr Vadagenalli Sathyanarayana Rao Prakash and Dr Varsha Rakshitha Prakash, for their invaluable guidance, support, and mentorship throughout this research journey. Their profound knowledge, encouragement, and unwavering dedication to academic excellence have been a constant source of inspiration.

References

1. Nedkoff L, Briffa T, Zemedikun D, et al. Global trends in atherosclerotic cardiovascular disease. Clin Ther 2023;45:1087–1091.
2. International Diabetes Federation. Diabetes facts and figures show the growing global burden for individuals, families, and countries. The latest IDF Diabetes Atlas (2025) reports that 11.1%—or 1 in 9—of the adult population (20–79 years) is living with diabetes, with over 4 in 10 unaware that they have the condition; 2023.
3. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143–3421.
4. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA 1979;241:2035–2038.
5. World Health Organization. Cardiovascular Diseases (CVDs) Fact Sheet; 2021.
6. Moss SE, Klein R, Klein BE. Cause-specific mortality in a population-based study of diabetes. Am J Public Health 1991;81:1158–1162.
7. Geiss LS, Herman WH, Smith PJ. Mortality in non-insulin-dependent diabetes. In: National Diabetes Data Group (Ed). Diabetes in America. Bethesda, MD: NIH & NIDDK; 2018.
8. 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;329:977–986.
9. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–412.
10. World Health Organization. Cardiovascular diseases (CVDs). 2021.
11. Global Burden of Disease Study. Economic costs of cardiovascular diseases. Lancet 2017;390(10100):2623–2636.
12. Brezinka V, Padmos I. Coronary heart disease risk factors in women. Eur Heart J 1994;15:1571–1584.
13. Malmberg K, Yusuf S, Gerstein HC, et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial

infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) registry. Circulation 2000;102:1014–1019.
14. Miettinen H, Lehto S, Salomaa V, et al. Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA Myocardial Infarction Register Study Group. Diabetes Care 1998;21:69–75.
15. Ceriello A, Hanefeld M, Leiter L, et al. Postprandial glucose regulation and diabetic complications. Arch Intern Med 2004;164:2090–2095.
16. Rampidis GP, Benetos G, Benz DC, et al. A guide for Gensini Score calculation. Atherosclerosis 2019;287:181–183.
17. Ibrahim RR, Tammam K, Ghoneim SM, et al. Non-traditional predictors for occurrence and severity of premature atherosclerosis in acute coronary syndrome. Egypt J Hosp Med 2022;88:2948–2954.
18. Muhammad A, Nizam A, Yousuf MH, et al. Angiographic severity of CAD in patients with acute coronary syndrome in correlation to their glycemic status. PJMHS 2019;13:312–316.
19. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. J Am Coll Cardiol 2020;76(25):2982–3021.
20. Maas AHEM, Appelman YEA. Gender differences in coronary heart disease. Neth Heart J 2010;18:598–603.
21. Mak KH, Moliterno DJ, Granger CB, et al. Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction. GUSTO-I Investigators. Global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries. J Am Coll Cardiol 1997;30:171–179.
22. Kumar D, Mishra GN, Chowdhury SP. Angiographic severity of CAD in patients with acute coronary syndrome in correlation to their glycaemic status in tertiary care centre of Bihar. Int J PharmClin Res 2022;14:27–35.
23. Sliema SS, Mohamed YG, Rayan MM. Impact of diabetes duration and control on the extent and severity of coronary artery disease in Egyptian patients: evaluation by coronary CT angiography. QJM 2023;116:hcad069.164.
24. Saleem T, Mohammad KH, Abdel-Fattah MM, et al. Association of glycosylated haemoglobin level and diabetes mellitus duration with the severity of coronary artery disease. Diab Vasc Dis Res 2008;5:184–189.
25. Fox CS, Sullivan L, D'Agostino RB Sr, et al. The significant effect of diabetes duration on coronary heart disease mortality: the Framingham Heart Study. Diabetes Care 2004;27:704–708.
26. Donahoe SM, Stewart GC, McCabe CH, et al. Diabetes and mortality following acute coronary syndromes. JAMA 2007;298:765–775.
27. Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;362:800–811.
28. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128.
29. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322.
30. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–657.
31. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 Diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019;394:121–130.
32. Buse JB, Ginsberg HN, Bakris GL, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care 2007;30:162–172.
33. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. Compr Physiol 2012;2:1143–1211.
34. Raggi P, Shaw LJ, Berman DS, et al. Prognostic value of coronary artery calcium screening in subjects with and without diabetes. J Am Coll Cardiol 2004;43:1663–1669.
35. O'Leary DH, Polak JF, Kronmal RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med 1999;340:14–22.
36. Ouchi N, Kihara S, Funahashi T, et al. Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. Circulation 2003;107:671–674.
37. Schalkwijk CG, Stehouwer CDA. Vascular complications in diabetes mellitus: the role of endothelial dysfunction. Clin Sci 2005;109:143–159.
38. Albus C. Psychological and social factors in coronary heart disease. AnnMed 2010;42:487–494.
39. Holt RIG, de Groot M, Golden SH. Diabetes and depression. Curr DiabRep 2014;14:491.

REVIEW ARTICLE

Newer Therapies for Osteoporosis: A Systematic Review

Parthajit Das[1*], Mohit Goyal[2], Debaditya Roy[3], Vinod Ravindran[4]

Received: 09 February 2025; *Accepted:* 04 July 2025

Abstract

Objective: The current management of osteoporosis has several unmet needs. Consequently, the newer and upcoming agents and targets are being expectantly looked at. We aim to appraise the evidence examining the efficacy of the newer therapies for the management of osteoporosis.

Methods: Scopus, Embase, and MEDLINE databases were screened from January 2013 to December 2023 to identify clinical trials that evaluated the efficacy of newer agents for the treatment of osteoporosis in men and postmenopausal women (PMO). Changes in bone mineral density (BMD) and incidences of vertebral fractures (VFs) and nonvertebral fractures (NVFs) or relative risk reduction (RRR) for VF and NVF were retrieved. The Oxford quality scoring system was applied to evaluate the methodological quality of the included clinical trials.

Results: Eighteen randomized controlled trials (RCTs) that had enrolled 22,868 PMO and 473 male participants were included. Anabolic agents abaloparatide and romosozumab exhibited significant BMD gain and relative RRR for fractures and greater efficacy than teriparatide. Blosozumab was reported to exhibit substantial BMD gains. The efficacy of a sequential therapeutic strategy with anabolic agent followed by antiresorptive agents was superior to the reverse sequence.

Conclusion: Newer therapies for osteoporosis exhibited significant BMD gain and fracture risk reduction in men and PMO. The newer anabolic agents demonstrated greater efficacy than any of the previously available therapeutic options.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1084

Introduction

Osteoporosis-related fractures are one of the leading causes of chronic disease morbidity following ischemic heart disease, dementia, and lung cancer.[1] The economic burden, morbidity, and mortality associated with fragility fractures are substantial and likely to rise in the future in the aging population.[2] Epidemiological studies have observed a robust concurrence between treatment-induced bone mineral density (BMD) accrual and fracture risk reduction. However, there is limited evidence examining the protracted efficacy and safety of the newer therapies for osteoporosis. It is, therefore, imperative that the next-generation antiosteoporosis drugs treat osteoporosis with sufficient antifracture efficacy and with minimal toxicity. Insights from basic bone pathophysiology have recognized several new therapeutic targets for the management of osteoporosis (Table 1). The objective of this systematic review was to study the evidence related to the efficacy of the newer therapies for osteoporosis.

Methods

This systematic literature review has been reported in accordance with the recommendations of the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines 2020[3] (Supplementary material).

Data Sources and Search Strategies

A thorough bibliographic search was performed in the Scopus, MEDLINE, and Embase databases to identify randomized controlled trials (RCTs) (either placebo or active-controlled) published between January 2013 and December 2023 that evaluated the efficacy of newer osteoporotic agents among postmenopausal women (PMO) and men with primary osteoporosis. A combination of appropriate Medical Subject Headings (MeSH) terms and keywords was used (Supplementary material). References were also manually searched among previously published reviews. The clinical trial registry (www.clinicaltrial.gov) was searched for any potential unpublished studies.

Study Selection

The selection criteria for this systematic review were framed using the PICO format: P (population): PMO or men with primary osteoporosis (i.e., age-related osteoporosis); I (intervention): newer therapies for osteoporosis; C (comparison): placebo or other active drugs; O (outcome): (1) evolution of BMD at lumbar spine (LS), total hip (TH), femoral neck (FN), (2) incidence of vertebral fracture (VF) and nonvertebral fracture (NVF) or RRR of VFs or NVFs (Table 2).

Studies published in non-English languages, those discussing secondary causes of osteoporosis, case reports or series, letters to the editor, review articles, pooled data analyses, and conference abstracts were excluded.

Data Extraction

Studies were obtained by two reviewers (DR, PD) using standardized data extraction strategies and were transferred to an Excel spreadsheet. The third and fourth reviewers (MG, VR) reviewed the extracted data. The following categories were considered for data extraction: study protocol (sample size, groups, and intervention), treatment (dosage, type of drugs, and route of administration), and clinical outcome (densitometric evaluation of the evolution of BMD, incidence of fracture). Finally, these studies were assessed independently by all four reviewers (PD, MG, DR, and VR), and a consensus settled disagreements.

The following outcome measures were extracted and tabulated: (1) evolution of BMD at LS, TH, and FN and (2) incidences of VF and NVF or RRR for VF or NVF. The evolution of BMD was defined as a difference in the percentage of BMD change between the intervention groups from the start to the completion of the study. There were wide variations in the reporting patterns and methodology used in these published trials. The respective authors of individual studies were contacted in case of incomplete data availability.

[1]Rheumatologist, Department of Rheumatology, Asian Institute of Immunology and Rheumatology, Kolkata, West Bengal; [2]Rheumatologist, Division of Rheumatology, CARE Pain and Arthritis Centre, Udaipur, Rajasthan; [3]Rheumatologist, Department of Clinical Immunology and Rheumatology, Institute of Post Graduate Medical Education and Research, Kolkata, West Bengal; [4]Rheumatologist, Department of Rheumatology, Centre for Rheumatology, Calicut, Kerala; Adjunct Professor, Department of Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India; *Corresponding Author

How to cite this article: Das P, Goyal M, Roy D, *et al.* Newer Therapies for Osteoporosis: A Systematic Review. J Assoc Physicians India 2025;73(8):67–76.

Table 1: Potential therapeutic targets

Pathways	*Groups*	*Drugs*
Antiresorptive drugs		
RANKL/RANK/OPG pathway	RANKL inhibitor	Denosumab
Targeting the molecules of the Howship's lacuna	Cathepsin K inhibitor	Odanacatib Balicatib ONO-5334 MIV-711
	αvβ3 integrin antagonist	L-000845704 HSA-ARLDDL M-CSFRGD
	Chloride channel-7 inhibitor	N53736
	C-src kinase inhibitors	
Selective estrogen receptor modulators (SERMs)		Arzoxifene Lasofoxifene Bazedoxifene
Anabolic drugs		
	Parathyroid hormone receptor agonist	Teriparatide Abaloparatide
WNT signaling antagonists	Sclerostin neutralizing antibodies	Romosozumab Blosozumab
	DKK-1 inhibitors	
	Calcium-sensing receptor antagonism	
	Activin inhibitors	ACE-011
	Matrix extracellular phosphoglycoprotein (MEPE) fragments	

Table 2: Inclusion criteria

PICO(S) criteria	
Patient	Men and postmenopausal women with osteoporosis (i.e., age-related osteoporosis)
Intervention	Newer therapies for osteoporosis
Comparator	Placebo or other active osteoporosis agents
Outcome	Evolution of BMD at lumbar spine, total hip, and femoral neck Incidence of vertebral fractures and nonvertebral fractures
Study design	Placebo-controlled randomized controlled trials (RCTs) RCTs including other active osteoporosis agents Controlled clinical trials (CCTs) >100 participants

Assessment of Quality

The methodological quality of the selected studies was analyzed by the Oxford quality scoring system, assessing the randomization, blinding, statistical analysis, withdrawal, and dropout processes.[4]

Results

A total of 1,038 potentially relevant publications were retrieved. After excluding duplicates, 866 eligible manuscripts were considered for evaluation. Following a screening pertaining to relevant titles and abstracts, 172 articles underwent a full-text review. Finally, 18 RCTs (9 placebo and 9 active controlled) were incorporated in this systematic review that fulfilled the inclusion criteria. A flow diagram illustrating the literature search strategy is depicted in Figure 1.

In these 18 studies, 22,868 women with PMO and 473 men with low BMD were included. Fourteen out of the 18 included studies (i.e., 77.77%) were double-blinded. The detailed characteristics of the studies discussing the newer therapies for osteoporosis, that is, abaloparatide (ABL) (n = 5),[5–9] romosozumab (ROM) (n = 6),[10–15] and blosozumab,[16] have been shown in Table 3. In addition, the efficacy of sequential therapy with these newer agents was also evaluated (n = 6),[17–22] as given in Table 4. All RCTs scored 3–5 (out of 5) using methodological quality assessment with the Oxford quality scoring system, qualifying as high-quality trials. The median duration of intervention was 24 weeks (ranging from 12 to 84 weeks).

The primary outcome was LS BMD in 11 studies (61.11%). Relative risk reduction (RRR) was calculated in five studies (29.41%), whereas the incidences of VF and NVF were reported in a narrative in seven studies (38.88%). Available evidence has been discussed under the following subheadings.

Effect of Anabolic Agents on Bone Mineral Density

Abaloparatide

Abaloparatide, a novel synthetic peptide analog of the first 34 amino acids of the human parathyroid hormone-related peptide (PTHrP), received its Food and Drug Administration (FDA) approval in April 2017 for the management of PMO in women at high fracture risk and in patients intolerant to other osteoporosis drugs. Five RCTs[5–9] on ABL have observed significant BMD gain at the LS, TH, and FN and a robust antifracture efficacy. *Abaloparatide vs placebo:* Leder et al.,[5] ACTIVE Trial—Miller et al.,[6] and Matsumoto et al.[7] evaluated 2,854 women with PMO and observed significant improvement in LS, TH, and FN BMD in comparison to placebo (Table 3). ATOM study[8] studied the efficacy and safety of ABL in 228 men with osteoporosis and reported significant improvement in LS, TH, and FN BMD in comparison to placebo.
Abaloparatide vs teriparatide: In the ACTIVE trial,[6] 2,643 women with PMO were randomized to receive ABL, teriparatide, and placebo for 18 months. The percentage difference from baseline BMD at 18 months was slightly greater with ABL than with teriparatide at the LS, TH, and FN, suggesting ABL was a more effective therapeutic option.
Abaloparatide vs alendronate: No head-to-head trial comparing the efficacy of ABL and antiresorptive therapy is available. In a *post hoc* analysis, at the end of the 43-months of integrated ACTIVE–ACTIVExtend study,[6,20] women receiving ABL (18 months) followed alendronate (24 months) showed significant BMD gain at the LS, TH, and FN in comparison to treatment with placebo (18 months) followed by alendronate (24 months), suggesting ABL succeeded by alendronate as an attractive strategy for sequential therapy.

The common adverse reactions of ABL that are reported in clinical trials were nausea, headache, fatigue, palpitations, vertigo, and upper abdominal pain. Other adverse effects include orthostatic hypotension, hypercalcemia, and urolithiasis. The prevalence of hypercalcemia was lower in the ABL group by 51% vs teriparatide.[6]

Romosozumab

Romosozumab, a humanized monoclonal antibody to sclerostin, received its FDA approval in April 2019. ROM demonstrated a "dual effect" of augmentation of bone formation and suppression of bone resorption by blocking sclerostin.
Romosozumab vs placebo: McClung et al.,[10] FRAME study,[11] and Ishibashi et al.[12] evaluated 7,851 women with PMO and observed

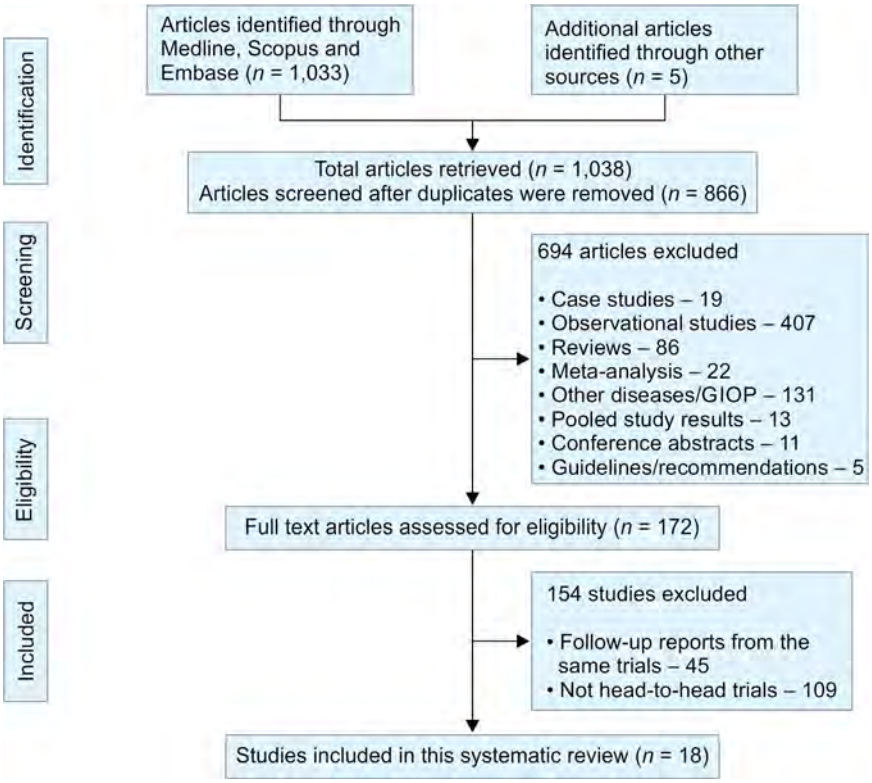


Fig. 1: Screening and selection process of studies on the newer therapies for osteoporosis

significant improvement in LS, TH, and FN BMD in comparison to placebo. BRIDGE study[13] examined the efficacy of ROM in 245 men with osteoporosis and demonstrated significant improvement in LS, TH, and FN BMD in the ROM group compared to placebo.

In the FRAME trial,[11] 7,180 women with PMO were randomized to receive ROM 210 mg subcutaneously (SC) or placebo once a month for 12 months, followed by denosumab 60 mg SC 6 monthly in both groups for a year, and reported significantly increased LS and TH BMD (13 and 7% respectively) compared to placebo.

Romosozumab vs alendronate: In the ARCH trial,[14] ROM (210 mg SC monthly) was compared with oral alendronate (70 mg weekly) for a year, followed by oral alendronate in both groups for 2 years, and a significantly higher BMD gain from baseline with ROM compared to alendronate after a year and further BMD gain following the transition to alendronate was observed. Although BMD gain with ROM in the ARCH trial was similar to that seen in the FRAME study[11] at 1 year, the observed BMD gain at 36 months was comparatively lower in the FRAME study.

Romosozumab vs teriparatide: In the STRUCTURE trial,[15] ROM (210 mg SC monthly) was compared with teriparatide (20 µg SC daily) for 12 months in women with PMO who had received oral bisphosphonates for at least 3–4 years and observed favorable BMD gain with ROM at LS (9.8 and 5.4%, respectively) and TH (2.6 and −0.6%, respectively), inferring that in patients transitioning from bisphosphonates to anabolic therapy, ROM may be more efficacious than teriparatide.

McClung et al.[10] compared five doses of ROM with teriparatide (20 µg SC daily), oral alendronate (70 mg weekly), and subcutaneous placebo, and observed BMD accrual at 12 months with ROM, teriparatide, and alendronate at LS was 11.3, 7.1, and 4.1%, respectively, and at TH was 4.1, 1.3, and 1.9%, respectively, confirming higher BMD gain at all skeletal sites with ROM.

The safety data analysis for ROM emerged from the FRAME and ARCH trials.[11,12] Major cardiovascular event (MACE) (composite of cardiovascular death, MI, and cerebrovascular events), hypocalcemia, osteonecrosis of the jaw, and atypical femoral fracture were higher with ROM in the ARCH and FRAME trials. A *post hoc* analysis demonstrated a higher incidence of MACE events in the ROM group (2%) when compared with the alendronate group (1.1%), with a hazard ratio of 1.7 (95% CI 1.1–2.6).[15] Further postmarketing surveillance studies are warranted to address these concerns.

Blosozumab

Blosozumab is a novel humanized monoclonal antibody against sclerostin. Evidence is accumulating confirming the role of blosozumab as a promising newer anabolic therapy for the management of osteoporosis. Recker et al.[16] evaluated 120 women with PMO and observed significant improvement in LS, TH, and FN BMD when in comparison to placebo. Fracture risk was not assessed.

Effect of Antiresorptive Agents on Bone Mineral Density

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) possess estrogen agonist or antagonist properties in different target tissues. Several newer generations of SERMs, for example, lasofoxifene and bazedoxifene (vide infra), have shown promising results on the BMD accrual, antifracture efficacy, and reduction in breast cancer risk. In two RCTs, the OPAL trial[23] and the PEARL trial,[24] lasofoxifene demonstrated a favorable impact on BMD, whereas only the PEARL trial exhibited diminished risks of vertebral and NVFs.

Cathepsin K Inhibitors

Odnacatib, balicatib, and ONO-5344 are inhibitors of cathepsin K. They have all been withdrawn from the market or had further development discontinued (vide infra).

Newer Agents that have been Discontinued

Bazedoxifene

Bazedoxifene, a third-generation SERM, is primarily used for the treatment of women with PMO.

Bazedoxifene vs placebo: Palacios et al.,[25,26] Beck et al.,[27] and Pinkerton et al.[28] evaluated 10,511 women with PMO and observed significant improvement in LS BMD when compared with placebo (Table 4). However, Palacios et al.[25] observed a smaller decrease in TH BMD in the bazedoxifene 20 mg (–1.19%) and 40 mg (–1.15%) groups in comparison to the placebo group (–2.53%; $p \leq 0.002$) following 7 years of therapy. Bazedoxifene has been withdrawn from sale in 2020 because of commercial reasons and is awaiting a relaunch with improved packaging.

Odanacatib

Odanacatib is a cathepsin K inhibitor. Several RCTs demonstrated the favorable efficacy of odanacatib at LS, TH, and FN and a substantial antifracture efficacy when compared with placebo.[29–35] However, a safety analysis perceived a significant increment in the risk of stroke, and odanacatib was, therefore, withdrawn from further development.

Table 3: Clinical trials assessing the efficacy of the newer anabolic agents on osteoporosis

	Study design	*Country*	*Number of patients/group*	*Treatment*	*Comparator*	*Length of intervention*	*Outcomes*	*Fracture risk reduction (RRR)*	*Oxford quality scoring system*	*FDA approval*
Abaloparatide										
Leder et al.[5]	Double-blind placebo-controlled RCT	Multicenter, multinational (United States, Argentina, India, and the United Kingdom)	222 women with postmenopausal osteoporosis	Abaloparatide (ABL): G1: 20 µg: (n = 43), G2: 40 µg: (n = 43), G3: 80 µg: (n = 45)	Teriparatide (TPT), 20 µg: (n = 45) orplacebo (PBO): (n = 45)	24 weeks,	Percentage change from baseline BMD at 24 weeks: LS ABL—2.9% (20 µg), 5.2% (40 µg), and 6.7% (80 µg); TPT—5.5%; PBO: 1.6% TH ABL—1.4% (20 µg), 2% (40 µg), and 2.6% (80 µg); TPT—0.5%; PBO: 0.4% FN ABL—2.7% (20 µg), 2.2% (40 µg), and 3.1% (80 µg); TPT—1.1%; PBO: 0.8%	RRR not calculated	3	FDA approved
Miller et al.[6]	Phase III double-blind placebo-controlled RCT	28 study centers in 10 countries	2,463 women with postmenopausal osteoporosis	Subcutaneous ABL: (n = 824)	Teriparatide: 818;PBO: (n = 821)	18 months	Percentage change from baseline BMD at 18 months: LS—(11.20 vs 10.49 vs 0.63%) TH—(4.18 vs 3.26 vs −0.10%) FN—(3.60 vs 2.66 vs −0.43%)	New morphometric vertebral fractures occurred ABL = 4 PBO = 30 [risk difference (RD) vs placebo, −3.64 (95% CI: −5.42 to −2.10); relative risk, 0.14 (95% CI: 0.05–0.39); p <.001] TPT = 6 [RD vs placebo, −3.38 (95% CI: −5.18 to −1.80); relative risk, 0.20 (95% CI: 0.08–0.47); p < 0.001]	5	
Matsumoto et al.[7]	Phase II, double-blind, placebo-controlled RCT	Japan	164 women with postmenopausal osteoporosis	ABL 40 µg (n = 55) or ABL 80 µg (n = 54)	PBO (n = 55)	48 months	Percentage change from baseline at 48 weeks: LS: ABL 40 µg vs PBO—6.6% [95% confidence interval (CI) 4.70–8.54; p < 0.001] ABL 80 µg vs PBO—11.5% (95% CI 9.59–13.45; p < 0.001) ABL 80 µg vs ABL 40 µg—4.9% (95% CI 2.98–6.83; p < 0.001) TH: PBO—0.4 ± 1.9%; ABL 40 µg—1.5 ± 2.2% (95% CI: 0.22–1.94 vs PBO) ABL 80 µg—2.9 ± 2.2% (95% CI: 1.61–3.35 vs PBO) and 0.51–2.30 vs ABL 40 µg FN: PBO—0.9 ± 3.0%, ABL 40 µg vs PBO—1.5 ± 2.5% (95% CI: 0.54–1.75) and ABL 80 µg—2.3 ± 3.3% (95% CI: 0.14–2.78 vs PBO and 0.33–2.05 vs ABL 40 µg)	RRR not calculated	5	
ATOM study (Czerwinski et al.[8])	Phase III double-blind placebo-controlled RCT	United States	228 men with osteoporosis	Abaloparatide (ABL): (n = 149)	Placebo: (n = 79)	12 months	Percentages change in BMD from baseline in lumbar LS, TH, and FN at 12 months were 8.48, 2.14, and 2.98% with ABL compared with PBO 1.17% (p < 0.0001)	ABL: 1 PBO: 3	4	
Lewiecki et al.[9]	Phase III, randomized, open-label, multicenter, noninferiority study	United States	511 women with postmenopausal osteoporosis	Abaloparatide-subcutaneous injection (ABL-SC) (n = 255)	ABL-microstructure transdermal system (ABL-sMTS) (n = 256)	12 months	The least significant percent change from baseline in LS BMD at 12 months was 7.14% (SE: 0.46%) for ABL-sMTS and 10.86% (SE: 0.48%) in the ABL-SC group	ABL-sMTS: 8 ABL-SC, 11	5	

Contd…

Contd…

	Study design	*Country*	*Number of patients/group*	*Treatment*	*Comparator*	*Length of intervention*	*Outcomes*	*Fracture risk reduction (RRR)*	*Oxford quality scoring system*	*FDA approval*
Romosozumab										
McClung et al.[10]	Phase II, multicenter, international, placebo-controlled RCT	International, multicenter study	419 women with postmenopausal osteoporosis	5 groups of romosozumab (ROMO): G1: 70 mg, monthly G2: 140 mg, monthly G3: 210 mg, monthly G4:140 mg, every 3 months G5: 210 mg, every 3 months	Subcutaneous PBO ororal alendronate (ALN) (70 mg weekly) orsubcutaneous teriparatide (TPT) (20 µg daily)	12 months	Percentage change from baseline BMD at 12 months Largest in ROMO 210 mg monthly: LS: 11.3%, TH: 4.1%, FN: 3.7% TPT—LS: 7.1%, TH: 1.3%, FN: 1.1% ALN—LS: 4.1%, TH:1.9%, FN: 1.2%	RRR not calculated	5	FDA approved
FRAME (Cosman et al.[11])	Phase III, international, placebo-controlled, double-blind, RCT	Multicenter, multinational	7,180 women with postmenopausal osteoporosis	Romosozumab (ROMO), 210 mg subcutaneously every month;(ROMO): *N* = 3,589	Placebo (PBO): 3,591	12 months	Percentage change from baseline BMD in 12 months: LS:96 to ≥3%, 89 to ≥6%, and 68% to ≥10%, compared with 22, 6, and 1% with PBO TH:78 to ≥3%, 47 to ≥6%, and 16 to ≥10%, compared with 16, 3, and 0% with PBO	With ROMO,RRRs of fracture were81% for vertebral fractures, 32% for clinical fractures, 25% for nonvertebral fractures, 55% for hip fractures, 39% for major osteoporotic fractures, and 32% for major nonvertebral fractures	5	
Ishibashi et al.[12]	Phase II, multicenter, placebo-controlled RCT	Japan	252 women with postmenopausal osteoporosis	G1: ROMO 70 mg QM: 63 G2: ROMO 140 mg QM: 63; and G3: ROMO 210 mg QM: 63	Placebo (PBO): 63	12 months	Percentage change from baseline BMD at 12 months: LS: 0.9% in the PBO and 8.4, 13.3, and 16.9% in the ROMO 70, 140, and 210 mg QM groups (all $p < 0.001$ vs PBO) TH/FN–largest gain (ROM: 210 mg) vs PBO ($p < 0.001$ for all)	RRR not calculated	5	
BRIDGE (Lewiecki et al.[13])		Multicenter, multinational	245 men with osteoporosis	Romosozumab ($n = 163$)	Placebo ($n = 82$)	12 months	Percentage change from baseline BMD at 12 months: LS (12.1 vs 1.2%; $p < 0.001$) TH (2.5 vs 20.5%; $p < 0.001$) FN (2.2 vs 20.2%; $p < 0.001$)	RRR not calculated	5	
ARCH (Saag et al.[14])	Phase III, multicenter, international, double-blind RCT	Multicenter, multinational	4,093 women with postmenopausal osteoporosis and a fragility fracture	Compared the cumulative incidence of new fractures between the romosozumab-to-alendronate (ROMO-ALN) group ($n = 2,046$) and the alendronate-to-alendronate (ALN-ALN) group	Alendronate (ALN): ($n = 2,047$)	24 months	Percentage change from baseline BMD in 24 months: LS—ROM-ALN: 15.2%; ALN-ALN: 7.1% TH—ROM-ALN: 7.1%; ALN-ALN: 3.4% FN—ROMO-ALN: 5.9%; ALN-ALN: 2.2%	ROMO-to-ALN group: 48% lower risk of new vertebral fractures than ALN alone (RR: 0.52) 38% lower risk of hip fracture, $p = 0.02$ 19% lower risk of nonvertebral fracture, $p = 0.04$	5	
STRUCTURE (Langdahl et al.[15])	Phase IIIb, randomized, open-label, active-controlled, parallel-group trial	Multicenter, multinational	436 women with postmenopausal osteoporosis transitioning from bisphosphonate therapy	Romosozumab (ROMO) ($n = 218$)	Teriparatide (TPT): ($n = 218$)	12 months	Percentage change from baseline BMD at 12 months: LS—ROM: 9.8%; TPT: 5.4% TH—ROM: 2·6% (95% CI: 2·2–3·0);TPT: 0·6% (–1·0 to –0·2) FN—ROMO: 3.2; TPT: –0.2%	ROMO: 8 (3%) TPT: 7 (4%)	3	
Blosozumab										
Recker et al. (2015)[16]	Phase II, double-blind placebo-controlled RCT	Multicenter, multinational (United States and Japan)	120 women with postmenopausal osteoporosis	Blosozumab: G1: 180 mg every 4 weeks (Q4W): ($n = 31$) G2: 180 mg every 2 weeks (Q2W): ($n = 30$),and G3: 270 mg every 2 weeks (Q2W): ($n = 30$)	Placebo ($n = 29$)	52 weeks	Percentage change from baseline BMD in 52 weeks: LS: G1: 180 mg Q4W 8.4% G2: 180 mg Q2W –14.9% G3: 270 mg Q2W –17.7% TH: G1: 180 mg Q4W –2.1% G2: 180 mg Q2W –4.5% G3: 270 mg Q2W –6.7% FN: G1: 180 mg Q4W –2.7% G2: 180 mg Q2W –3.9% G3: 270 mg Q2W –6.3%	RRR not calculated	5	Not approved

Table 4: Clinical trial assessing the efficacy of sequential therapy with newer therapies for osteoporosis

Author	*Study design*	*Country*	*Number of patients/ group*	*Treatment*	*Comparator*	*Length of intervention (months)*	*Outcomes*	*Fracture risk reduction*	*Oxford quality scoring system*
VICTOR study (Kobayakawa et al.[17])	Multicenter, RCT	Japan	294 women with postmenopausal osteoporosis with severe risk of fracture	12 months of ROM followed by either ibandronate (IBA)/DMab for an additional 12 months	124 patients (62 each in IBA and DMab group)	24	Mean changes in BMD in the sequential phase: LS: 2.5 ± 0.8% IBA 5.4 ± 0.8% iDMAb TH: 2.5 ± 0.8% IBA 4.0 ± 0.9% DMab FN: 2.7 ± 0.8% IBA 3.1 ± 0.8% DMab	No new fractures in IBA 1 (1.6%) new vertebral fracture in a DMab patient	3
McClung et al.[18]	Phase II, dose-finding RCT	Multicenter, multinational (United States, Australia, Saudi Arabia, Belgium, Denmark, Canada)	141 women with low BMD	Randomized to DENO (60 mg SC Q6M) or PBO for 12 months Followed by open-label ROMO (210 mg QM) for 12 months At month 48: if on active treatment for 48 months further active treatment All other subjects: Zoledronate (ZOL) 5 mg IV *N* = 51 in no further active treatment *N* = 90 in ZOL group	Within groups	72	Mean BMD t-score LS No further active t/t group Baseline (month 0): –2.32 Month 48: –1.04 ZOL 5 mg IV single dose group; Baseline (month 0): –2.34 Month 48: 1.28 TH: No further active t/t group Baseline (month 0): –1.63 Month 48: –1.29 ZOL 5 mg IV single dose group Baseline (month 0): –1.42 Month 48: –1.16 FN: No further active t/t group Baseline (month 0): –1.98 Month 48: –1.70 ZOL 5 mg IV single-dose group Baseline (month 0): –1.86 Month 48: –1.63	RRR not calculated. No further active treatment group: 1 radius and 1 fibula fracture ZOL group: 1 radius and 1 rib fracture	5
McClung et al.[19]	Phase II RCT	Multicenter, multinational (United States, Australia, Saudi Arabia, Belgium, Denmark, Canada)	28 women with postmenopausal osteoporosis	Group 1: PBO (24 months) to PBO (12 months) to ROMO (12 months) (*n* =12) Group 2: PBO (24 months) to DENO (12 months) to ROMO (12 months) (*n* = 16)	PBO	48	Increase in BMD with romosozumab Group 1: PBO to PBO to ROMO LS: 9.1% TH: 4.6% FN: 3.9% Group 2: PBO to DENO to ROMO LS: 11.5% TH: 3.8% FN: 3.2%	RRR not calculated	5

Contd…

Contd…

Author	*Study design*	*Country*	*Number of patients/ group*	*Treatment*	*Comparator*	*Length of intervention (months)*	*Outcomes*	*Fracture risk reduction*	*Oxford quality scoring system*
ACTIVExtend trial (Bone et al.[20])	Phase III RCT	Multicentric	558 women with postmenopausal osteoporosis from ACTIVE's ABL group and 581 from PBO group	Women who completed ABL or PBO in ACTIVE trial were eligible to receive up to 24 months of ALN	PBO	43	Mean absolute increases in BMD from ACTIVExtend baseline to ACTIVExtend month 24 LS: ABL/ALN: 0.0265 PBO/ALN: 0.0479 TH: ABL/ALN: 0.0166 PBO/ALN: 0.0210 FN: ABL/ALN: 0.0114 PBO/ALN: 0.0143	New radiographic vertebral fracture ABL/ALN group: 0.9% PBO/ALN: 5.6% RRR: 84% RRR for ACTIVExtend only for vertebral fractures for ABL/ALN vs PBO/ALN: 87% Hip fractures: 0 in ABL/ALN 5 in PBO/ALN	5
McClung et al.[21]	Phase II RCT	Multicenter, multinational (Australia, Canada, Spain, Belgium, Australia, United States, Argentina, United Kingdom)	364 women with postmenopausal osteoporosis	ROMO: 70, 140, and 210 mg monthly (QM); 140 mg Q3M; 210 mg Q3M) for 24 months or PBO for 24 months or open-label alendronate (ALN) for 12 months followed by ROMO 140 mg QM for 12 months	Rerandomized 1:1 within the original treatment groups to PBO or denosumab (DMab) 60 mg Q6M for another 12 months	36	Gain in BMD at months 12 and 24: ROMO 210 mg QM: LS: 11.3, 15.1% TH: 4.1, 3.7% FN: 5.4%, 5.2% Other ROMO treatment groups: (all $p \leq 0.01$ vs PBO) ALN to ROMO 140 mg QM: LS: 4, 9% TH: 1.9, 2.6% FN: 1.3, 2.6% ROMO 210 mg QM for 24 months-DMab during extension (till month 36): LS: 2.6% TH: 1.9% FN: 1.4%	Incidence of fragility fractures from months 24 to 36: 5 (3.9%) PBO 4 (3.2%) DMab ROMO to PBO: no vertebral fractures ROMO to DMab: two vertebral fractures	5
FRAME EXTENSION (Lewiecki et al.[22])	Phase III RCT	Multicenter, multinational	5,743 women with postmenopausal osteoporosis (2,851 ROMO-DENO; 2892 PBO-DENO)	Blinded ROMO (s.c) 210 mg or PBO once, monthly—12 months, followed by open-label denosumab (DMab) (s.c) 60 mg every 6 months for 12 months, f/b open-label DMab (s.c) 60 mg every 6 months for a further 12 months (total 36 months)	PBO	36	Differences in relative increases from baseline in BMD ROMO-DMab vs PBO-DMab at 36 months LS: 10.5% TH: 5.2% FN: 4.8%	RRR in the first 12 months ROMO to DMab vs PBO to DMab Vertebral: 66% Clinical: 27% Nonvertebral: 21% Hip: 41% RRR of new vertebral fractures through 24 and 36 months Month 24: 75% Month 36: 66%	5

Balicatib

Balicatib is an emerging cathepsin K inhibitor. In a phase II RCT, 675 women with PMO were treated with four treatment arms of balicatib or placebo over 12 months and showed significantly increased LS BMD (upto 4.46%) and TH BMD when compared with placebo (0.25%).[36] Balicatib was, however, discontinued due to the development of morphea-like skin lesions.

ONO-5334

ONO-5334 is an oral cathepsin K inhibitor. In the OCEAN trial,[37] 285 women with low BMD or PMO with one fragility fracture were randomized to receive five treatment arms of ONO-5334, alendronate (70 mg once weekly), or placebo for 12 months. Patients receiving all doses of ONO-5334 and alendronate exhibited a significant increase in LS, TH (except ONO-5334, 100 mg once daily), and FN BMD, suggesting a potential target for treating osteoporosis. RRR was not calculated. There were no safety concerns. ONO-5334 also exhibited significant gain vs placebo for cortical, trabecular, and integral BMD at the LS and TH ($p < 0.001$).[38] ONO-5334 was withdrawn from the market for competitive reasons.

Effect on Fractures

The ACTIVE trial[6] reported four new morphometric VF occurring in the ABL group, whereas 30 of those occurred in the placebo group, with an RRR of 0.14 (95% CI: 0.05–0.39); ACTIVE–ACTIVExtend study[6,20] observed RRR for all clinical fractures (34%), VF (84%), NVF (39%), and major osteoporotic fractures (MOFs) (50%) in the ABL–alendronate group in comparison to the placebo–alendronate group. ABL has also been proven to be more efficacious than teriparatide with the NNT data analysis for clinical (37 for ABL vs 59 for teriparatide), VF (28 for ABL vs 30 for teriparatide), NVF (55 for ABL vs 92 for teriparatide), and MOF (34 for ABL vs 75 for teriparatide).[39]

In the FRAME trial, the ROM–denosumab group demonstrated 81% RRR for VF, 32% RRR for clinical fractures, 25% RRR for NVF, 55% RRR for hip fractures, and 39% RRR for MOF.[11] The ARCH study also reported a 48% RRR for new VF and 19% RRR for NVF, respectively, in the ROM–alendronate group in comparison to the alendronate–alendronate group.[12]

Palacios et al.[26] reported a considerable reduction of cumulative incidences of new VF and NVF after 7 years of therapy with bazedoxifene when compared with placebo (Table 4).

Sequential Therapy

In the aging population with osteoporosis, plural drugs are often needed to optimize the treatment-related fracture risk reduction, either as a sequence or in combination. The ACTIVE–ACTIVExtend analysis[6,20] showed that the participants in the ABL–alendronate group had favorable BMD accrual at the LS, TH, and FN and better antifracture efficacy when compared with the placebo–alendronate group.

The VICTOR study[17] evaluated the efficacy of denosumab or ibandronate as a sequential therapeutic strategy following ROM therapy for 1 year, where denosumab was found to be more efficacious than ibandronate. It was observed that inceptive treatment with ROM for 1 year produced large BMD gains at the LS and TH, and subsequent transition to robust antiresorptive agents (alendronate or denosumab) resulted in augmentation of the BMD at skeletal sites.[18,19,21,22] Following 2 years of therapy, significant BMD gains were observed at the LS and FN when ROM was sequenced with denosumab or alendronate. However, BMD gain following a 2-year therapy with denosumab transitioning to ROM was reported to be comparably poorer, with a differential effect on hip BMD. ROM also effectively increased LS and TH BMD when used following alendronate therapy. It could, therefore, be concluded that BMD gains are larger with anabolic followed by antiresorptive compared to the reverse sequence.

Other Potential Targets

Anabolic Agents

Calcilytics (calcium-sensing receptor antagonists): Ronacalcet is a calcium-sensing receptor antagonist that promotes bone formation by stimulating endogenous PTH release. Fitzpatrick et al.[40] demonstrated modest gain in BMD at LS at 12 months with ronacalcet (0.3–1.6%), teriparatide (9.1%), or alendronate (4.5%), but exhibited a decrease in TH and FN BMD with ronacalcet as opposed to an increase in teriparatide and alendronate arms. ATF936, a novel oral calcilytic, showed encouraging results in animal models.[41]

Dickkopf-1 inhibiton: Dickkopf-1 (Dkk-1), an inhibitor of the WNT/β-catenin signaling pathway, acts by forming a ternary complex with Kremen and LRP5/6. Treatment with anti-Dkk-1 monoclonal antibody exhibited enhanced BMD in ovariectomized monkeys[42] and is under development as a potential anabolic agent.

Matrix extracellular phosphoglycoprotein fragments: Matrix extracellular phosphoglycoprotein (MEPE) fragments are SIBLING (small integrin-binding ligand N-linked glycoproteins) proteins that are usually expressed in differentiated osteoblasts and osteocytes and play an essential role in phosphate regulation and osteogenesis. Although preclinical studies demonstrated new bone formation and fracture healing,[43] further studies are warranted to establish their efficacy as skeletal anabolic agents.

Endocannabinoids: It is well-recognized that the skeletal endocannabinoid system and its receptors play a crucial role in the regulation of BMD and bone turnover. Hanus et al.[44] demonstrated that CP-55,940 (a nonselective cannabinoid receptor agonist) and HU 308 (a cannabinoid CB 2 selective agonist) have facilitated early maturation of bone marrow derived osteoblast precursors and enhancement of BMD.

Activin-follistatin-inhibin hormonal system: Bone metabolism is perceived to be influenced by the activin-follistatin-inhibin (AFI) hormonal system. Activin inhibits bone formation and stimulates bone resorption. Follistatin-inhibin and other proteins antagonize and downregulate activin signaling. Fajardo et al.[45] reported that ACE-011 has dual antiresorptive and anabolic effects on the skeletal system and a marked increment in BMD and bone strength in animal studies.

Stem cell therapy: Mesenchymal stem cells (MSCs) differentiate and evolve into osteoblasts under the influence of various cytokines, growth factors, for example, transforming growth factor beta (TGFβ), fibroblast growth factor (FGF), insulin-like growth factor 1 (IGF 1), bone morphogenetic protein (BMP), Wnt, and hormones such as parathyroid hormone,[46] whereas hematopoietic stem cells differentiate to osteoclasts *via* stimulation of NF-κB ligand (RANKL), receptor activation of monocyte/macrophage colony-stimulating factor.[47] Following transplantation, MSCs display their anabolic effect either by differentiating into osteoblasts or by their paracrine effects through the secretion of growth factors and recruitment of reparative cells.[48] Interestingly, MSCs can escape allogeneic rejection by creating an immunosuppressive locus and being hypoimmunogenic.[49] Genetically modified MSCs such as biomaterial scaffolds in combination with gene delivery systems for PDGF-B and BMP-7 expression have demonstrated better long-term engraftment outcomes.[50,51] López-Delgado et al.[52] evaluated *in vivo* bone health in 103 stem cell implant recipients (47 patients with osteoporosis, 56 patients with osteoarthritis) and observed new bone formation in 45% of the recipients

with osteoporosis cells and 46% of those with osteoarthritis cells.

Antiresorptive Agents

αVβ3 integrin antagonists: Integrins such as $\alpha_V\beta_3$ integrin receptors are transmembrane receptors that facilitate the binding of osteoclasts with bone matrix proteins. The $\alpha_V\beta_3$ integrin crosstalks with extracellular matrix proteins containing the arginine–glycine–aspartic acid amino acid sequences, and destruction of this linkage hinders osteoclast adhesion. In a phase II trial, L-000845704, an $\alpha_V\beta_3$ integrin receptor antagonist, showed significant enhancement of LS BMD by 3.5% and a decrease in bone turnover markers by 40%, advocating L-000845704 as a promising drug for osteoporosis.[53]

Chloride channel inhibitors: Chloride channel activity plays a crucial role in the maintenance of an acidic milieu within the sealing zone of osteoclasts. ClC-7, a member of the voltage-gated chloride channels family, is found in the ruffled membrane and lysosomes of osteoclasts. Schaller et al.[54] reported that NS3736, a ClCN7 inhibitor, inhibits bone decay in ovariectomized rats, resulting in net BMD gain.

Discussion

This systematic review has appraised the current evidence exploring the efficacy of newer therapies for osteoporosis such as ABL, ROM, bazedoxifene, and ONO-5334.

Abaloparatide, in several RCTs, has exhibited substantial BMD gain at LS, TH, and FN[5–9,25] and a substantial reduction in VF, NVF, clinical, and MOF[6,20] compared to the placebo group. However, there is growing evidence to suggest that BMD accrual from ABL to teriparatide may dissipate soon after treatment withdrawal,[55] but more certainty of evidence is warranted to advocate judicious use of sequential therapy with robust antiresorptive agents to preserve the BMD gain.

Following a year of treatment with ROM, the BMD gain at LS in FRAME,[11] ARCH,[14] and Ishibashi et al.[12] was 13.7, 13.1, and 16.9%, TH was 6.2, 6.0, and 4.7%, respectively. When ROM was prescribed for 1 year following an antiresorptive therapy such as denosumab[56] or alendronate (STRUCTURE), BMD gain in LS was 9.8 and 5.3% and TH 2.9 and 0.9%, respectively, which was less favorable compared to treatment-naïve patients. These results are consistent with a multicenter, prospective, and observational study including 130 treatment-naïve patients receiving ROM for 12 months.[57] Over 2 years, sequential therapy with ROM followed by denosumab demonstrated better BMD gain at LS and TH (ROM-denosumab group 16.6 and 8.5%, respectively) compared with alendronate (ROM–alendronate group 15.2 and 7.1%) and (denosumab–ROM group 11.5 and 3.8%). This justifies the clinical use of anabolic followed by antiresorptive therapy, especially in severe osteoporosis and elevated risk of fractures. Keaveny et al.[58] demonstrated a better anabolic effect at the LS with ROM at 1 year, both at the trabecular and cortical bone compartments, when compared to teriparatide (27.3 vs 18.5%; $p = 0.005$) and placebo (27.3 vs –3.9%; $p < 0.0001$).

The evidence surrounding optimum approaches for sequential and combination therapy with conventional and newer therapies for osteoporosis remains unclear. DATA-SWITCH study reported the largest BMD gain at the LS, TH, and wrist in women treated with combined teriparatide–denosumab therapy for 2 years, followed by denosumab monotherapy for 2 years, compared to teriparatide for 2 years followed by denosumab for 2 years and denosumab for 2 years followed by teriparatide for 2 years.[59] Further structured studies are required to investigate the optimum sequential and combination therapy regimes that can be employed in clinical practice to improve skeletal integrity in osteoporosis.

There is a dearth of evidence exploring the association between sequential therapy and fracture outcomes. It was observed that fracture risk reduction of VF and NVF was more robust with anabolic agents compared with antiresorptive agents in PMO and men, and the results were independent of baseline risk indicators. Several RCTs have demonstrated the antifracture efficacy of ABL and ROM. Bazedoxifene also exhibited efficacy for all fracture outcomes.[25,26]

The major strength of this systematic review is the robust methodology as per PRISMA guidelines. We used a comprehensive search strategy to minimize publication bias and included methodologically robust 18 RCTs assessing the efficacy of newer agents on BMD gain and fracture risk reduction among men and PMO with osteoporosis.

However, there are a few limitations relevant to this systematic review. First, there was limited evidence measuring the efficacy of newer therapies for osteoporosis in men, and therefore, the level of evidence may be considered as poor. Second, we observed a wide variation in the duration of osteoporosis-related treatment in these studies. Despite having significantly improved BMD at LS, several studies failed to demonstrate significant BMD gain or antifracture efficacy at TH, which could partially be explained by the shorter duration of intervention. Third, only a handful of studies examined the antifracture efficacy of these newer agents, and therefore, further studies are warranted to validate the pharmacotherapy-related RRR of the VF, NVF, or MOF in clinical practice.

Conclusion

In this systematic review, we have identified and discussed newer therapies for osteoporosis that enhance BMD at all skeletal sites and reduce VF and NVF risk in both PMO and men with osteoporosis. We envisage that real-world data over time will provide more evidence for the efficacy of these novel therapies in terms of comparative effectiveness and antifracture efficacy in men, and to explore the optimal strategy for sequential or combination therapy in severe osteoporosis.

Supplementary Material

Supplementary files are available with author. Please connect with author for the Supplementary content.

Orcid

Parthajit Das https://orcid.org/0000-0002-1788-846X
Mohit Goyal https://orcid.org/0000-0002-7228-2890
Debaditya Roy https://orcid.org/0000-0001-9306-545X
Vinod Ravindran https://orcid.org/0000-0001-5842-1877

References

1. Hernlund E, Svedbom A, Ivergård M, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 2013;8:136.
2. Genant HK, Cooper C, Poor G, et al. Interim report and recommendations of the World Health Organization task-force for osteoporosis. Osteoporos Int 1999;10:259–264.
3. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
4. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.
5. Leder BZ, O'Dea LS, Zanchetta JR, et al. Effects of abaloparatide, a human parathyroid hormone-related peptide analog, on bone mineral density in postmenopausal women with osteoporosis. J Clin Endocrinol Metab 2015;100:697–706.
6. Miller PD, Hattersley G, Riis BJ, et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. JAMA 2016;316:722–733.
7. Matsumoto T, Sone T, Yamashita A, et al. Abaloparatide dose-dependently increases bone mineral density in postmenopausal women with osteoporosis: a phase 2 study. J Bone Miner Metab 2023;41:807–816.

8. Czerwinski E, Cardona J, Plebanski R, et al. The efficacy and safety of abaloparatide-SC in men with osteoporosis: a randomized clinical trial. J Bone Miner Res 2022;37:2435–2442.
9. Lewiecki EM, Czerwinski E, Recknor C, et al. Efficacy and safety of transdermal abaloparatide in postmenopausal women with osteoporosis: a randomized study. J Bone Miner Res 2023;38:1404–1414.
10. McClung MR, Grauer A, Boonen S, et al. Romosozumab in postmenopausal women with low bone mineral density. N Engl J Med 2014;370:412–420.
11. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med 2016;375:1532–1543.
12. Ishibashi H, Crittenden DB, Miyauchi A, et al. Romosozumab increases bone mineral density in postmenopausal Japanese women with osteoporosis: a phase 2 study. Bone 2017;103:209–215.
13. Lewiecki EM, Blicharski T, Goemaere S, et al. A phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis. J Clin Endocrinol Metab 2018;103:3183–3193.
14. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. N Engl J Med 2017;377:1417–1427.
15. Langdahl BL, Libanati C, Crittenden DB, et al. Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial. Lancet 2017;390:1585–1594.
16. Recker RR, Benson CT, Matsumoto T, et al. A randomized, double-blind phase 2 clinical trial of blosozumab, a sclerostin antibody, in postmenopausal women with low bone mineral density. J Bone Miner Res 2015;30:216–224.
17. Kobayakawa T, Miyazaki A, Takahashi J, et al. Verification of efficacy and safety of ibandronate or denosumab for postmenopausal osteoporosis after 12-month treatment with romosozumab as sequential therapy: the prospective VICTOR study. Bone 2022;162:116480.
18. McClung MR, Bolognese MA, Brown JP, et al. A single dose of zoledronate preserves bone mineral density for up to 2 years after a second course of romosozumab. Osteoporos Int 2020;31:2231–2241.
19. McClung MR, Bolognese MA, Brown JP, et al. Skeletal responses to romosozumab after 12 months of denosumab. JBMR Plus 2021;5:e10512.
20. Bone HG, Cosman F, Miller PD, et al. ACTIVExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis. J Clin Endocrinol Metab 2018;103:2949–2957.
21. McClung MR, Brown JP, Diez-Perez A, et al. Effects of 24 months of treatment with romosozumab followed by 12 months of denosumab or placebo in postmenopausal women with low bone mineral density: a randomized, double-blind, phase 2, parallel group study. J Bone Miner Res 2018;33:1397–1406.
22. Lewiecki EM, Dinavahi RV, Lazaretti-Castro M, et al. One year of romosozumab followed by two years of denosumab maintains fracture risk reductions: results of the FRAME extension study. J Bone Miner Res 2019;34:419–428.
23. McClung MR, Siris E, Cummings S, et al. Prevention of bone loss in postmenopausal women treated with lasofoxifene compared with raloxifene. Menopause 2006;13:377–386.
24. Cummings SR, Ensrud K, Delmas PD, et al. Lasofoxifene in postmenopausal women with osteoporosis. N Engl J Med 2010;362:686–696.
25. Palacios S, Williams R, Mirkin S, et al. Efficacy and tolerability of bazedoxifene in Mexican women with osteoporosis: a subgroup analysis of a randomized phase 3 trial. Menopause 2016;23:771–777.
26. Palacios S, Silverman SL, de Villiers TJ, et al. A 7-year randomized, placebo controlled trial assessing the long-term efficacy and safety of bazedoxifene in postmenopausal women with osteoporosis: effects on bone density and fracture. Menopause 2015;22:806–813.
27. Beck TJ, Fuerst T, Gaither KW, et al. The effects of bazedoxifene on bone structural strength evaluated by hip structure analysis. Bone 2015;77:115–119.
28. Pinkerton JV, Harvey JA, Lindsay R, et al. Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: a randomized trial. J Clin Endocrinol Metab 2014;99:E189–E198.
29. Papapoulos S, Bone H, Cosman F, et al. Incidence of hip and subtrochanteric/femoral shaft fractures in postmenopausal women with osteoporosis in the phase 3 long-term odanacatib fracture trial. J Bone Miner Res 2021;36:1225–1234.
30. Binkley N, Orwoll E, Chapurlat R, et al. Randomized, controlled trial to assess the safety and efficacy of odanacatib in the treatment of men with osteoporosis. Osteoporos Int 2021;32:173–184.
31. Recker R, Dempster D, Langdahl B, et al. Effects of odanacatib on bone structure and quality in postmenopausal women with osteoporosis: 5-year data from the phase 3 Long-Term Odanacatib Fracture Trial (LOFT) and its extension. J Bone Miner Res 2020;35:1289–1299.
32. Rizzoli R, Benhamou CL, Halse J, et al. Continuous treatment with odanacatib for up to 8 years in postmenopausal women with low bone mineral density: a phase 2 study. Osteoporos Int 2016;27:2099–2107.
33. Bone HG, Dempster DW, Eisman JA, et al. Odanacatib for the treatment of postmenopausal osteoporosis: development history and design and participant characteristics of LOFT, the Long-Term Odanacatib Fracture Trial. Osteoporos Int 2015;26:699–712.
34. Nakamura T, Shiraki M, Fukunaga M, et al. Effect of the cathepsin K inhibitor odanacatib administered once weekly on bone mineral density in Japanese patients with osteoporosis—a double-blind, randomized, dose-finding study. Osteoporos Int 2014;25:367–376.
35. Brixen K, Chapurlat R, Cheung AM, et al. Bone density, turnover, and estimated strength in postmenopausal women treated with odanacatib: a randomized trial. J Clin Endocrinol Metab 2013;98:571–580.
36. Chappard D, Libouban H, Mindeholm L, et al. The cathepsin K inhibitor AAE581 induces morphological changes in osteoclasts of treated patients. Microsc Res Tech 2010;73:726–732.
37. Engelke K, Nagase S, Fuerst T, et al. The effect of the cathepsin K inhibitor ONO-5334 on trabecular and cortical bone in postmenopausal osteoporosis: the OCEAN study. J Bone Miner Res 2014;29:629–638.
38. Eastell R, Nagase S, Ohyama M, et al. Safety and efficacy of the cathepsin K inhibitor ONO-5334 in postmenopausal osteoporosis: the OCEAN study. J Bone Miner Res 2011;26:1303–1312.
39. Reginster JY, Hattersley G, Williams GC, et al. Abaloparatide is an effective treatment option for postmenopausal osteoporosis: review of the number needed to treat compared with teriparatide. Calcif Tissue Int 2018;103:540–545.
40. Fitzpatrick LA, Dabrowski CE, Cicconetti G, et al. The effects of ronacaleret, a calcium-sensing receptor antagonist, on bone mineral density and biochemical markers of bone turnover in postmenopausal women with low bone mineral density. J Clin Endocrinol Metab 2011;96:2441–2449.
41. John MR, Widler L, Gamse R, et al. ATF936, a novel oral calcilytic, increases bone mineral density in rats and transiently releases parathyroid hormone in humans. Bone 2011;49:233–241.
42. Li X, Grisanti M, Fan W, et al. Dickkopf-1 regulates bone formation in young growing rodents and upon traumatic injury. J Bone Miner Res 2011;26:2610–2621.
43. Hayashibara T, Hiraga T, Yi B, et al. A synthetic peptide fragment of human MEPE stimulates new bone formation in vitro and in vivo. J Bone Miner Res 2004;19:455–462.
44. Hanus L, Breuer A, Tchilibon S, et al. HU-308: a specific agonist for CB(2), a peripheral cannabinoid receptor. Proc Natl Acad Sci USA 1999;96:14228–14233.
45. Fajardo RJ, Manoharan RK, Pearsall RS, et al. Treatment with a soluble receptor for activin improves bone mass and structure in the axial and appendicular skeleton of female cynomolgus macaques (*Macaca fascicularis*). Bone 2010;46:64–71.
46. Linkhart TA, Mohan S, Baylink DJ. Growth factors for bone growth and repair: IGF, TGF beta and BMP. Bone 1996;19:1S–12S.
47. Xu F, Teitelbaum SL. Osteoclasts: new insights. Bone Res 2013;1:11–26.
48. Lee K, Kim H, Kim JM, et al. Systemic transplantation of human adipose-derived stem cells stimulates bone repair by promoting osteoblast and osteoclast function. J Cell Mol Med 2011;15:2082–2094.
49. Liu H, Kemeny DM, Heng BC, et al. The immunogenicity and immunomodulatory function of osteogenic cells differentiated from mesenchymal stem cells. J Immunol 2006;176(5):2864–2871.
50. von Bahr L, Batsis I, Moll G, et al. Analysis of tissues following mesenchymal stromal cell therapy in humans indicates limited long-term engraftment and no ectopic tissue formation. Stem Cells 2012;30:1575–1578.
51. Zhang Y, Cheng N, Miron R, et al. Delivery of PDGF-B and BMP-7 by mesoporous bioglass/silk fibrin scaffolds for the repair of osteoporotic defects. Biomaterials 2012;33:6698–6708.
52. López-Delgado L, Del Real A, Sañudo C, et al. Osteogenic capacity of mesenchymal stem cells from patients with osteoporotic hip fractures in vivo. Connect Tissue Res 2022;63:243–255.
53. Murphy MG, Cerchio K, Stoch SA, et al. Effect of L-000845704, an alphaVbeta3 integrin antagonist, on markers of bone turnover and bone mineral density in postmenopausal osteoporotic women. J Clin Endocrinol Metab 2005;90:2022–2028.
54. Schaller S, Henriksen K, Sveigaard C, et al. The chloride channel inhibitor NS3736 [corrected] prevents bone resorption in ovariectomized rats without changing bone formation. J Bone Miner Res 2004;19:1144–1153.
55. Leder BZ. Optimizing sequential and combined anabolic and antiresorptive osteoporosis therapy. JBMR Plus 2018;2:62–68.
56. Kendler DL, Bone HG, Massari F, et al. Bone mineral density gains with a second 12-month course of romosozumab therapy following placebo or denosumab. Osteoporos Int 2019;30:2437–2448.
57. Ebina K, Hirao M, Tsuboi H, et al. Effects of prior osteoporosis treatment on early treatment response of romosozumab in patients with postmenopausal osteoporosis. Bone 2020;140:115574.
58. Keaveny TM, Crittenden DB, Bolognese MA, et al. Greater gains in spine and hip strength for romosozumab compared with teriparatide in postmenopausal women with low bone mass. J Bone Miner Res 2017;32:1956–1962.
59. Leder BZ, Tsai JN, Uihlein AV, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Lancet 2015;386:1147–1155.

REVIEW ARTICLE

A Multispecialty Consensus on Individualized Treatment Strategies for Hypertension Phenotypes and Comorbidities

Gurpreet S Wander[1], Kamlesh Tewary[2], A Muruganathan[3], Agam C Vora[4], Girish Mathur[5], Chenniappan Meenakshisundaram[6], Narinder P Singh[7], Anup Barman[8], Munish Prabhakar[9], Nandini Chatterjee[10], Sujoy Ghosh[11], Puneet Saxena[12], Nihar Mehta[13], Jayanta K Panda[14], Sekhar Chakraborty[15], GD Ramchandani[16], Debaprasad Chakraborty[17], Saikat Datta[18], Mrinal K Roy[19], Amit A Saraf[20], Dwijen Das[21], Chandni Radhakrishnan[22], Devendra P Singh[23], Ravikeerthy M[24], Sandip Mitra[25*]

Received: 20 June 2025; *Accepted:* 08 July 2025

Abstract

Hypertension (HTN) remains a leading contributor to global morbidity and mortality, often coexisting with major comorbidities such as diabetes, chronic kidney disease (CKD), coronary artery disease (CAD), heart failure (HF), and obesity. In India, a significant proportion of hypertensive individuals remain undiagnosed or inadequately treated. This multispecialty consensus provides comprehensive, evidence-based recommendations for individualized HTN management tailored to specific phenotypes and comorbidities. Developed through structured expert panel discussions and a review of international and national guidelines, the consensus emphasizes out-of-office blood pressure (BP) monitoring, phenotype recognition (e.g., white-coat, masked, nocturnal HTN), and early detection of target organ damage. The document outlines practical algorithms and a therapeutic wheel to guide antihypertensive therapy based on patient-specific factors, promoting use of angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), beta-blockers (BB), and diuretics, as per clinical context. Special considerations are provided for managing HTN in young adults, patients with tachycardia, stroke, and respiratory disorders. The consensus also advocates for lifestyle modifications, treatment adherence, and multidisciplinary care to improve BP control and long-term outcomes. By promoting a holistic, patient-centered approach, this consensus aims to bridge gaps in clinical practice and standardize the management of HTN in diverse healthcare settings.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1092

[1]Professor and Head, Department of Cardiology, Dayanand Medical College and Hospital, Ludhiana, Punjab; [2]Former Professor and Head, Department of Medicine, Sri Krishna Medical College, Muzaffarpur, Bihar; [3]Senior Consultant Physician and Chairman, Department of Medicine, Shristi AG Hospital, Tiruppur, Tamil Nadu; [4]Chest Physician and Medical Director, Department of Pulmonology, Vora Clinic and Brahma Kumaris Global Hospital and Research Centre, Mumbai, Maharashtra; [5]Consultant Physician, Department of Medicine, Alka Diagnostic Centre, Kota, Rajasthan; [6]Consultant Cardiologist, Department of Cardiology, Heart Care Unit, Ramakrishna Nursing Home, Tiruchirappalli, Tamil Nadu; [7]Consultant Physician, Department of Nephrology, Max Super Speciality Hospital, Delhi; Dean, Department of Research, Eternal University, Rajgarh, Himachal Pradesh; [8]Director of Medical Education, Department of Nephrology, Government of Assam, Guwahati, Assam; [9]Senior Consultant Physician and Medical Director, Department of Medicine, IMA AKN Sinha Institute; Member at Governing Body, National API; Chairman, Research Society for the Study of Diabetes in India, Gurugram, Haryana; [10]Professor, Department of Internal Medicine; [11]Professor, Department of Endocrinology, Institute of Post Graduate Medical Education and Research (IPGMER), Kolkata, West Bengal; [12]Consultant Physician and Senior Professor, Department of Medicine, Sawai Man Singh Medical College and Hospital, Jaipur, Rajasthan; [13]Associate Director, Department of Structural Heart, Jaslok Hospital and Research Centre, Mumbai, Maharashtra; [14]Consultant Physician and Professor, Department of Medicine, Srirama Chandra Bhanja Medical College and Hospital, Cuttack, Odisha; [15]Senior Consultant Physician and Director, Department of Medicine, KINS Diabetes Speciality Clinic and KINS Hospital, Siliguri, West Bengal; [16]Physician and Diabetologist, Department of Endocrinology, Diabetes Care and Research Center, Kota, Rajasthan; [17]Consultant Physician and Cardiologist, Professor and Head, Department of Medicine, Tripura Medical College, Agartala, Tripura; [18]Consultant Physician, Professor and Head, Department of Medicine, Maharaja Jitendra Narayan Medical College and Hospital, Cooch Behar; [19]Consultant Physician, Department of Medicine, Medical College, Kolkata, West Bengal; [20]Consultant Physician, Department of Internal Medicine, Jupiter Hospital, Thane, Maharashtra; [21]Consultant Physician, Professor and Head, Department of Medicine, Tezpur Medical College and Hospital, Tezpur, Assam; [22]Consultant Physician, Department of Medicine, Government Medical College, Kozhikode, Kerala; [23]Consultant Physician and Professor, Department of General Medicine, Jawaharlal Nehru Medical College, Bhagalpur, Bihar; [24]Consultant Physician and Diabetologist, Department of Medicine, V2K Diagnostics and Speciality Clinic, Bengaluru, Karnataka; [25]Senior Vice President, Department of Medical Affairs, Mankind Pharma Limited, Delhi, India; *Corresponding Author

How to cite this article: Wander GS, Tewary K, Muruganathan A, *et al.* A Multispecialty Consensus on Individualized Treatment Strategies for Hypertension Phenotypes and Comorbidities. J Assoc Physicians India 2025;73(8):77–84.

Introduction

Noncommunicable diseases, including hypertension (HTN), are highly prevalent in developed and developing countries worldwide. HTN is emerging as a serious threat to public health, as it is a chief causative factor responsible for global deaths from stroke to coronary heart disease.[1] In India, HTN is the leading risk factor for death and disability, with prevalence rates of 24% in men and 21% in women, as reported by the 2019–2020 National Family Health Survey (NFHS-5).[2] The recently published ICMR-INDIAB study involved a total of 1,13,043 participants, with 79,506 individuals from rural areas and 33,537 from urban areas, reporting a 35.5% prevalence of HTN, with higher rates in urban areas compared to rural ones. A significant number of existing HTN cases in India, close to 58%, are undiagnosed as per the recent data from NFHS. Undiagnosed HTN is a significant concern, particularly in rural areas, highlighting the necessity for accurate measurements and awareness campaigns.[3]

Hypertension is invariably diagnosed along with multiple comorbidities, particularly type 2 diabetes mellitus (T2DM), obesity, chronic kidney disease (CKD), coronary artery disease (CAD), and heart failure (HF).[4] Recognizing and managing these risk factors and target organ effects is crucial for effectively treating hypertensive patients. As individuals in these high-risk groups are more prone to target organ

damage, clinical guidelines recommend stricter blood pressure (BP) control targets.[5] Despite advancements in BP measurement methods and the availability of effective and safe antihypertensive medications, these resources are not always utilized to their full potential in clinical practice. As a result, a considerable number of patients on antihypertensive treatment do not achieve adequate BP control. This leads to a higher risk of HTN-related cardiovascular (CV) complications, contributing to increased morbidity and mortality.[6]

The aim of this consensus paper is to provide comprehensive guidance on the management of HTN and its associated comorbidities, with a focus on personalized, patient-centered care. The paper emphasizes the importance of phenotype-specific strategies in managing HTN. A key feature of this consensus is the proposal of a therapeutic wheel, designed to guide clinicians in selecting appropriate treatment strategies based on individual patient profiles and comorbid conditions. By increasing awareness among healthcare providers and advocating for the holistic management of comorbidities, this consensus seeks to optimize BP control, minimize HTN-related complications, and enhance overall patient well-being.

Need for Consensus

The growing prevalence of HTN and its associated comorbidities necessitates a unified approach to management. HTN is a leading modifiable risk factor for numerous CV and renal diseases. However, its management is complicated by diverse phenotypes such as sustained normotension, masked HTN, and nocturnal HTN, as well as the frequent coexistence of comorbidities like diabetes, dyslipidemia, and obesity. These comorbidities often remain undiagnosed, delaying effective intervention. A "one-size-fits-all" approach to HTN is inadequate, as treatment based solely on BP levels overlooks the broader clinical picture, patient-specific factors, and diverse population needs.

To improve outcomes, HTN management must adopt a holistic, patient-centered approach. This includes early detection of comorbidities, personalized therapy that accounts for individual differences, and collaborative care involving multidisciplinary teams. Routine screenings, evidence-based guidelines, and phenotype-specific strategies, such as monitoring out-of-office BP, are essential. A consensus on individualized management strategies for HTN, its phenotypes, and associated comorbidities is essential to ensure consistent, evidence-based care across diverse healthcare settings. A standardized approach helps prevent fragmented care, improves outcomes, and promotes collaboration among specialists, ensuring comprehensive management.

Methodology

A comprehensive review of national and international HTN management guidelines was conducted to incorporate the latest evidence-based practices. An expert panel comprising cardiologists, endocrinologists, nephrologists, and primary care physicians was convened to discuss and deliberate on key issues, including diagnostic challenges, phenotype-specific strategies, and holistic management approaches. Multiple rounds of structured discussions were held to address the limitations of existing practices and to identify areas requiring consensus. The panel's insights were synthesized to formulate practical, patient-centered recommendations aimed at improving management of HTN and its associated comorbidities.

Results

Ambulatory blood pressure monitoring (ABPM) and home blood pressure monitoring (HBPM) are both valuable tools for managing HTN. ABPM provides a comprehensive 24-hour BP profile, capturing variations throughout the day and night, including nocturnal HTN, which is a strong predictor of CV risk. HBPM, on the contrary, offers a practical and cost-effective alternative, allowing patients to monitor their BP regularly at home, leading to better long-term management and adherence to treatment (Table 1).

Clinical Characteristics—Phenotypes

Advances in out-of-office BP monitoring have led to the identification of various BP phenotypes, each with distinct prognostic implications for long-term CV risk. Accurate diagnosis of these phenotypes requires both in-office and out-of-office BP measurements. These phenotypes are as shown in Tables 2 and 3.[7]

Out-of-office BP monitoring has identified various phenotypes, such as white-coat HTN, masked HTN, nocturnal HTN, and high BP variability, each with distinct prognostic implications for long-term CV risk.

Treatment of Uncomplicated Hypertension

For patients with uncomplicated HTN, treatment should begin with a dual combination therapy, ideally as a single-pill combination. Recommended combinations include an angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) with a calcium channel blocker (CCB)

Table 1: Summary of recommendations of BP measurement methods and their clinical implications by Indian guidelines on HTN[14]

Method	*Cutoff for diagnosis*	*Recommendations*
Clinic (office) BP measurement	SBP: ≥140 DBP: ≥90	• Diagnosis based on multiple readings over several visits • Aneroid, large dial apparatus preferred; requires calibration every 6 months • BP cuff should cover 80% of upper arm length (standard: 12 × 35 cm)
HBPM	SBP: ≥135 DBP: ≥85	• Helps differentiate sustained vs white coat HTN • Only validated oscillometric devices (brachial artery) should be used • Finger and wrist monitors are not recommended • Recommended readings: morning and evening for 3–5 days • Average of multiple readings provides a true BP estimate • May not be accurate in atrial fibrillation or arrhythmias
ABPM	Day mean: SBP: ≥135; DBP: ≥85 Night mean: SBP: ≥120; DBP: ≥70 24h mean: SBP: ≥130; DBP: ≥80	• Detects white coat, masked, nocturnal, resistant, and episodic HTN • Identifies BP variations: dipping, nondipping, extreme dipping, and reverse dipping • Uses a portable monitor for 24–48 hours • Early morning BP surge (>3 hours) increases CV risk

ABPM, Ambulatory blood pressure monitoring; BP, blood pressure; CV, cardiovascular; HBPM, Home blood pressure monitoring; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension

Table 2: HTN phenotypes, prognostic implications, and management strategies

Phenotype	*Description*	*Prognostic implications*	*Management*
Controlled HTN	Normal BP readings in-office and out-of-office due to antihypertensive therapy	Reduced CV risk compared to uncontrolled HTN[9]	Adherence to prescribed antihypertensive therapy; lifestyle modifications
Masked HTN	Office BP is not elevated, but the 24-hour ambulatory BP average is ≥130/80 mm Hg (or awake average is ≥135/85 mm Hg) and Home BP is >135/85[8]	Increased risk of CV events and organ damage[7]	HBPM, lifestyle changes, initiation or intensification of antihypertensive therapy
WCH/WCE	Office BP is elevated, but the Home BP is <135/85 and 24-hour ambulatory BP average is <130/80 mm Hg[8]	Lower CV risk than sustained HTN, but higher than normotension	Regular BP monitoring, lifestyle modifications, and pharmacotherapy, only if CV risk is high
Uncontrolled HTN/ sustained HTN	Persistent BP elevation in-office and out-of-office settings	• May indicate suboptimal treatment or stress-related BP elevation • Increased risk of CV disease, stroke, and mortality	• Reassess treatment adherence; consider alternative therapies or HBPM • Treatment with a 3-drug regimen: RAAS inhibitor (ACEI/ARB), long-acting CCB, and a thiazide or thiazide-like diuretic [hydrochlorothiazide (HCTZ), chlorthalidone or indapamide] • Lifestyle modifications
Nocturnal HTN	Average sleep BP ≥120/70 mm Hg	Associated with increased CV risk, target organ damage, and mortality	Antihypertensive medications such as diuretics, BBs, CCBs, ACEI, or ARBs; bedtime dosing may be beneficial
ISH[10]	SBP >140 mm Hg with DBP <90 mm Hg, commonly seen in older adults	Increased risk of CV disease, stroke, and mortality	First-line: thiazide-like diuretics or CCBs; ACEI/ARB reserved for comorbid conditions; combination therapy if SBP >160 mm Hg or >20/10 mm Hg above target. BB are less effective for stroke prevention. Secondary causes should be ruled out
IDH[11–13]	SBP <140 mm Hg with DBP >90 mm Hg. More common in younger adults	Uncertain CV risk may indicate early HTN progression	Treatment options include ACEI, thiazide diuretics, or CCBs. Lifestyle modifications are recommended

ALLHAT, antihypertensive and lipid-lowering treatment to prevent heart attack trial; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; WCE, white coat effect; WCH, white coat hypertension

Table 3: HTN phenotypes as per Indian guidelines for HTN 2019[14]

Category	*Office BP*	*Home BP*
White coat HTN incidence: 10–15%	High	Normal
Masked HTN incidence: 5–10%	Normal	High
Sustained HTN	High	High
True normotension	Normal	Normal

or a thiazide/thiazide-like diuretic (Fig. 1). Monotherapy may be reserved for specific cases, such as low-risk grade 1 HTN, very elderly individuals, or frail patients. If BP remains uncontrolled, escalation to a triple combination of an ACEI/ARB + CCB + diuretic is advised. In cases of resistant HTN, adding a fourth drug such as spironolactone, another diuretic, alpha (α)-blocker, or beta-blocker (BB) is recommended. Referral to a specialist should be considered if adequate control is not achieved.

Comorbidities Associated with Hypertension and Evidence-based Approaches

Hypertension and Diabetes

Hypertension and T2DM frequently coexist as comorbid conditions. Patients with HTN often show insulin resistance and have a higher likelihood of developing diabetes than those with normal BP.[15] In a study by Geldsetzer et al., the crude prevalence of diabetes was reported at 7.5%, while that of HTN was 25.3%.[16] In India, the coexistence of diabetes and HTN is a growing trend, with individuals with diabetes having a 1.5–2 times higher prevalence of HTN compared to those without diabetes.[17] In a retrospective study of 2,672 patients conducted in an Indian state (Haryana), 11.83% of patients with essential HTN had new-onset diabetes.[18] HTN in diabetes results from fluid overload and vascular remodeling driven by insulin resistance, hyperinsulinemia, and hyperglycemia. Early-stage diabetes leads to HTN due to fluid retention, while later stages see increased vascular resistance.[19] The main goal of treatment focuses on achieving the target BP (Fig. 2).

Hypertension and Chronic Kidney Disease

Chronic kidney disease and end-stage kidney disease (ESKD) are increasingly common due to the growing prevalence of noncommunicable diseases like T2DM and HTN. The bidirectional relationship between HTN and CKD not only contributes to kidney damage but also accelerates the decline of renal function in diabetic patients. T2DM and HTN are responsible for close to half of all cases of CKD in India.[20] As per a narrative review of Asian populations, the overall prevalence of CKD was 17.2%, whereas HTN was present in 43.1% of the participants. ESRD due to HTN was reported to be 12.8%.[21] The Indian Chronic Kidney Disease (ICKD) study reports the prevalence of HTN to be 87% in CKD patients.[22] Management is decided based on the CKD stage (Fig. 3).

Hypertension and Coronary Artery Disease

Hypertension is a significant risk factor for CAD, as it accelerates coronary atherosclerosis and contributes to narrowing of the coronary arteries. Elevated systolic blood pressure (SBP) is particularly linked to complications such as ischemia, cardiac hypertrophy, and myocardial fibrosis. The frequent coexistence of HTN and CAD arises from overlapping risk factors and shared pathophysiological mechanisms. Patients with both conditions typically experience worse clinical outcomes and prognosis compared to those with either condition alone, emphasizing the need for effective management strategies for both conditions together (Fig. 4). About 50–60% of individuals with CAD also have HTN, while approximately 13% of those with HTN have CAD.[23]

Hypertension and Heart Failure

Hypertension is a major and prevalent risk factor for the development of HF across all levels of left ventricular ejection fraction (LVEF), particularly playing a key role in HF with preserved ejection fraction (HFpEF).[24] In

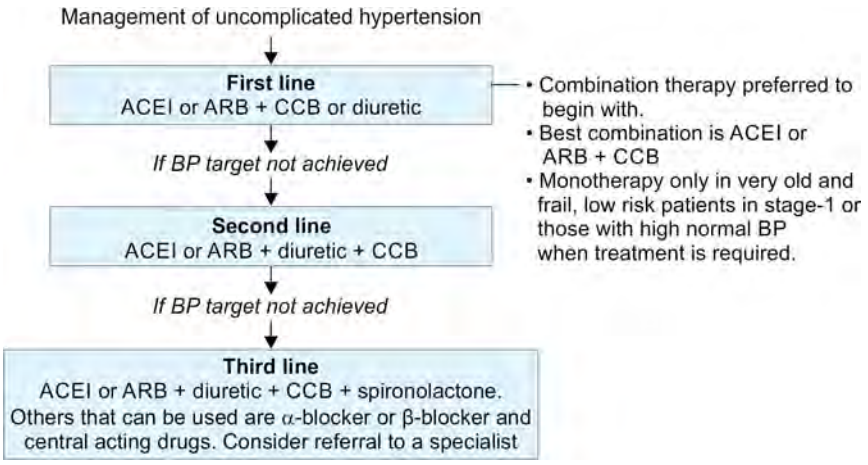


Fig. 1: Treatment of uncomplicated HTN

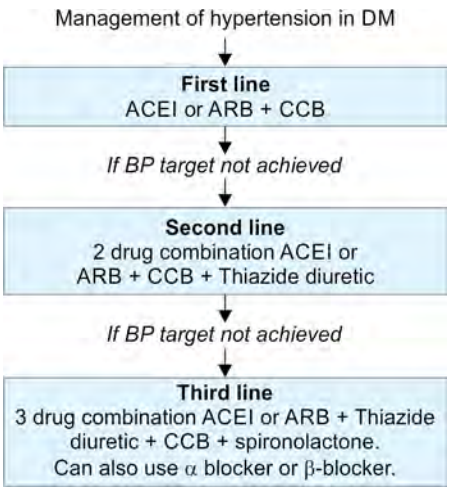


Fig. 2: HTN treatment algorithm in diabetic patients

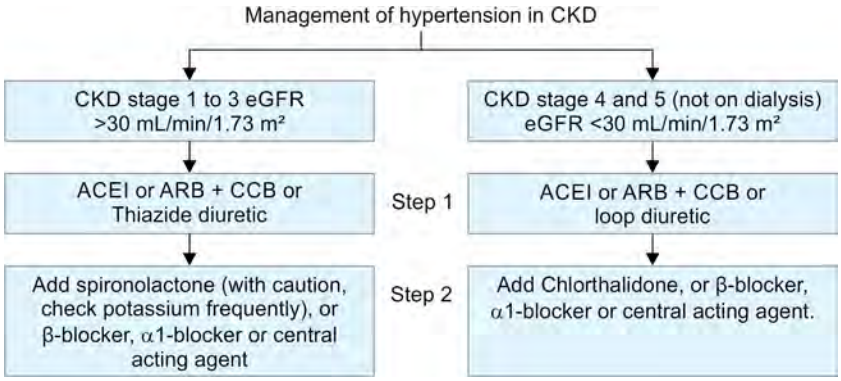


Fig. 3: Algorithm for HTN in CKD; eGFR, estimated glomerular filtration rate

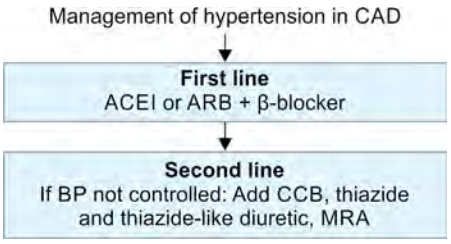


Fig. 4: Antihypertensive therapy selection in patients with CAD

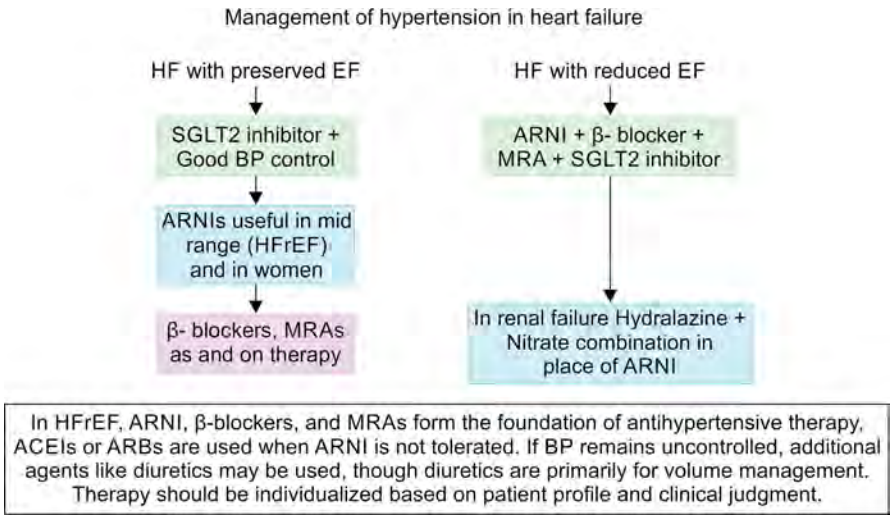


Fig. 5: Antihypertensive strategy in patients with HF

the Framingham Heart Study cohort, 91% of individuals diagnosed with HF had a prior history of HTN, emphasizing the strong connection between the two conditions.[25,26] Several clinical trials have evaluated various therapies in HF. The CONSENSUS study showed that enalapril significantly reduced 1-year mortality by 31% in severe HF patients.[27] Other studies reported improved BP control and outcomes with angiotensin receptor neprilysin inhibitor (ARNI), eplerenone, finerenone, and loop diuretics, particularly in resistant or mineralocorticoid receptor antagonist (MRA)-resistant HTN and older HF patients (Fig. 5).[28–31]

Hypertension and Dyslipidaemia

Hypertension and dyslipidemia are major CV risk factors that often coexist. Population studies show a correlation between rising BP levels and increased lipid levels, likely driven by shared mechanisms like obesity-induced adipocytokine dysregulation. Dyslipidemia impairs arterial function, promotes atherosclerosis, and disrupts BP regulation, increasing the risk of HTN.[32] Epidemiological studies indicate that HTN and dyslipidemia coexist in 15–31% of cases, with up to 40% of newly diagnosed hypertensive individuals having at least one lipid abnormality.[33] Management depends on the effect the drugs have on the lipid profile (Fig. 6).

Hypertension and obesity

Obesity-related HTN is a complex condition influenced by multiple genetic and physiological factors. Key contributors include hyperinsulinemia, activation of the renin-angiotensin-aldosterone system (RAAS), heightened sympathetic activity, and imbalances in adipokines like leptin or endothelial-targeting cytokines.[34] Population-based studies suggest that obesity may contribute to approximately 75% of HTN cases.[35] Management of HTN in obesity, with tailored approaches for patients with or without metabolic syndrome (Fig. 7)

Hypertension and Tachycardia

Tachycardia is linked to an increased risk of HTN and greater CV morbidity and mortality.[36] Tachycardia [heart rate (HR) ≥ 100 bpm][37]

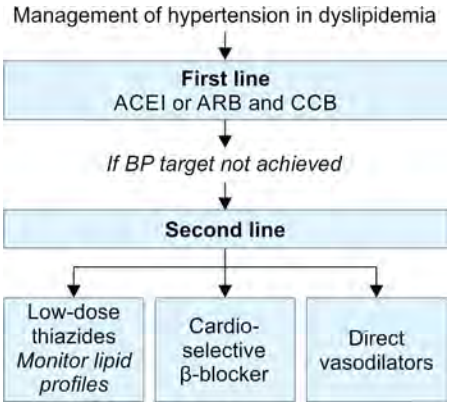


Fig. 6: Antihypertensive therapy in patients with dyslipidaemia

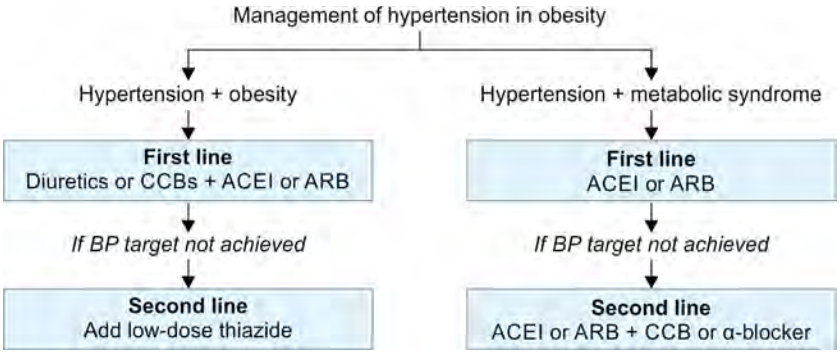


Fig. 7: Antihypertensive management in obesity and metabolic syndrome; GLP-1RA, glucagon-like peptide-1 receptor agonist; RAS inhibitors; renin-angiotensin system inhibitors

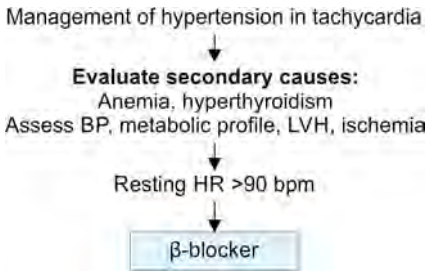


Fig. 8: Treatment approach for HTN in tachycardic patients; DHP, dihydropyridine; LVH, left ventricular hypertrophy

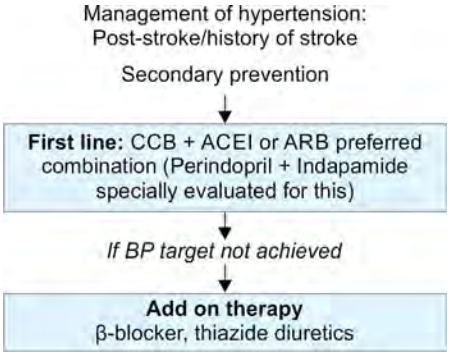


Fig. 9: Treatment of HTN following stroke

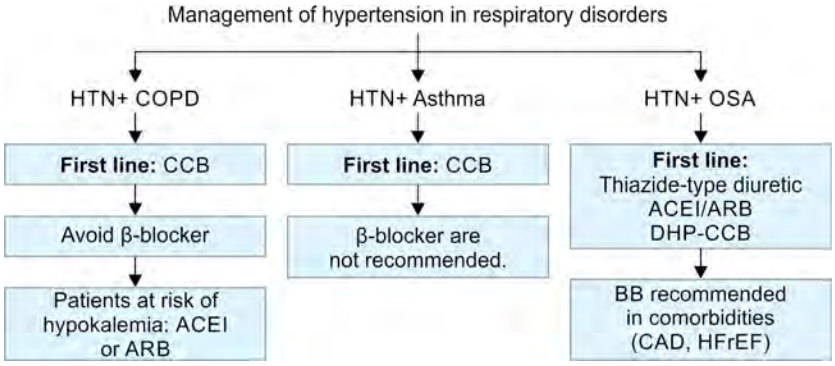


Fig. 10: Antihypertensive management in patients with coexisting respiratory disorders; ADR, adverse drug reactions; DPAH, drug-induced pulmonary arterial hypertension; HFrEF, heart failure with reduced ejection fraction; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance

is observed in over 30% of hypertensive patients.[38] Studies indicate a 3–4 times higher risk of developing HTN with an elevated HR, even after adjusting for traditional risk factors. Furthermore, the rising HR in hypertensive patients correlates with worse CV outcomes. Therefore, managing elevated HR is essential in HTN treatment.[39] Masked tachycardia, affecting up to 10% of hypertensive individuals, is significant because it often goes undetected during routine examinations. Despite this, it poses a heightened risk of target organ damage and CV events, underscoring the need for vigilant diagnosis and management.[40] The link between high HR and CV disease is due to a heightened sympathetic activity. Management strategy for HTN with tachycardia, recommending BBs when resting HR exceeds 90 bpm after ruling out secondary causes (Fig. 8).

Hypertension and Stroke

Stroke is a significant global health issue, being the second leading cause of death and long-term disability. It has accounted for approximately 5.7 million deaths, with the majority occurring in low- and middle-income countries. While 85% of strokes are ischemic, 15% are hemorrhagic. The incidence of stroke has risen in South Asian countries, while it has decreased in European nations. The South Asian population is at higher risk due to factors like HTN, DM, smoking, and family history.[41] In a hospital-based retrospective study conducted by Misgana et al., out of 583 hypertensive patients, 106 (18.18%) developed a stroke.[42] In India, HTN accounts for 57% of all stroke-related deaths.[43]

A combination of perindopril with indapamide and other intensive combination regimens has shown greater benefit in reducing recurrent stroke and cerebrovascular events.[44–46]

Telmisartan, an ARB, has been investigated for its role in secondary stroke prevention due to its antihypertensive and vascular protective properties. In a large multicenter trial involving patients aged ≥55 years with a recent ischemic stroke, telmisartan was compared to placebo for secondary stroke prevention in over 10,000 participants. Treatment with telmisartan led to a modest reduction in BP of 3.8/2.0 mm Hg compared to placebo[47] (Fig. 9).

Hypertension and Pulmonary Disorders

According to the World Health Organization (WHO), asthma impacted approximately 262 million individuals worldwide in 2019 and was responsible for around 4,55,000 deaths that year.[48] Chronic obstructive pulmonary disease (COPD) ranked as the fourth leading cause of death globally in 2021, accounting for an estimated 3.5 million deaths, which represents about 5% of all deaths worldwide.[49] Obstructive sleep apnea (OSA), the most prevalent form of sleep-disordered breathing, is estimated to affect around 1 billion people globally, out of the 7.3 billion population, specifically within the 30–69-year age-group.[50] In Asia, the estimated population-level prevalence of pulmonary hypertension (PH) ranges from 1 to 3%, while pulmonary arterial hypertension (PAH) remains rare, affecting approximately 15–30 individuals per million.[51] HTN management in respiratory disorders emphasizes calcium channel blockers as first-line agents and cautious use of BB based on the underlying pulmonary condition (Fig. 10).

Young-onset Hypertension

Hypertension among young people is common.[52] As per a study by Geevar et al., 11.2% of young adults were found to have HTN.[53] Management of HTN in young adults emphasizes lifestyle changes for borderline cases and pharmacotherapy with ACEIs, ARBs, or BBs when BP is persistently elevated or organ damage is present (Fig. 11).

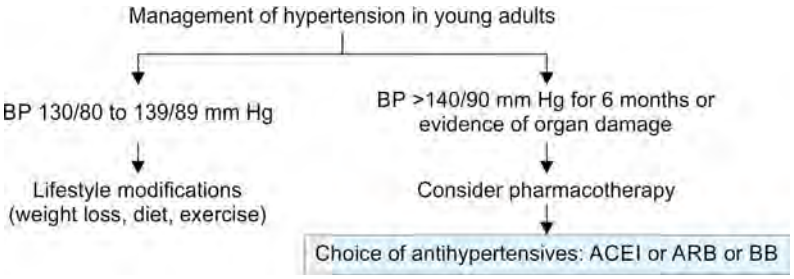


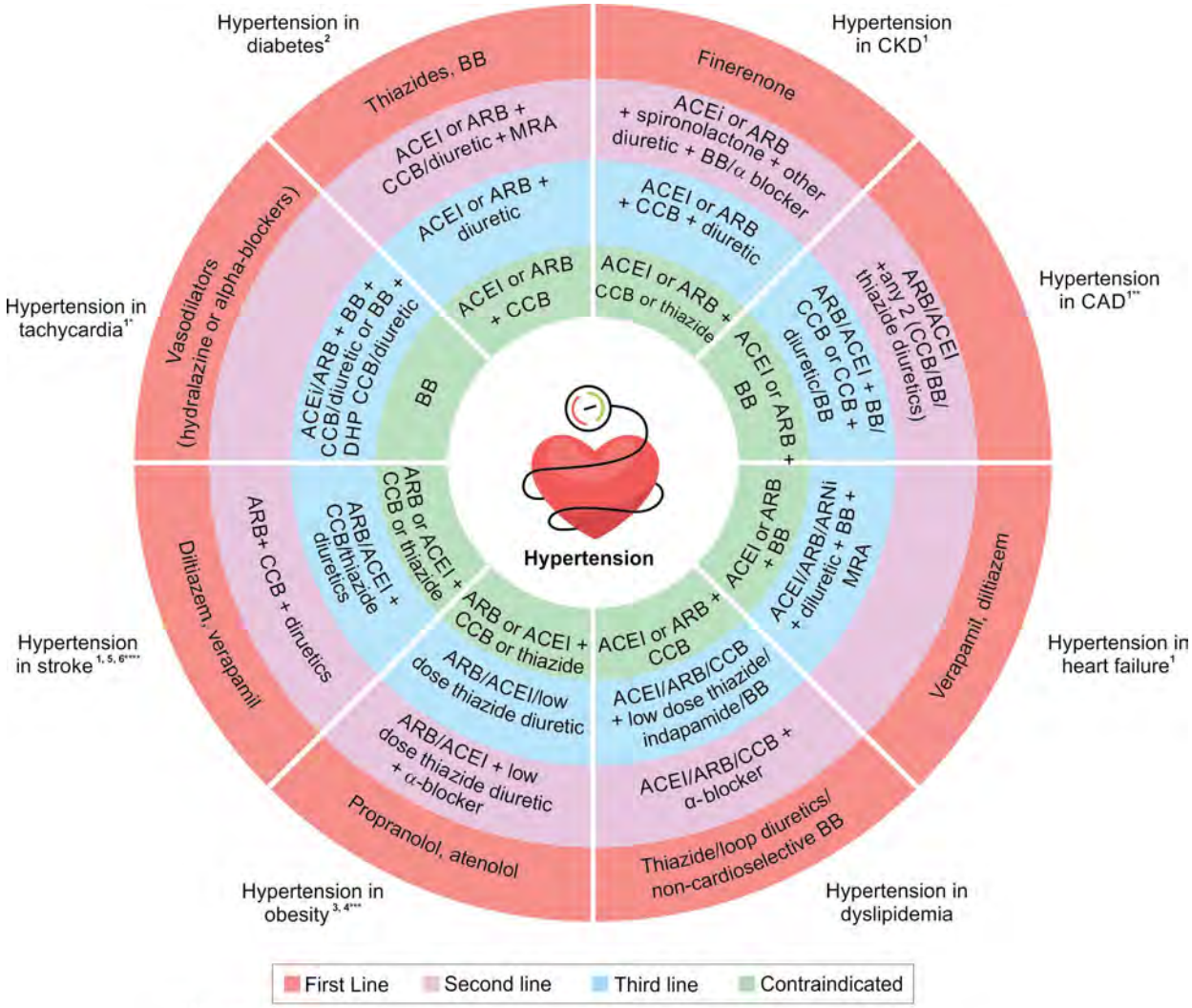
Fig. 11: Approach to HTN management in young adults

Therapeutic Wheel for the Management of HTN-associated Comorbidities

We propose India's first therapeutic wheel for HTN management outlining the first-line, second-line, and contraindicated antihypertensive medications for each comorbidity mentioned in the previous section (Fig. 12).

Monitoring of Blood Pressure

Hypertension is defined using the same cutoff as for ambulatory BP (135/85 mm Hg).



* Hypertension in Tachycardia: Consider non-DHP CCBs, or beta-blocker + CCB
** Hypertension in CAD: Consider monotherapy in low risk grade 1 HTN (SBP < 150 mmHg), or elderly (> 80 years) or frailer patients
*** Hypertension in Obesity: Consider ARB / ACEI monotherapy (ref -#3); ARB + CCB as first line: (ref #4), second line (ref #1), third line recommendation based on real world practice and Indian expert consensus
**** Hypertension in Stroke: Consider first line (ref #1), second and third line recommendation based on real world practice and Indian expert consensus

Fig. 12: Therapeutic wheel for HTN management with comorbidities

Conclusion

In conclusion, this multispecialty consensus underscores the critical importance of tailoring HTN management to individual patient profiles, considering specific BP phenotypes and associated comorbidities. By integrating comprehensive BP monitoring with personalized therapeutic strategies, healthcare providers can enhance treatment efficacy and improve patient outcomes. This approach not only addresses the unique characteristics of each patient but also aligns with the principles of precision medicine, ensuring that interventions are both targeted and effective.

Acknowledgments

This landmark consensus initiative, representing India's First Therapeutic Wheel for the Management of Hypertension and Co-morbidity, was conceptualized and developed by Mankind Pharma in collaboration with the Association of Physicians of India (API), whose expert participation and scientific validation were integral to its success. The authors would also like to thank Intellimed Healthcare Solutions Pvt. Ltd. for assistance in medical writing.

Orcid

Girish Mathur https://orcid.org/0000-0003-1484-7774
Narinder P Singh https://orcid.org/0000-0002-7065-8217
Nandini Chatterjee https://orcid.org/0000-0002-7729-812X
Saikat Datta https://orcid.org/0000-0001-5221-2054
Chandni Radhakrishnan https://orcid.org/0000-0002-0732-0651

References

1. Desai N, Unni G, Agarwala R, et al. Risk factors and comorbidities in young indian patients with hypertension: REAL YOUNG (hypertension) study. Integr Blood Press Control 2021;14:31–41.
2. Anjana RM, Unnikrishnan R, Deepa M, et al. Metabolic non-communicable disease health report of India: the ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). Lancet Diabetes Endocrinol 2023;11(7):474–489.
3. Appadurai PD, Rajanayagam ARN, Asharaf RM, et al. Undiagnosed hypertension and its correlates among adults attending urban and rural health training centers in a South Indian district. J Educ Health Promot 2023;12:162.
4. Shrestha PL, Shrestha PA, Vivo RP. Epidemiology of comorbidities in patients with hypertension. Curr Opin Cardiol 2016;31(4):376–380.
5. Schmieder RE, Ruilope LM. Blood pressure control in patients with comorbidities. J Clin Hypertens 2008;10(8):624–631.
6. Parati G, Lombardi C, Pengo M, et al. Current challenges for hypertension management: from better hypertension diagnosis to improved patients' adherence and blood pressure control. Int J Cardiol 2021;331:262–269.
7. Tewari J, Qidwai KA, Roy S, et al. Different phenotypes of hypertension and associated cardiovascular and all-cause mortality: a systematic review and meta-analysis. Egypt Heart J 2024;76(1):162.
8. Viera AJ, Shimbo D. Ambulatory blood pressure phenotypes and the risk for hypertension. Curr Hypertens Rep 2014;16(10):481.
9. Asayama K, Li Y, Franklin SS, et al. Cardiovascular risk associated with white-coat hypertension. Hypertension 2017;70(4):676–682.
10. Tan JL, Thakur K. Systolic hypertension. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025.
11. Jacobsen AP, McKittrick M, Daya N, et al. Isolated diastolic hypertension and risk of cardiovascular disease: controversies in hypertension—con side of the argument. Hypertension 2022;79(8):1571–1578.
12. Zhang X, Wang X, Wang M, et al. Prevalence, awareness, and treatment of isolated diastolic hypertension in the United States. Eur J Intern Med 2023;112:93–99.
13. Wang SY, Hanna JM, Gongal P, et al. Choice of antihypertensive agent in isolated systolic hypertension and isolated diastolic hypertension: a secondary analysis of the ALLHAT trial. Am Heart J 2022;254:30–34.
14. Shah SN, Munjal YP, Kamath SA, et al. Indian guidelines on hypertension-IV (2019). J Hum Hypertens 2020;34(11):745–758.
15. Petrie JR, Guzik TJ, Touyz RM. Diabetes, hypertension, and cardiovascular disease: clinical insights and vascular mechanisms. Can J Cardiol 2018;34(5):575–584.
16. Geldsetzer P, Manne-Goehler J, Theilmann M, et al. Diabetes and hypertension in India. JAMA Intern Med 2018;178(3):363–372.
17. Kumar V, Agarwal S, Saboo B, et al. RSSDI guidelines for the management of hypertension in patients with diabetes mellitus. Int J Diabetes Dev Ctries 2022;42(4):576–605.
18. Jhawat V, Gupta S, Agarwal BK, et al. Prevalence and risk factors of essential hypertension and new onset of diabetes in essential hypertension in rural population of Haryana. Int J Pharm Pharm Sci 2018;10:142–148.
19. Ohishi M. Hypertension with diabetes mellitus: physiology and pathology. Hypertens Res 2018;41(6):389–393.
20. Agarwal SK. Chronic kidney disease and its prevention in India. Kidney Int Suppl 2005;68:S41–S45.
21. Teo BW, Chan GC, Leo CCH, et al. Hypertension and chronic kidney disease in Asian populations. J Clin Hypertens 2021;23(3):475–480.
22. Kumar V, Yadav AK, Sethi J, et al. The Indian Chronic Kidney Disease (ICKD) study: baseline characteristics. Clin Kidney J 2021;15(1):60–69.
23. Chen Y, Zhou ZF, Han JM, et al. Patients with comorbid coronary artery disease and hypertension: a cross-sectional study with data from the NHANES. Ann Transl Med 2022;10(13):745.
24. Gallo G, Savoia C. Hypertension and heart failure: from pathophysiology to treatment. Int J Mol Sci 2024;25(12):6661.
25. Oh GC, Cho HJ. Blood pressure and heart failure. Clin Hypertens 2020;26:1.
26. Iyer AS, Ahmed MI, Filippatos GS, et al. Uncontrolled hypertension and increased risk for incident heart failure in older adults with hypertension: findings from a propensity-matched prospective population study. J Am Soc Hypertens 2010;4(1):22–31.
27. Consensus Trial Study Group. Effects of Enalapril on Mortality in Severe Congestive Heart Failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316(23):1429–1435.
28. Jackson AM, Jhund PS, Anand IS, et al. Sacubitril–valsartan as a treatment for apparent resistant hypertension in patients with heart failure and preserved ejection fraction. Eur Heart J 2021;42(36):3741–3752.
29. Faselis C, Arundel C, Patel S, et al. Loop diuretic prescription and 30-day outcomes in older patients with heart failure. J Am Coll Cardiol 2020;76(6):669–679.
30. Chimura M, Wang X, Jhund PS, et al. Finerenone in women and men with heart failure with mildly reduced or preserved ejection fraction: a secondary analysis of the FINEARTS-HF randomized clinical trial. JAMA Cardiol 2025;10(1):59–70.
31. Serenelli M, Jackson A, Dewan P, et al. Mineralocorticoid receptor antagonists, blood pressure, and outcomes in heart failure with reduced ejection fraction. JACC Heart Fail 2020;8(3):188–198.
32. Otsuka T, Takada H, Nishiyama Y, et al. Dyslipidemia and the risk of developing hypertension in a working-age male population. J Am Heart Assoc 2016;5(3):e003053.
33. Dalal JJ, Padmanabhan TNC, Jain P, et al. LIPITENSION: interplay between dyslipidemia and hypertension. Indian J Endocrinol Metab 2012;16(2):240–245.
34. Vaněčková I, Maletínská L, Behuliak M, et al. Obesity-related hypertension: possible pathophysiological mechanisms. J Endocrinol 2014;223(3):R63–R78.
35. Wu X, Li G, Liu L, et al. Trends in prevalence of obesity and its association with hypertension across socioeconomic gradients in rural Yunnan Province, China. BMC Cardiovasc Disord 2024;24:75.
36. Palatini P, Casiglia E, Pauletto P, et al. Relationship of tachycardia with high blood pressure and metabolic abnormalities: a study with mixture analysis in three populations. Hypertension 1997;30(5):1267–1273.
37. Gopinathannair R, Olshansky B. Management of tachycardia. F1000Prime Rep 2015;7:60.
38. Palatini P. Treatment of tachycardia in hypertension: where do we stand now? Curr Hypertens Rev 2005;1(2):129–140.
39. Dalal J, Dasbiswas A, Sathyamurthy I, et al. Heart rate in hypertension: review and expert opinion. Int J Hypertens 2019;2019:2087064.
40. Cierpka-Kmieć K, Hering D. Tachycardia: the hidden cardiovascular risk factor in uncomplicated arterial hypertension. Cardiol J 2020;27(6):857–867.
41. Pathak A, Kumar P, Pandit AK, et al. Is prevalence of hypertension increasing in first-ever stroke patients?: a hospital-based cross-sectional study. Ann Neurosci 2018;25(4):219–222.
42. Misgana S, Asemahagn MA, Atnafu DD, et al. Incidence of stroke and its predictors among hypertensive patients in Felege Hiwot comprehensive specialized hospital, Bahir Dar, Ethiopia, a retrospective follow-up study. Eur J Med Res 2023;28:227.
43. Sethi R, Hiremath JS, Ganesh V, et al. Correlation between stroke risk and systolic blood pressure in patients over 50 years with uncontrolled hypertension: results from the SYSTUP-India study. Cardiovasc Ther 2021;2021(1):6622651.
44. Yusuf S, Diener HC, Sacco RL, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. N Engl J Med 2008;359(12):1225–1237.
45. Arima H, Chalmers J, Woodward M, et al. Lower target blood pressures are safe and effective for the prevention of recurrent stroke: the PROGRESS trial. J Hypertens 2006;24(6):1201–1208.
46. Bath PM, Scutt P, Blackburn DJ, et al. Intensive versus guideline blood pressure and lipid lowering in patients with previous stroke: main results from the pilot 'prevention of decline in cognition after stroke

trial' (PODCAST) randomised controlled trial. PLoS One 2017;12(1):e0164608.
47. Schrader J, Lüders S, Kulschewski A, et al. Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: principal results of a prospective randomized controlled study (MOSES). Stroke 2005;36(6):1218–1224.
48. Asthma. Available from: https://www.who.int/news-room/fact-sheets/detail/asthma.
49. Chronic obstructive pulmonary disease (COPD). Available from: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd).
50. Lyons MM, Bhatt NY, Pack AI, et al. Global burden of sleep-disordered breathing and its implications. Respirology 2020;25(7):690–702.
51. Anderson JJ, Lau EM. Pulmonary hypertension definition, classification, and epidemiology in Asia. JACC Asia 2022;2(5):538–546.
52. Hinton TC, Adams ZH, Baker RP, et al. Investigation and treatment of high blood pressure in young people: too much medicine or appropriate risk reduction? Hypertension 2020;75(1):16–22.
53. Geevar Z, Krishnan MN, Venugopal K, et al. Prevalence, awareness, treatment, and control of hypertension in young adults (20–39 years) in Kerala, South India. Front Cardiovasc Med 2022;9:765442.

REVIEW ARTICLE

Introducing a Novel Once-weekly Dipeptidyl Peptidase 4 Inhibitor: Trelagliptin in India

Bhupesh Dewan[1*], Sanjaykumar Navale[2], Siddheshwar Shinde[3], Rishima Ganiga[4]

Received: 07 May 2025; *Accepted:* 09 June 2025

Abstract

India faces a growing burden of type 2 diabetes mellitus (T2DM), necessitating innovative treatments that improve glycemic control, reduce glycemic variability (GV), and enhance patient adherence. Dipeptidyl peptidase 4 (DPP-4) inhibitors are established antidiabetic agents; however, once- or twice-daily dosing often limits long-term compliance. Trelagliptin, a novel once-weekly DPP-4 inhibitor, addresses this issue with an extended half-life and superior molecular stability, enabling sustained DPP-4 inhibition and significant GV reduction. Improved glycemic control with trelagliptin can potentially lower the risk of macrovascular and microvascular complications associated with T2DM. Trelagliptin, developed and launched in India by Zuventus Healthcare Limited under the brand name Trelaglip®, offers prolonged efficacy and high selectivity in inhibiting the DPP-4 enzyme, helping minimize side effects. Development began with in-house active pharmaceutical ingredient (API) synthesis, followed by successful formulation and stability studies. A bioequivalence study confirmed pharmacokinetic equivalence with the reference product by Takeda, Japan. In a randomized phase 3 clinical trial involving patients with glycated hemoglobin (HbA1c) ≥8%, trelagliptin showed greater HbA1c reduction (−1.25%) as compared to vildagliptin (−1.15%) and a similar safety profile. Mild adverse events occurred in 6.67% of trelagliptin users compared to 9.17% with vildagliptin. This article outlines the development and regulatory journey leading to trelagliptin's first approval in India by the Central Drugs Standard Control Organization (CDSCO) in December 2024. Phase 4 real-world evidence studies are currently ongoing in India to assess long-term safety and efficacy.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1093

Introduction

Type 2 diabetes mellitus (T2DM) represents a significant and growing public health challenge in India, with over 77 million adults currently affected.[1] Rapid urbanization, sedentary lifestyles, and dietary changes have contributed to this alarming rise, earning India the unfortunate title of the "diabetes capital of the world." Managing this chronic condition requires effective, accessible, and patient-friendly therapeutic options to control blood glucose levels and mitigate complications such as cardiovascular disease, neuropathy, and retinopathy.[2] Additionally, managing glycemic variability (GV)—the fluctuations in blood glucose levels—is essential, as it is now well established that GV induces oxidative stress, inflammation, and endothelial dysfunction, contributing to macrovascular and microvascular complications.[3]

To address these challenges, therapies with extended dosing intervals have been developed. For instance, several glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as dulaglutide and semaglutide, are now available as once-weekly injectable formulations. While GLP-1RAs offer potent glucose-lowering effects and promote weight loss, they require subcutaneous injection and, besides being painful, are often associated with gastrointestinal side effects like nausea and vomiting.[4] In contrast, DPP-4 inhibitors—which work by inhibiting the DPP-4 enzyme to preserve endogenous incretin hormones—are orally administered and exceptionally well tolerated. Though they are generally weight neutral and offer more modest HbA1c reductions compared to GLP-1RAs, DPP-4 inhibitors have a clear edge in tolerability, with a low risk of gastrointestinal upset and an excellent overall safety profile.[5]

Among the pharmacological options available, DPP-4 inhibitors have become a cornerstone in T2DM therapy due to their glucose-dependent mechanism of action, low risk of hypoglycemia, and favorable side effect profile. However, a major limitation of most DPP-4 inhibitors is the need for daily dosing, which can undermine adherence, particularly for individuals managing complex treatment regimens.[6]

Poor adherence to long-term therapy is a major challenge in managing T2DM, especially in low- and middle-income countries like India.[7] Adherence often declines sharply after the first 6 months of treatment, leading to poor glycemic control, increased risk of complications, and higher healthcare costs. Therefore, effective T2DM management must go beyond pharmacological efficacy to prioritize strategies that improve adherence—particularly in reducing the burden of multiple daily dosing.[8]

Against this backdrop, the introduction of trelagliptin, marketed in India as Trelaglip® by Zuventus Healthcare Limited, a once-weekly oral DPP-4 inhibitor, marks a transformative shift in diabetes management.[9] Trelaglip® offers an effective, safe, and more convenient therapeutic option that addresses both clinical efficacy and the practical needs of patients. Available in 100, 50, and 25 mg doses, Trelaglip® reduces dosing frequency, enhancing treatment adherence and potentially improving long-term glycemic outcomes—particularly in populations with limited access to healthcare or a high treatment burden. A comprehensive understanding of trelagliptin's pharmacological profile and therapeutic advantages is therefore essential to appreciate its role in advancing diabetes care.

Trelagliptin: A Novel Once-weekly Dipeptidyl Peptidase 4 Inhibitor

Trelagliptin is a novel, orally active, and highly selective dipeptidyl peptidase 4 (DPP-4) inhibitor developed for the management of T2DM. It has the molecular formula $C_{18}H_{20}FN_5O_2$, and its chemical structure is depicted in Figure 1.

As a member of the DPP-4 inhibitor class, trelagliptin enhances the activity of incretin hormones, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These hormones are essential for maintaining glucose homeostasis, as they stimulate insulin secretion and suppress glucagon release in a glucose-dependent manner. By inhibiting

[1]Director; [2]Deputy General Manager; [3]Manager; [4]Assistant Manager, Department of Medical Services, Zuventus Healthcare Limited, Mumbai, Maharashtra, India; *Corresponding Author

How to cite this article: Dewan B, Navale S, Shinde S, *et al.* Introducing a Novel Once-weekly Dipeptidyl Peptidase 4 Inhibitor: Trelagliptin in India . J Assoc Physicians India 2025;73(8):85–90.

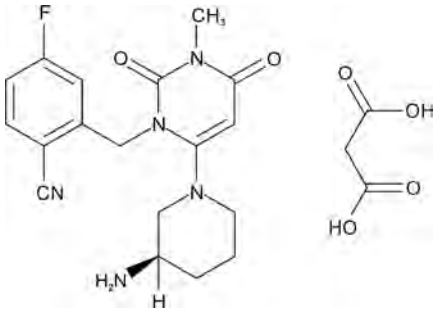


Fig. 1: Chemical structure of trelagliptin

the DPP-4 enzyme, trelagliptin prevents the degradation of GLP-1 and GIP, thereby improving glycemic control while minimizing the risk of hypoglycemia—a common concern with many other antidiabetic therapies.[10] DPP-4 inhibitors, including trelagliptin, have been shown to reduce GV by enhancing GLP-1 activity. This contributes to more stable blood glucose levels throughout the day. Meta-analyses have also demonstrated that these agents significantly reduce the mean amplitude of glycemic excursions (MAGE) compared to other antidiabetic drugs, further underscoring their role in managing GV.[11]

A defining feature of trelagliptin is its once-weekly dosing schedule, enabled by a prolonged elimination half-life of approximately 54.3 hours. This extended pharmacological activity stems from its advanced molecular design, which was achieved using structure-based drug design techniques to optimize both binding affinity and enzyme selectivity.[9] The drug exhibits a dissociation half-life of about 30 minutes, significantly longer than that of other DPP-4 inhibitors such as vildagliptin (<2 minutes) and sitagliptin (~3.5 minutes). This slower dissociation rate underlies its sustained DPP-4 inhibition throughout the dosing interval.[9] In a 12-week monotherapy study, a 100 mg once-weekly dose maintained a mean DPP-4 inhibition of 77.4% even 7 days after the final dose, compared to just 2.4% in the placebo group—demonstrating potent and durable efficacy.[12]

Trelagliptin also exhibits exceptional molecular specificity, with IC_{50} values exceeding 100,000 nmol/L for structurally related enzymes such as DPP-2, DPP-8, DPP-9, prolyl endopeptidase (PEP), and fibroblast activation protein alpha (FAPα). This >10,000-fold selectivity for DPP-4 minimizes side effects, supporting its favorable safety and tolerability profile.[10]

Clinical trials have affirmed trelagliptin's safety and tolerability, showing a low incidence of adverse effects, comparable to daily DPP-4 inhibitors. This combination of efficacy, safety, and convenience positions trelagliptin as a transformative option in the pharmacological management of T2DM—particularly valuable in improving adherence and long-term glycemic control.[13–15]

By offering an effective, safe, and more convenient therapeutic option, trelagliptin addresses both the clinical and practical needs of patients with T2DM. Its introduction in India represents a significant advancement in diabetes care, providing a solution that aligns with the country's growing need for innovative and patient-centric treatments. The development and introduction of this therapy in the Indian market began with the capability and capacity to synthesize its active pharmaceutical ingredient (API) by Zuventus Healthcare Limited—marking the first step in Indian advancement.

How the Journey Began

Development of Trelagliptin Active Pharmaceutical Ingredient

The journey to introduce trelagliptin in India began with a significant challenge: the unavailability of a domestically available API. Recognizing the strategic importance of self-sufficiency and uninterrupted supply, Zuventus Healthcare Limited initiated the development of the trelagliptin API in-house. This initiative went beyond technical formulation—it represented a decisive shift toward reducing dependency on imports and strengthening India's pharmaceutical manufacturing capabilities. The animal toxicology studies were done on the API and were found to be safe.

A dedicated research and development (R&D) team at Zuventus worked rigorously to establish a robust and scalable synthesis process for the API. Through multiple rounds of process optimization and stringent quality testing, the team ensured the compound met all regulatory and pharmacopoeial standards. Comprehensive analytical assessments were performed to validate the API's purity, potency, and batch-to-batch consistency. Following these efforts, the finalized API dossier was submitted to the Central Drugs Standard Control Organization (CDSCO). The subsequent approval under (API Approval Number: Bulk-ND-52/2024) marked a pivotal milestone in the product's development timeline, enabling progression toward formulation and clinical evaluation.

From Formulation to Stability

Following API approval, the focus shifted to formulation development. The goal was to formulate a dosage form that matches the internationally available formulation from Takeda, so that all the available clinical literature for the standardized international formulation is applicable to this new formulation. This required careful selection of excipients, optimization of the manufacturing process, and rigorous stability testing. Formulation development is both an art and a science. Zuventus's R&D team faced challenges such as maintaining the drug's bioavailability and preventing degradation over time.

A comprehensive series of stability studies—both accelerated (6 months) and long-term (24 months)—were conducted to evaluate the formulation's stability under various simulated climatic conditions representative of India's storage and distribution environments. These studies were carried out under controlled temperature and relative humidity (RH) conditions, specifically 30 ± 2°C for long-term and 40 ± 2°C for accelerated testing, with a consistent RH of 75 ± 5%.

The results validated that the Trelaglip® formulation retained its potency, release profile, and purity, with no significant degradation or formation of impurities over the testing period. These outcomes confirmed the formulation's stability and viability for mass production and wide distribution across India's varied climatic zones. This successful formulation stabilization served as the foundation for the next phase—bioequivalence studies, marking a crucial advancement toward clinical evaluation and regulatory submission.

Bioequivalence Study

To ensure that Zuventus's Trelaglip® could be brought to market in India, it was essential to establish its bioequivalence to the reference listed drug (RLD) Zafatek® developed by Takeda. Bioequivalence confirmed that the test formulation delivers the active ingredient into the bloodstream at a rate and extent comparable to the RLD, ensuring equivalent therapeutic outcomes. This step was critical in the regulatory approval process overseen by the CDSCO.

Zuventus initiated the bioequivalence study following review and approval of the study protocol by the Subject Expert Committee (SEC) on Endocrinology and Metabolism. Zuventus obtained permission from the CDSCO to import the RLD from Japan (Import Permission No.: ND/CT-17/41/2022, dated 15th December 2022) and conduct the bioequivalence study (BENOC No.: BE/ND/30/2022, dated 15th December 2022). The study was prospectively registered with the Clinical Trials Registry–India (CTRI/2023/01/048758, dated 5th January 2023). The study was conducted in 32 healthy volunteers, comparing Zuventus's formulation (T) to the reference drug (R) in accordance with international guidelines. Blood samples were collected at multiple time intervals to evaluate key pharmacokinetic parameters. The pharmacokinetic parameters are summarized in

Table 1, and the mean plasma concentration vs. time profile of trelagliptin is shown in Figure 2.

The similarity in AUC_{0-72} values and Cmax, along with statistical analysis confirming that the 90% confidence intervals for both parameters (as shown in Table 2) fell within the regulatory bioequivalence range of 80.00–125.00%, demonstrates bioequivalence.

This successful outcome affirmed that Zuventus's formulation met the necessary standards for therapeutic equivalence, marking a pivotal milestone. This achievement paved the way for the subsequent phase 3 clinical trial in India and eventual marketing permission.

Clinical Development: Designing and Executing of the Trial

Following the successful demonstration of bioequivalence, Zuventus moved forward to the next phase by proposing a clinical trial to the SEC under the CDSCO. The SEC suggested several amendments to the protocol to enhance safety monitoring, which were incorporated as follows: inclusion of provisions for safety monitoring for pancreatitis; specification of an eGFR threshold below which patients would be excluded; exclusion of patients with a previous history of pancreatitis.

After submission of these amendments, Zuventus received a No Objection Certificate (CT NOC No. CT/ND/58/2022) to proceed with the clinical study. The trial was subsequently registered with the Clinical Trials Registry of India on 9th January 2023 (Reg. No.: CTRI/2023/01/048826).

The trial was a randomized, controlled, noninferiority study comparing once-weekly trelagliptin to twice-daily vildagliptin in patients with T2DM, aiming to assess efficacy and safety over 16 weeks. Results were robust in patients with HbA1c ≥ 8%, with the trelagliptin group showing a greater mean HbA1c reduction (–1.25%) compared to vildagliptin (–1.15%) (p = 0.7629). The mean difference was 0.11% (95% CI: –0.28 to 0.50; p = 0.5899), with the upper confidence limit below the 0.5% margin, confirming noninferiority. Approximately 48.57% of trelagliptin patients and 47.57% of vildagliptin patients achieved HbA1c <7% (p = 0.8850), indicating comparable efficacy, while secondary endpoints showed no significant differences in fasting glucose (Δ1.11; 95% CI: –16.79 to 19.02, p = 0.9025), postprandial glucose (Δ3.33; 95% CI: –30.55 to 23.88, p = 0.8093), fasting serum insulin (Δ5.22; 95% CI: –15.01 to 25.45, p = 0.6113), glucagon (Δ0.72; 95% CI: –96.34 to 94.90, p = 0.9882), C-peptide (Δ0.36; 95% CI: –0.31 to 1.03, p = 0.2912), and GLP-1 levels (Δ–0.02; 95% CI: –0.06 to 0.02, p = 0.3995). The change in glycemic parameters from baseline to week 16 is shown in Figure 3.

Safety data revealed that both drugs were well tolerated, with adverse events occurring in 6.67% of trelagliptin patients and 9.17% of vildagliptin patients, all mild and resolving without complications, and no serious adverse events reported, reinforcing trelagliptin's favorable safety profile.

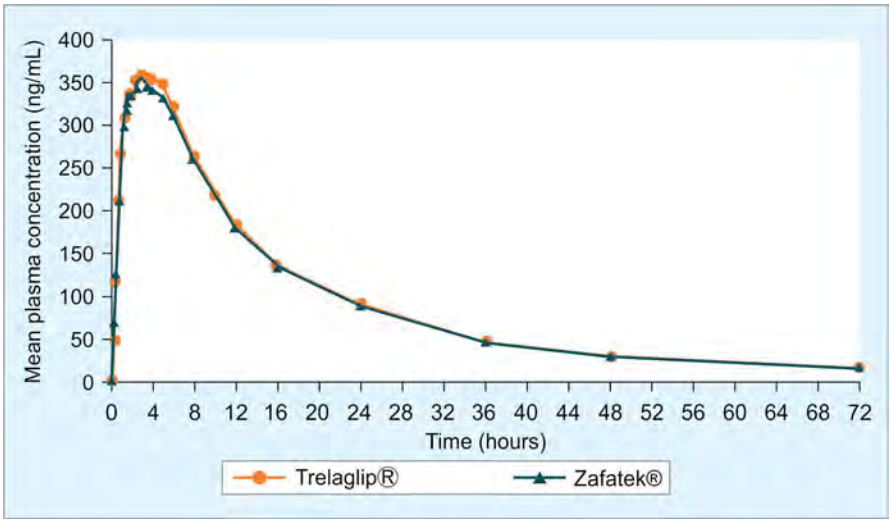


Fig. 2: Trelagliptin mean plasma concentration vs time

Table 1: Pharmacokinetic parameters of test and reference product

Parameter	*Arithmetic mean ± SD (%CV), N = 31*	
	Trelaglip® (T)	*Zafatek® (R)*
C_{max} (ng/mL)	437.55 ± 120.449 (27.53)	429.03 ± 174.309 (40.63)
AUC_{0-72} (ng × hour/mL)	6710.97 ± 797.947 (11.89)	6558.39 ± 795.249 (12.13)
T_{max} (hour)[a]	3.50 (0.33–6.00)	3.00 (0.33–6.00)

CV, coefficient of variance; SD, standard deviation; [a]T_{max}, median (range)

Approval by Central Drugs Standard Control Organization

Following the clinical trial, Zuventus submitted a comprehensive dossier to the CDSCO, encompassing preclinical, bioequivalence, and clinical data. On 13th November 2024, the SEC committee granted permission to manufacture and market trelagliptin in 100 mg, 50 mg, and 25 mg strengths. Subsequently, on 26th December 2024, the CDSCO approved trelagliptin (Approval Number: MF-ND-53/2024) for the treatment of T2DM in India. This milestone marked the approval of the country's first once-weekly DPP-4 inhibitor, highlighting its potential to streamline diabetes care. The clinical development journey of trelagliptin in India is illustrated in Figure 4.

When should Therapy with Trelagliptin be Initiated?

Initiation of Trelagliptin Therapy as per the International Diabetes Management Guidelines

According to diabetes management guidelines, subsequent to dietary and lifestyle modifications, treatment should begin with metformin. If blood glucose levels are not adequately controlled with

Table 2: Ratio analysis and 90% confidence intervals

	Geometric LS mean (N = 31)						
	Trelaglip®	*Zafatek®*	*T/R ratio (%)*	*ISCV (%)*	*Power (%)*	*90% CI*	*Conclusion*
LnC_{max} (ng/mL)	422.78	404.38	104.55	23.04	98.05	94.77–115.34	Bioequivalent
$LnAUC_{0-72}$ (ng × hour/mL)	6662.06	6511.66	102.31	4.25	99.99	100.45–104.20	Bioequivalent

CI, confidence interval; ISCV, intrasubject coefficient of variance; LS, least square

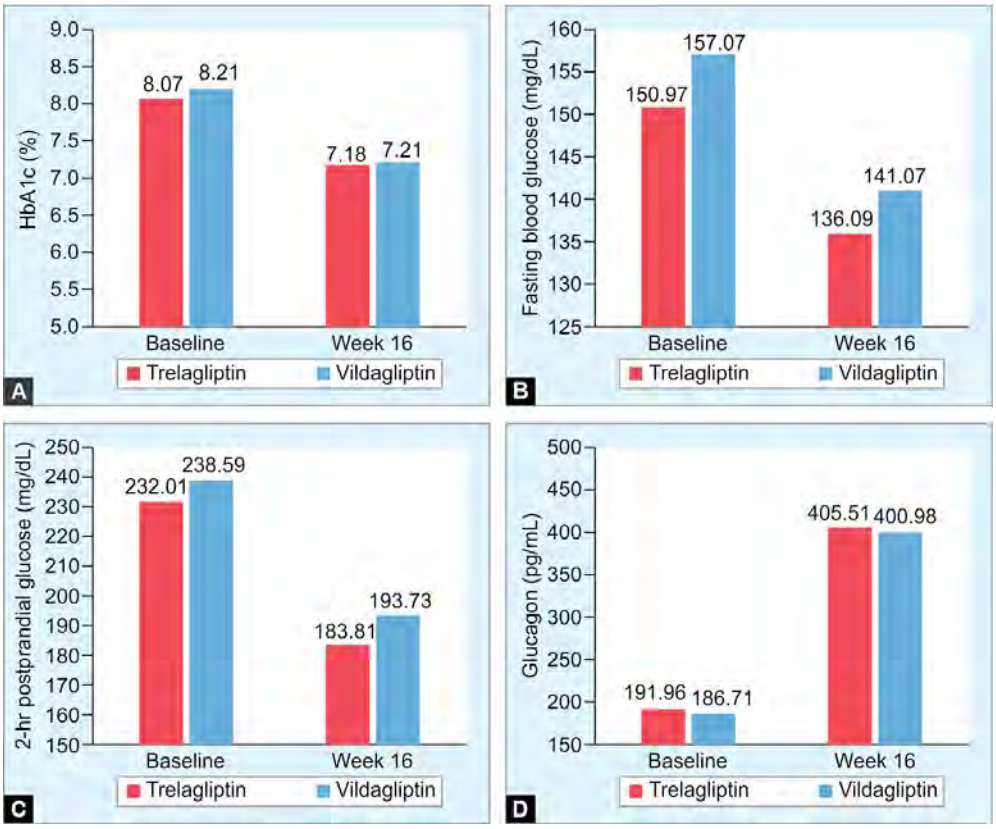
metformin monotherapy, a DPP-4 inhibitor or another class of antidiabetic agents should be added. Since metformin is typically administered once or twice daily, the patient can continue with the same dosage regimen, and trelagliptin can be added as a once-weekly dose to complement the existing treatment. The recommended approach for incorporating trelagliptin into therapy is outlined in Figure 5.[16]

Adjunct to Insulin Therapy in Patients with Inadequate Glycemic Control

Trelagliptin may also be considered in patients with T2DM who are unable to achieve sufficient glycemic control with insulin therapy alone.[15] Studies are available where trelagliptin was added to sulfonylureas, biguanides, thiazolidinediones, and alpha-glucosidase inhibitors.[13]

Patients Unable or Unwilling to Regularly Monitor Blood Glucose

Trelagliptin's once-weekly dosing schedule significantly reduces the need for frequent blood glucose monitoring. This makes it a practical choice for patients who are unable or unwilling to perform regular self-monitoring of blood glucose (SMBG). Such convenience supports better adherence in real-world



Figs 3A to D: Change in glycemic control parameters from baseline to week 16; (A) HbA1c; (B) Fasting blood glucose; (C) 2-hour postprandial glucose; (D) Glucagon

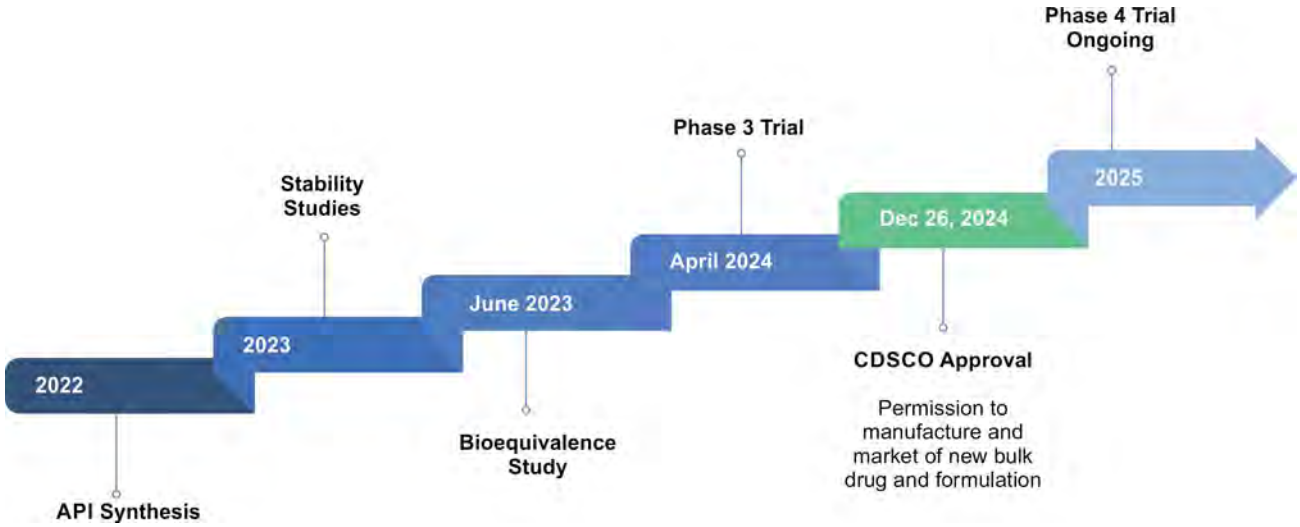


Fig. 4: Clinical development of trelagliptin in India

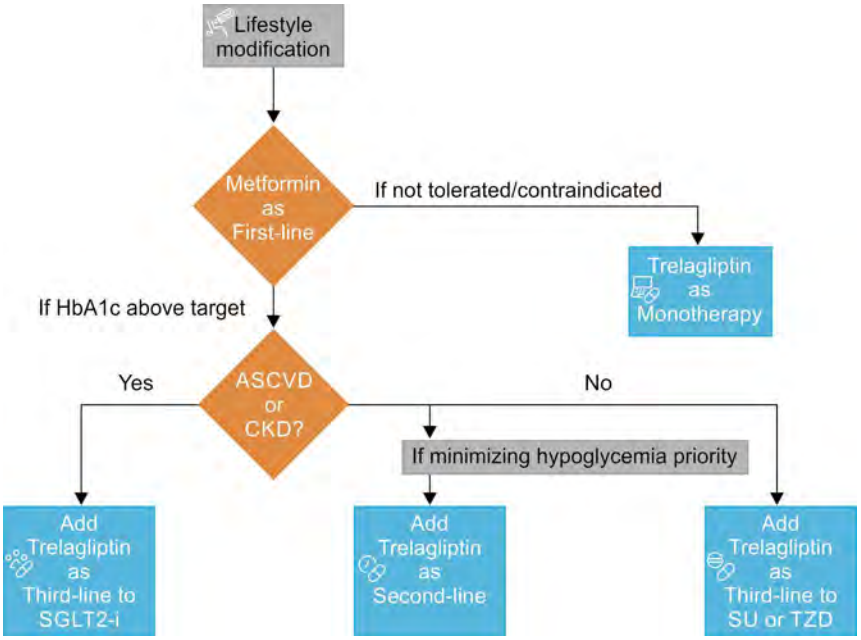


Fig. 5: Treatment algorithm for T2DM with trelagliptin; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DPP-4 inhibitor, dipeptidyl peptidase 4 inhibitor; SGLT2-I, sodium–glucose cotransporter-2 inhibitor; sulfonylurea; TZD, thiazolidinedione

scenarios, especially for individuals with barriers to frequent testing.[17]

Geriatric Patients with Dementia or Those Requiring Nursing Care

In elderly patients with dementia or those requiring nursing care, simplifying treatment regimens can substantially reduce the caregiving burden. Trelagliptin's weekly administration helps decrease the number of daily medications, offering relief to family members and caregivers. It thus represents a valuable therapeutic option in the geriatric population, where polypharmacy and adherence challenges are common.[18]

Primary Care and Rural Healthcare Settings

Trelagliptin once-weekly therapy may especially be useful in primary and rural health settings, as minimal counselling and monitoring are required to use it effectively.[18]

Global Availability and Clinical Development

Trelagliptin, a once-weekly DPP-4 inhibitor, has demonstrated promising efficacy and growing international reach. In India, phase I and III trials have been completed, and phase IV studies are currently underway. The drug is marketed under various names globally: Trelaglip® (India, Zuventus Healthcare), Zafatek (Japan and China, Takeda Pharmaceuticals), Wedica and Triliptin (Bangladesh), Truli-1 (Kenya), Trelaget (Pakistan), and TRELA (Myanmar and Cambodia).

Although Takeda Pharmaceuticals, the original developer, discontinued further development in the US and EU in 2014 due to high regulatory costs, trelagliptin has continued to expand its footprint across Asia and other emerging markets as a convenient, once-weekly oral therapy for T2DM.[9]

Looking Ahead: Phase 4 and Real-world Evidence

Zuventus is now initiating phase 4 studies of Trelaglip® 100 mg in patients with normal and mild renal function, 50 mg in moderate renal stage, and 25 mg in severe and end-stage renal stage patients to generate real-world evidence on trelagliptin. These postmarketing studies will include a larger and more diverse patient population, focusing on long-term safety, efficacy, and the identification of rare adverse events. Additionally, these studies will evaluate Trelaglip®'s effect on GV in real-world settings, patient adherence, real-life clinical outcomes, and the durability of glycemic control over time. The findings are expected to inform clinical practice and may support the expansion of trelagliptin's therapeutic indications, ensuring it continues to meet the evolving needs of Indian patients.

Conclusion

The introduction of once-weekly trelagliptin in India marks a significant advancement in diabetes care. Through domestic API development, successful demonstration of bioequivalence with the global standard, and a robust clinical trial confirming noninferiority, Zuventus Healthcare Limited has taken key steps toward improving treatment options for type 2 diabetes.

As phase 4 studies commence and real-world evidence begins to emerge, trelagliptin is well positioned to become a transformative option in the diabetes treatment landscape—simplifying therapy, improving adherence, and enhancing long-term outcomes for patients across the country. As India's first once-weekly DPP-4 inhibitor, Trelaglip® not only enhances current therapeutic options but also sets a new standard in diabetes care—with its full potential just beginning to unfold.

Orcid

Bhupesh Dewan https://orcid.org/0000-0002-0367-3142
Sanjaykumar Navale https://orcid.org/0009-0007-4419-810X
Siddheshwar Shinde https://orcid.org/0000-0002-4790-9161
Rishima Ganiga https://orcid.org/0009-0003-3481-3130

References

1. World Health Organization. Diabetes in India. Available at: https://www.who.int/india/diabetes last accessed on 21st April 2025
2. Kumar A, Goel MK, Jain RB, et al. India towards diabetes control: key issues. Australas Med J 2013;6(10):524.
3. Alfieri V, Myasoedova VA, Vinci MC, et al. The role of glycemic variability in cardiovascular disorders. Int J Mol Sci 2021;22(16):8393.
4. Gorgojo-Martínez JJ, Mezquita-Raya P, Carretero-Gómez J, et al. Clinical recommendations to manage gastrointestinal adverse events in patients treated with Glp-1 receptor agonists: a multidisciplinary expert consensus. J Clin Med 2022;12(1):145.
5. Gomez-Peralta F, Abreu C, Gomez-Rodriguez S, et al. Safety and efficacy of DPP4 inhibitor and basal insulin in type 2 diabetes: an updated review and challenging clinical scenarios. Diabetes Ther 2018;9:1775–1789.
6. Godinho R, Mega C, Teixeira-de-Lemos E, et al. The place of dipeptidyl peptidase-4 inhibitors in type 2 diabetes therapeutics: A "me too" or "the special one" antidiabetic class? J Diabetes Res 2015;2015(1):806979.
7. Chauke GD, Nakwafila O, Chibi B, et al. Factors influencing poor medication adherence amongst patients with chronic disease in low- and-middle-income countries: a systematic scoping review. Heliyon 2022;8(6).
8. García-Pérez LE, Álvarez M, Dilla T, et al. Adherence to therapies in patients with type 2 diabetes. Diabetes Ther 2013;4:175–194.
9. McKeage K. Trelagliptin: first global approval. Drugs 2015;75(10):1161–1164.

10. Grimshaw CE, Jennings A, Kamran R, et al. Trelagliptin (SYR-472, Zafatek), novel once-weekly treatment for type 2 diabetes, inhibits dipeptidyl peptidase-4 (DPP-4) via a non-covalent mechanism. PLoS One 2016;11(6):e0157509.
11. Lee S, Lee H, Kim Y, et al. Effect of DPP-IV inhibitors on glycemic variability in patients with T2DM: a systematic review and meta-analysis. Sci Rep 2019;9(1):13296.
12. Inagaki N, Onouchi H, Sano H, et al. SYR-472, a novel once-weekly dipeptidyl peptidase-4 (DPP-4) inhibitor, in type 2 diabetes mellitus: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2014;2:125–132.
13. Inagaki N, Sano H, Seki Y, et al. Long-term safety and efficacy of a novel once-weekly oral trelagliptin as monotherapy or in combination with an existing oral antidiabetic drug in patients with type 2 diabetes mellitus: a 52-week open-label, phase 3 study. J Diabetes Investig 2016;7(5):718–726.
14. Kaku K, Ishida K, Shimizu K, et al. Efficacy and safety of trelagliptin in Japanese patients with type 2 diabetes with severe renal impairment or end-stage renal disease: results from a randomized, phase 3 study. J Diabetes Investig 2020;11(2):373–381.
15. Kaku K, Kuroda S, Ishida K, et al. Efficacy and safety of trelagliptin in combination with insulin therapy in Japanese patients with type 2 diabetes: results from a randomized, phase IV study. Diabetes Obes Metab 2018;20(10):2490–2493.
16. Gallwitz B. Clinical use of DPP-4 inhibitors. Front Endocrinol (Lausanne) 2019;10:389.
17. Kalra S, Gupta Y. Weekend therapy in diabetes. J Pak Med Assoc 2016;66(5):627–628.
18. Tosaki T, Kamiya H, Yamamoto Y, et al. Efficacy and patient satisfaction of the weekly DPP-4 inhibitors trelagliptin and omarigliptin in 80 Japanese patients with type 2 diabetes. Intern Med 2017;56(19):2563–2569.

UPDATE ARTICLE

Unlocking the Future of Alzheimer's Disease: Innovations in Diagnosis and Therapy

Man Mohan Mehndiratta[1*], Monika Singla[2], Abhishek Dixit[3]

Received: 16 March 2025; *Accepted:* 25 April 2025

Abstract

Alzheimer's disease (AD) is one of the most common forms of dementia, making up around two thirds of all dementia cases globally. Despite its high prevalence, it is estimated to remain undiagnosed in 41 million people with dementia, and with only about 25% of dementia individuals being clinically identified. AD is the major neurodegenerative disorder leading to dementia, characterized by neuronal atrophy and loss. The accumulation of toxic amyloid-beta (Aβ) oligomers, protein aggregates, along with the formation of neurofibrillary tangles (NFTs) within neurons, is the key pathological feature of AD. NFTs are composed of hyperphosphorylated tau protein. These abnormalities contribute to a decline in cerebral glucose metabolism in the brain, synaptic dysfunction, and mitochondrial impairment. The progression of AD occurs in three stages: (1) the presymptomatic stage, (2) mild cognitive impairment (MCI), and (3) the clinical stage of AD. Many biomarkers have been identified for diagnosing AD and differentiating it from atypical AD. It has emerged as a key area of research, offering significant potential for early detection of AD, prognostication, as well as planning drug therapy and monitoring.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1075

Introduction

Auguste Deter, a woman from Germany who was admitted to a psychiatric institution in 1901 at the age of 51, was the first patient diagnosed with Alzheimer's disease (AD). She had exhibited signs of severe memory loss, confusion, and disorientation, which were initially misunderstood as a form of senile dementia, but the attending physician, Dr Alois Alzheimer, noticed unusual patterns in her cognitive decline. Dr Alzheimer carefully documented her case by noting her memory problems, hallucinations, and changes in her behavior. After her death in 1906, Dr Alzheimer performed an autopsy on her brain, revealing two key features that would become hallmark characteristics of the disease: neurofibrillary tangles (NFTs) made up of tau protein and amyloid plaques. These specific pathological features led Dr Alzheimer to recognize the disease as distinct from other forms of dementia. Eventually, this condition was named "Alzheimer's disease (AD)" in honor of Dr Alzheimer's pioneering work, and his observations of Auguste Deter's case laid the foundation for the study and understanding of this progressive neurodegenerative disorder.

Alzheimer's disease is a neurodegenerative disorder having diverse pathological subtypes and clinical manifestations. It is defined by distinctive neuropathological changes, including the presence of amyloid plaques, containing aggregated amyloid-beta (Aβ), and NFTs formed of tau aggregates. Over time, these plaques and NFTs lead to neuronal atrophy, synaptic loss, deficiencies of neurotransmitters, neuroinflammation, as well as reactive astrogliosis, eventually, all of these result in cognitive decline. In total, 50–70% cases of neurodegenerative dementias are constituted by AD. Around 44 million people globally are currently living with dementia, and this figure is expected to triple by 2050 as the global population continues to age.[1] In 2020, healthcare costs associated with dementia care were estimated at $305 billion.[2] It accounts for the huge economic burden in the United States, surpassing that of cancer as well as cardiovascular disease. Efforts to develop effective treatments for AD are ongoing, but with mixed results. It is believed that once a certain neuropathological threshold is reached, therapeutic interventions may no longer be effective in altering the disease's course.

Pathophysiology

Alzheimer's disease is a progressive condition that damages the brain, causing a gradual decline in memory and cognitive function. It is marked by the buildup of abnormal protein clumps in the brain, which disrupt normal brain activity and lead to the symptoms of the disease. These plaques develop when amyloid precursor protein (APP) is cleaved incorrectly, causing Aβ peptides to clump together and accumulate between neurons, interfering with synaptic function. Tau, a protein involved in stabilizing microtubules, becomes hyperphosphorylated in AD, which leads to the formation of NFTs inside the neurons. Abnormalities in cellular functions, such as protein misfolding or accumulation, can indeed trigger a chain reaction that involves inflammation, oxidative stress, and neuronal damage. This cascade can disrupt communication between neurons and ultimately lead to cell death. With further progression of disease, there is a significant loss of brain volume in the areas vital for higher cognitive functions, particularly in the hippocampus and cortex. Pathophysiology of AD is further complicated by genetic, environmental, and lifestyle factors, and while the exact cause remains unclear, the accumulation of these pathological changes is central to the progression of the disease. The changes in cerebrospinal fluid (CSF) Aβ levels have been detected quite early, as early as 25 years before it could manifest clinically in patients with hereditary AD. The changes in CSF phosphorylated tau (P-tau) may occur approximately 10 years before the symptom onset.[3] The gradual buildup of tau and Aβ pathologies, leading to cellular dysfunction in the brain, causes neurodegeneration that typically occurs just before the clinical onset of AD, such as cognitive decline.[4]

As per various epidemiological studies, inflammation is shown to be linked between AD and factors such as previous infections or diabetes, in initiating AD pathology.[5] Aβ can trigger an activation response in these immune cells, leading to the release of chemokines and local inflammation.[5,6]

[1]Principal-Director Senior Consultant, Department of Neurology, BLK-Max Super Speciality Hospital; MAX Healthcare, Delhi; [2]Professor, Department of Neurology, Dayanand Medical College and Hospital, Ludhiana, Punjab; [3]Associate Consultant, Department of Neurology, BLK-Max Super Speciality Hospital; MAX Healthcare, Delhi, India; *Corresponding Author

How to cite this article: Mehndiratta MM, Singla M, Dixit A. Unlocking the Future of Alzheimer's Disease: Innovations in Diagnosis and Therapy. J Assoc Physicians India 2025;73(8):92–97.

This inflammation impairs Aβ clearance and promotes tau phosphorylation, leading to ensuing neurodegeneration[7] (Table 1). The sustained inflammatory response not only contributes to neuronal damage but also impairs synaptic function and plasticity, key processes involved in learning and memory. The National Institute on Aging–Alzheimer's Association (NIA-AA) developed a new research framework for diagnosing AD. Using an A/T/N classification system, for AD biomarkers, this framework shifts the focus from a symptomatic to a biological perspective. In A/T/N system, "A" refers to the concentration of Aβ biomarkers, "T" represents tau biomarkers, and "N" indicates neurodegeneration biomarkers. Based on their pathological mechanisms and their role in the disease's progression, this classification helps in the categorization of AD markers.[8] Diagnostic utility of A/T/N system for AD could be further enhanced by incorporating additional markers as Lewy body pathology, brain vascular changes, as well as neuroinflammation.[9]

In AD, the brain experiences a persistent, low-level inflammatory response primarily driven by microglia, the immune cells of the central nervous system. In a healthy brain, microglia help maintain balance and clear cellular debris. However, in AD, they become overly activated by the presence of Aβ plaques and tau tangles. This activation triggers the release of proinflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and IL-6, which intensify neuroinflammation.

Biomarkers of Alzheimer's Disease

The identification of biomarkers for AD has become a crucial area of investigation. It is due to its potential for early detection, prognosis, and treatment monitoring. Various approaches are being investigated to monitor AD progression, including the use of plasma-based markers such as tau protein, Aβ, and neurofilament light polypeptide (NFL). Monitoring these markers holds great potential for the early diagnosis of AD and for assessing the effectiveness of Aβ-targeting therapies, ultimately improving clinical decision-making and patient outcomes. Along with other pathological proteins, recent literature highlights the significant potential of Aβ and tau, as the biomarkers for diagnosing AD and assessing disease progression. Beyond these proteins, additional promising biomarker categories have emerged, including those associated with neurodegeneration, inflammation, and lipid metabolism, which are increasingly being explored to further understand the multifaceted nature of AD.

A major obstacle in advancing AD biomarkers is the invasive nature of existing diagnostic methods. Methods such as positron emission tomography (PET) imaging and CSF protein testing provide valuable insights but are both invasive and expensive. Consequently, there is a concerted effort to identify less invasive, yet reliable, biomarkers derived from fluids such as ocular, blood, saliva, and olfactory fluids.[11] These noninvasive biomarkers have the potential to overcome the limitations of current diagnostic methods, offering a more accessible means for the timely diagnosis and monitoring of course and treatment of AD (Table 2).

The latest clinical guidelines from the International Working Group have updated the diagnostic criteria for AD, highlighting the significance of distinct AD phenotypes and supporting biomarker evidence. These guidelines propose that the cognitively

Table 1: Critical role of inflammatory markers in the pathophysiology of AD and contribution to its progression[10]

Inflammatory marker	*Role*	*Associated effect*
Microglia	Brain's immune cells, central in neuroinflammation in AD	Respond to amyloid plaques, modulate immune response
ABCA7	ATP-binding cassette transporter involved in lipid transport	Mutations increase AD risk, affects microglial function
CD33	A receptor that affects immune responses and microglial activation	Alters microglial activity, linked to AD susceptibility
CR1	Complement receptor involved in immune responses	Involved in clearing amyloid plaques and neuroinflammation
EPHA1	Gene regulating neuronal growth and synapse function	May influence synaptic function and neuroinflammation
MS4A	Family of proteins involved in immune responses	Variations linked to AD, affecting microglial activation
TREM2	Expression of triggering receptor on myeloid cells, involved in microglial activation	Affects microglial response to neurodegeneration
IL-1α, IL-1β	Proinflammatory cytokines that activate inflammatory pathways	Raise neuroinflammation, contribute to cognitive decline
IL-6	Proinflammatory cytokines are elevated in AD	Drives neuroinflammation and exacerbates cognitive decline
CCL2 (MCP-1)	Monocyte chemoattractant protein, a chemokine that attracts immune cells	Increased levels in AD, recruit immune cells to the brain
IL-8	Proinflammatory cytokine involved in immune cell recruitment and BBB permeability	Elevated in AD, linked to inflammation and BBB dysfunction
SDF-1	Stromal cell-derived factor 1, a chemokine that helps attract immune cells	Contributes to immune cell recruitment in neuroinflammation
Progranulin	A growth factor that supports neuronal survival and regulates microglia	Elevated before clinical symptoms, modulates neuroinflammation
YKL-40	Chitinase-3-like protein 1 is involved in the inflammation response	Increased in AD, correlates with cognitive decline
ICAM-1	Intercellular adhesion molecule-1 (ICAM-1) plays a key role in promoting immune cell adhesion to the blood–brain barrier (BBB)	Elevated in AD, linked to microvascular changes and inflammation
VCAM-1	Like ICAM-1, vascular cell adhesion molecule-1 is also involved in immune cell adhesion	Elevated in AD, promotes immune cell infiltration into the brain
IL-33	Cytokine involved in inflammation has a protective role in AD	Downregulated in the brain, but elevated in plasma; affects cognition
sST2 (soluble ST2)	Soluble receptor for IL-33 modulates IL-33's protective effects	Elevated in AD, possibly contributes to cognitive decline

Table 2: Various methods and biomarkers, key blood-based and fluid biomarkers, and the use of ocular markers, particularly retinal degeneration *via* advanced imaging technologies such as OCT in early Alzheimer's disease diagnosis other neurodegenerative diseases, along with their strengths and limitations[11,12]

Diagnostic marker	*Method*	*Description*	*Notes*
Brain atrophy	Structural MRI	Detects brain shrinkage (atrophy) associated with Alzheimer's disease (AD)	–
Brain metabolism	18F-2-fluoro-2-deoxy-D-glucose [FDG (18F)] PET	Measures brain metabolism to detect early AD changes	–
Amyloid deposits (Aβ plaques)	Amyloid-PET	Helps in the quantification of amyloid deposits in the brain	–
Tau protein deposits	Tau-PET [flortaucipir (18F)]	Quantification of tau deposits, especially pathologic tau	Can precede clinical symptoms by several years, important for pre-AD detection
CSF Aβ1-42	CSF sampling	Measurement of amyloid-β protein in cerebrospinal fluid (CSF)	High diagnostic accuracy, especially in combination with other biomarkers
Hyperphosphorylated tau (P-tau)	CSF sampling	Measurement of hyperphosphorylated tau peptide in CSF	High diagnostic accuracy when combined with other biomarkers
Total tau (T-tau)	CSF sampling	Measurement of total tau protein in CSF	High diagnostic accuracy, especially in combination with other biomarkers
Mixed pathologies	Various (CSF, PET, MRI)	Detection of mixed pathologies (AD with other neurodegenerative diseases)	Detection remains difficult and could lead to misdiagnosis
Blood-based and fluid biomarkers	*Type*	*Description*	*Notes*
Biomarker			
Tau (plasma)	Blood-based	Measures tau protein in plasma for AD detection	Emerging biomarker, compatible with primary healthcare settings
miRNAs (various)	Blood-based (plasma, serum, CSF)	Small RNA molecules that regulate gene expression related to cardiovascular diseases, cancer, and neurodegenerative disorders	miRNA expressed in the CNS and influencing brain physiology, aging, and mental illness
miRNAs (in AD)	Blood-based (plasma, serum, CSF)	Specific miRNAs targeting key disease genes related to Alzheimer's disease	May have neurodegenerative or neuroprotective effects in AD
Ocular marker	*Method*	*Purpose/description*	*Notes*
Retinal degeneration	Optical coherence tomography (OCT)	Detects changes of retina linked to AD	Studies in animal models and human patients have shown retinal changes associated with AD
Retinal changes (presymptomatic)	OCT	Retinal changes detection in patients before clinical symptoms of dementia appear	Correlates retinal changes in AD patients in asymptomatic stage

unimpaired, biomarker-positive individuals should be considered potential candidates to progress to the symptomatic stage. As biomarkers become more widely available, they will aid in distinguishing between various neurodegenerative disorders and targeting individuals at increased risk for the clinically symptomatic stage.

Despite these complexities, both typical and atypical phenotypes of AD generally present the canonical biomarkers, including molecular neuroimaging and fluid biomarkers. These tools enable *in vivo* confirmation of AD pathology and enhance diagnostic accuracy, contributing to the growing understanding of AD's clinical and biological heterogeneity.

Genetics of Alzheimer's Disease

Genetics has a major role to play in the predisposition to AD. Although the majority of AD cases are sporadic, familial AD, which represents <5% of cases, is directly associated with genetic mutations. The apolipoprotein E ε4 genotype (APOE-e4) allele, the most recognized genetic factor, is associated with a substantially higher risk of developing late-onset AD. People who carry one copy of the APOE-e4 allele face an increased risk, and those with two copies have an even greater risk, although it does not guarantee the development of the disease. Other genetic variants, such as mutations in the genes APP, presenilin 1 and 2 (PSEN1 and PSEN2), are linked to autosomal dominant forms of early-onset AD.[13] However, it is pertinent to understand that genetics alone does not determine the onset of AD; lifestyle and environmental factors play a crucial role.

Clinical Manifestations

Table 3 summarizes the diverse presentations of AD, emphasizing that the challenge of diagnosing this entity may be related to its heterogeneous nature and the influence of coexisting pathologies.

Diagnosis

A comprehensive evaluation of a patient with memory loss is mandatory to diagnose AD including a thorough history, detailed cognitive assessment, along with other relevant investigations. Details of symptoms such as recent memory impairment, confusional episodes, and difficulty performing daily tasks need to be inquired about. Cognitive examination in the form of Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE), and detailed lobe batteries helps in the assessment of person's memory, problem-solving abilities, and executive functions. Imaging techniques, such as CT scan head, magnetic resonance imaging (MRI) or PET scan can help exclude other potential causes and detect specific brain changes, including atrophy or amyloid plaques (Fig. 1). Blood tests are increasingly being used to rule out other conditions or detect specific biomarkers, such as amyloid and tau proteins, that may indicate AD. Additionally, genetic testing can be considered in certain cases, particularly when early-onset AD is suspected. While no single test can definitively diagnose AD, imaging can help establish a diagnosis and rule out other causes of cognitive impairment.

Role of Imaging

Imaging plays an important role in differentiating the asymptomatic stage of AD, mild cognitive impairment (MCI), and symptomatic AD by providing objective insights into brain changes and helping differentiate Alzheimer's from other cognitive disorders.[16,17]

Asymptomatic or Preclinical Alzheimer's Disease

In the early phase, patients show no significant symptoms of cognitive decline, but subtle changes in the brain may already be present. Advanced imaging techniques, such as PET, help detect Aβ plaques and tau aggregates, which are hallmarks of AD. In the absence of cognitive symptoms, amyloid deposits in certain areas of the brain may signal an increased risk of developing AD in the future. Functional MRI (fMRI) may also show changes in brain activity and connectivity patterns that can be early signs of AD before clinical symptoms appear.

Mild Cognitive Impairment

Mild cognitive impairment is marked by a noticeable decline in cognitive abilities that exceeds what is typical for a person's age, though it is not severe enough to be classified as dementia. In this stage, imaging can reveal early signs of neurodegeneration. MRI scans may show hippocampal atrophy, a common feature of AD-related MCI, which is associated with memory problems. PET scans can also detect amyloid and tau deposits, helping to predict which MCI patients may progress to AD (Fig. 2B). Fluorodeoxyglucose (18F) (FDG)-PET imaging can highlight areas of decreased glucose metabolism, often seen in the parietal and posterior cingulate regions, which are sites of early neuronal dysfunction in AD.

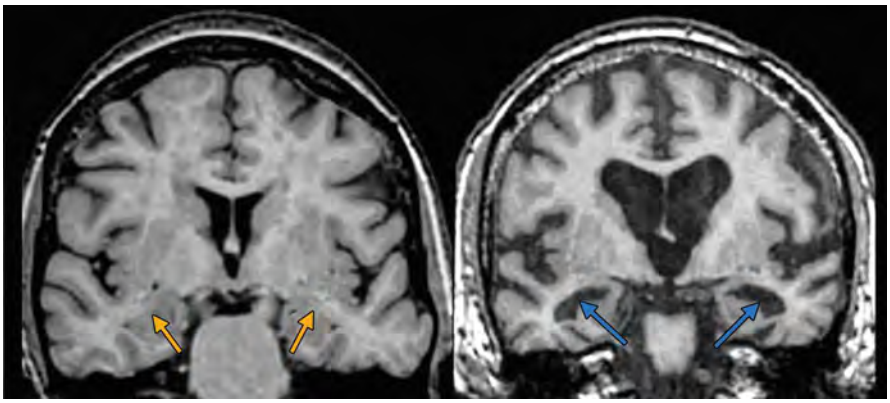
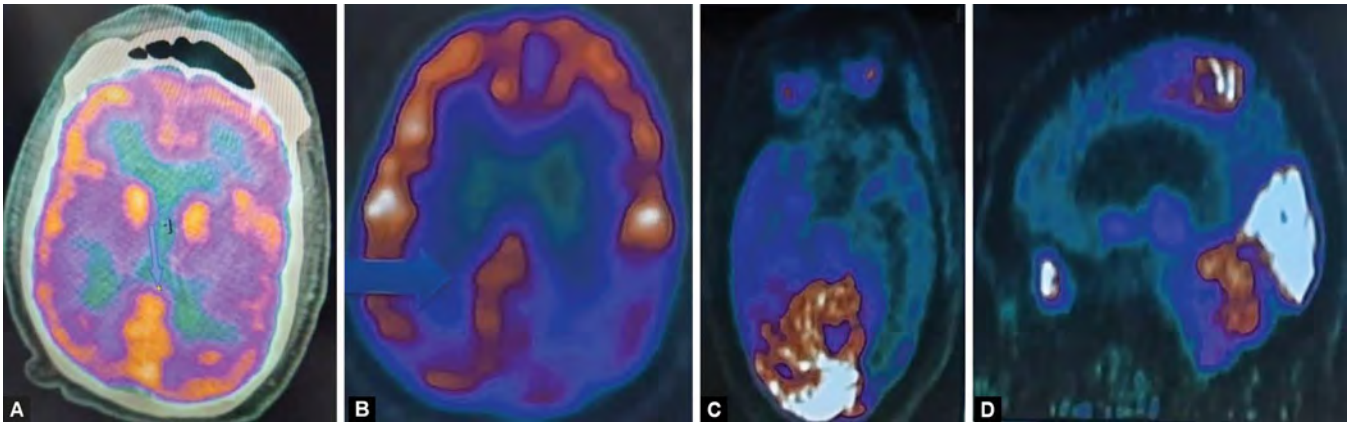


Fig. 1: MRI brain, coronal section (left side) shows normal volume of hippocampus bilaterally (orange arrows) of normal brain, on the right side shows atrophy of bilateral hippocampus (blue arrows) of a patient with AD

Table 3: The clinical manifestations of AD, highlighting its various presentations and subtypes[14,15]

Clinical manifestation	*Description*
Amnestic syndrome (most common, ~85%)	Recognized by significant deficits in learning and short-term memory. Patients have difficulty in recalling newly acquired information. Assessments done by using MMSE, MoCA, Wechsler Memory Scale (WMS), semantic cueing techniques, showing poor recall, and difficulties with information retrieval
Logopenic variant primary progressive aphasia (lvPPA)	Involves problems in motor speech abilities (phonemic paraphasia), single-word retrieval, and sentence repetition may be difficult. Linked to damage in the left perisylvian language areas of the brain
Posterior cortical atrophy (PCA)	Visuospatial as well as visuoperceptual abilities are affected. This may lead to visual inattention, known as Balint's syndrome. Impairments in arithmetic and reading, suggestive of dysfunction in the bilateral occipital and parietal cortices and visual streams
Corticobasal syndrome (CBS)	The condition is marked by Parkinsonian rigidity, myoclonus, apraxia of the eyes and limbs, cortical sensory impairments, and the phenomenon of an alien limb
Frontal variant of AD	Involves progressive behavioral changes such as apathy, loss of empathy, disinhibition, and occasionally compulsive behaviors or dietary changes. The dysexecutive-variant primarily affects executive function, including deficits in short-term memory and mental flexibility
Nonfluent primary progressive aphasia (nfPPA)	Characterized by difficulties in syntax, grammar, and buccofacial apraxia
Semantic variant primary progressive aphasia (svPPA)	Defined by semantic deficits, particularly in word comprehension. While most cases are linked to non-AD pathologies, a small proportion (16%) may be attributed to AD pathology
Copathologies (e.g., α-synuclein, TDP-43, and vascular pathology)	The presence of other neurodegenerative and vascular pathologies can influence AD's clinical presentation, often leading to more pronounced symptoms or variations in presentation. Copathologies complicate diagnosis. Biomarkers may help phenotype identification, or HPE of postmortem samples may help in differentiation



Figs 2A to D: (A) PET imaging normal FDG uptake in posterior cingulate gyrus; (B) Decreased FDG uptake in posterior cingulate gyrus suggestive of MCI; (C and D) Hypometabolism in parietotemporal and frontal areas suggestive of classical advanced AD

Table 4: Information about monoclonal antibodies and emerging research in AD[18]

Category	*Lecanemab (Leqembi)*	*Donanemab*	*Emerging research*
Type	Target-β-amyloid plaques	Target-β-amyloid plaques	Investigational drugs and studies on AD
Dosing regimen	10 mg/kg, given every 2 weeks (IV)	First three doses, 700 mg every 4 weeks, followed by 1400 mg every 4 weeks (IV)	Varies by drug (buntanetap, saracatinib, etc.)
Efficacy	30% reduction in clinical decline over 18 months (ADCOMS), 26% reduction in CDR-SB	15% reduction in clinical decline over 18 months (ADCOMS), 17% reduction in CDR-SB	Varies by study (early potential shown for some)
Safety	Infusion reactions, amyloid-related imaging abnormalities (ARIA)	Infusion-related reactions, ARIA	Safety concerns for each emerging drug
Key focus	Amyloid plaques reduction	Reduces amyloid plaques	Tau protein targeting, inflammation modulation, and insulin resistance

Clinical Alzheimer's Disease

In clinical AD, imaging provides critical information for confirming the diagnosis, assessing the extent of brain damage, and monitoring disease progression. Structural MRI is commonly used to evaluate brain atrophy, most commonly and early affected regions in AD are hippocampus and entorhinal cortex. In clinical AD, these regions show considerable shrinkage. PET scans continue to be valuable, as they can demonstrate widespread amyloid and tau deposition, which lead to the clinical manifestations of AD. FDG-PET also shows reduced metabolic activity in parietal and temporal lobes, which correlates with cognitive decline (Figs 2C and D). These imaging findings, in combination with cognitive assessments, help clinicians determine the stage of AD and predict disease progression.

Treatment—Recent Update

Existing FDA-approved medications primarily aim to alleviate symptoms rather than modify the disease course. As cholinergic deficiency has an important role in AD, cholinesterase inhibitors, such as donepezil, tacrine, rivastigmine, and galantamine, play an important role in the treatment of AD. Donepezil is a highly selective drug for acetylcholinesterase enzyme (AChE), rivastigmine inhibits reversibly both AChE and butyrylcholinesterase. Memantine (Namenda) regulates glutamate activity to improve memory and learning. These treatments are effective in the early and moderate stages of AD. Advanced research is going on in the development of therapies targeting the underlying mechanisms of AD Table 4.

Emerging research shows that ongoing studies are exploring various avenues, as follows:

- Tau protein targeting: Researchers are investigating tau aggregation inhibitors and vaccines to prevent the formation of tau tangles, another characteristic of AD.[17]
- Inflammation modulation: Increased levels of inflammatory markers, including C-reactive protein (CRP) and soluble receptors such as soluble receptor for advanced glycation end-products (sRAGE), have been detected in the CSF and blood of AD patients, highlighting the role of inflammation in the progression of the disease. Inflammation accelerates the deposition of Aβ and tau aggregates, creating a vicious cycle that amplifies neurodegeneration. Thus, targeting inflammation may be one of the preferred strategies in managing AD, although the complexity of the inflammatory response requires a nuanced approach.[19]
- Investigations into reducing chronic brain inflammation aim to protect neurons from damage. For instance, sargramostim (Leukine) is being studied for its potential to stimulate the immune system to clear harmful proteins.[20]
- Insulin resistance: Studies are examining how insulin resistance may affect brain function, with some trials testing insulin nasal sprays to slow AD progression. However, recent trials have not shown effectiveness.[21]
- Lifestyle modifications, such as regular exercise, healthy diet, and mental activities, are recommended to support brain health. Additionally, nonpharmacological interventions, including cognitive therapies and caregiver support programs, play a major role in reducing memory problems and improving quality of life.

Conclusion

Alzheimer's disease is a progressive condition of the brain, leading to a decline in cognitive function and memory. This

review emphasizes the significance of three main biomarker categories for AD diagnosis: (1) protein markers (Aβ, tau, and NFL), (2) miRNAs, and (3) noninvasive sources such as blood and saliva. Imaging techniques, particularly PET and MRI, play a pivotal role throughout the disease course of AD, from detecting early biomarkers in preclinical Alzheimer's disease (pre-AD) to assessing structural and functional brain changes in MCI and clinical AD. These imaging tools not only aid in diagnosis but also contribute to monitoring treatment efficacy and disease progression. While no cure currently exists, recent advancements in treatment strategies offer hope by targeting the disease pathology and improving memory as well as other cognitive domains. While challenges remain, the breakthroughs are happening in the AD treatment at a faster pace. One possible explanation for the limited success of clinical trials is that treatments are typically introduced at an advanced stage of the disease. Ongoing research into disease-modifying therapies and supportive care strategies offers hope for more effective interventions in the near future.

References

1. Winblad B, Amouyel P, Andrieu S, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. Lancet Neurol 2016;15(5):455–532.
2. 2020 Alzheimer's disease facts and figures. Alzheimers Dement 2020.
3. McDade E, Wang G, Gordon BA, et al. Longitudinal cognitive and biomarker changes in dominantly inherited Alzheimer disease. Neurology 2018;91(14):e1295–e1306.
4. Long JM, Holtzman DM. Alzheimer disease: an update on pathobiology and treatment strategies. Cell 2019;179(2):312–339.
5. Jack CR Jr, Wiste HJ, Weigand SD, et al. Age-specific population frequencies of cerebral beta-amyloidosis and neurodegeneration among people with normal cognitive function aged 50–89 years: a cross-sectional study. Lancet Neurol 2014;13(10):997–1005.
6. Dunn N, Mullee M, Perry VH, et al. Association between dementia and infectious disease: evidence from a case–control study. Alzheimer Dis Assoc Disord 2005;19(2):91–94.
7. Heneka MT, Kummer MP, Latz E. Innate immune activation in neurodegenerative disease. Nat Rev Immunol 2014;14(7):463–477.
8. Gauthier S, Zhang H, Ng KP, et al. Impact of the biological definition of Alzheimer's disease using amyloid, tau and neurodegeneration (ATN): what about the role of vascular changes, inflammation, Lewy body pathology? Transl Neurodegener 2018;7:12.
9. Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? Nat Rev Neurol 2021;17:157–172.
10. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018;14(4):535–562.
11. Ashton NJ, Pascoal TA, Karikari TK, et al. Plasma p-tau231: a new biomarker for incipient Alzheimer's disease pathology. Acta Neuropathol 2021;141(5):709–724.
12. Klyucherev TO, Olszewski P, Shalimova AA, et al. Advances in the development of new biomarkers for Alzheimer's disease. Transl Neurodegener 2022;11:25.
13. Bekris LM, Yu CE, Bird TD, et al. Genetics of Alzheimer disease. J Geriatr PsychiatryNeurol 2010;23(4):213–227.
14. Ferreira D, Nordberg A, Westman E. Biological subtypes of Alzheimer disease: a systematic review and meta-analysis. Neurology 2020;94(10):436–448.
15. Mandelli ML, Lorca-Puls DL, Lukic S, et al. Network anatomy in logopenic variant of primary progressive aphasia. Hum Brain Mapp 2023;44(11):4390–4406.
16. Weiner MW, Veitch DP, Aisen PS, et al. Recent publications from the Alzheimer's disease neuroimaging initiative: reviewing progress toward improved AD clinical trials. Alzheimers Dement 2017;13(4):e1–e85.
17. Johnson KA, Fox NC, Sperling RA, et al. Brain imaging in Alzheimer disease. Cold Spring Harb Perspect Med 2012;2(4):a006213.
18. Bomasang-Layno E, Bronsther R. Diagnosis and treatment of Alzheimer's disease: an update. Dela J Public Health 2021;7(4):74–85.
19. Heneka MT, van der Flier WM, Jessen F, et al. Neuroinflammation in Alzheimer disease. Nat Rev Immunol 2025;25(5):321–352.
20. Potter H, Woodcock JH, Boyd TD, et al. Safety and efficacy of sargramostim (GM-CSF) in the treatment of Alzheimer's disease. Alzheimer's Dement 2021;7:e12158.
21. Talbot K. Brain insulin resistance in Alzheimer's disease and its potential treatment with GLP-1 analogs. Neurodegener Dis Manag 2014;4(1):31–40.

POINT OF VIEW

Chance vs Probability in Medical Practice: Bhagavad Gita and Karma

Abhaya Indrayan*

Received: 19 August 2024; *Accepted:* 11 March 2025

Abstract

As exhorted by the Bhagavad Gita, physicians do their best karma to manage a patient. The uncertainties and chance can never be altogether eliminated from medical practice despite using best practices because of inherent human and environmental variations. No management is perfect with a 100% probability of success in all cases. The outcome remains with him. The physicians and the patients need to be reminded of this limitation all the time.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1061

I recently came across an article in the *European Heart Journal* on the Bhagavad Gita and the conflict of burnout.[1] We all know that the Gita focuses on karma and not the outcome. This carries a great message for medical professionals who relentlessly work to improve human health, and the message has tremendous implications for not getting an adequate response in a particular patient despite adopting the most efficacious regimen for the treatment known to us. To understand this phenomenon, my first target was to search the literature for a treatment regimen with 100% efficacy. I could not find any. This is expected in view of unpredictable human variation and intricate environmental interactions. Epistemic uncertainties due to knowledge gaps are additional confounders that deny formulating a perfect regimen that works for all. Even if a regimen has 100% efficacy, the effectiveness in use may be lower because of cost and compliance issues. Thus, no regimen can deliver results with absolute certainty. Locating a regimen with >90% efficacy yielded many articles on vaccines but few on treatment regimens. Details of two of these treatment regimens with high efficacy are as follows.

da Costa et al.[2] carried out a meta-analysis of 192 trials comprising 1,02,829 participants of knee and hip osteoarthritis. These were on 90 different preparations. Five oral preparations (diclofenac 150 mg/day, etoricoxib 60 and 90 mg/day, and rofecoxib 25 and 50 mg/day) were found to have at least 99% probability of more pronounced treatment effects than the minimal clinically relevant reduction in pain. Rokkas et al.[3] meta-analyzed 68 eligible randomized controlled trials with 22,975 patients of *Helicobacter pylori* infection randomized to eight first-line regimens. Vonoprazan triple therapy and reverse hybrid therapy were found to have >90% cure rate.

When such impressive results are obtained after meta-analysis of several relevant studies, there is a high degree of confidence to use such therapies on almost all patients of that type. When such regimens do not give the desired results in some patients, there is a suspicion that something is wrong, even with such highly effective therapies. The catch is in the small percentages of cases in which the therapy was not found effective despite the meta-analysis that included such a large number of patients from different settings. Thus, it is not surprising that some patients do not respond the way a clinician expects on the basis of the available evidence. Efficacy is an aggregate indicator for a group of patients and transforms to probability in the context of individuals.

It is generally not possible to identify a patient in advance who would not respond. Chance plays a disruptive role. Statisticians define chance as comprising those factors which are either unknown or beyond human control.[4] Spiritually, the chance may be called the will of God. This varies from patient to patient depending on the quantum of faith one has. While discussing adverse outcomes in COVID-19 cases despite perseverance with the best available treatment, Samajdar et al.[5] aptly explained the importance of the often-ignored spiritual component of health in the context of lessons from the Gita. They also explored how spiritual beliefs can influence treatment decisions in diabetes management[6] and separately argue integration of spirituality into medical education.[7]

Chance, comprising unknown underlying conditions, idiopathic or idiosyncratic reactions, or unknown interactions beyond the ability of body to handle,[1] cannot be altogether avoided. The universal measure of chance is the statistical probability that is reflected in <100% efficacy and the *p*-values so prominently displayed while developing and evaluating the performance of various regimens in different subgroups of patients. Probability is an essential and vital component of medical practice.

A clinician does what best can be done for a patient as dictated by his or her acumen after the assessment of the condition of the patient, guided by the previous evidence. The evidence could be in the form of the literature or the accumulated experience and wisdom of the treating clinician for that kind of patient. That the available evidence may be inadequate is one thing, and the role of unknown or unanticipated factors is another. Thus, the outcome is not solely in the hands of the doctor. This is what the Bhagavad Gita teaches us. Do the Karma (duty) as best as you can and leave the result to destiny. Understand that other possibilities exist, however rare. Karma is in our hands, but the fruits are determined by a multitude of factors, many of which are not in our control. Probability plays a prominent role in medicine without our ever realizing it. This occurs perhaps because the unknown domain of medicine is still much more than the known domain. That brings humility in our endeavors when trying to provide the best relief to the patients. We must realize that, in some cases, epistemic uncertainties due to omnipresent incomplete knowledge can dominate the outcome. Clinicians and patients need to be continuously reminded of this limitation. However, a recurrence of treatment failure with high efficacy must set the alarm.

Former Professor and Head, Department of Clinical Research, MAX Healthcare, New Delhi, India; *Corresponding Author

How to cite this article: Indrayan A. Chance vs Probability in Medical Practice: Bhagavad Gita and Karma. J Assoc Physicians India 2025;73(8):98–99.

Orcid

Abhaya Indrayan https://orcid.org/0000-0002-5940-9666

References

1. Kalra A, Chinnaiyan KM, Lala A, Bhagavad Gita, dichotomy of control and metric medicine: the conflict of burnout. Eur Heart J 2022;43:ehac545.
2. da Costa BR, Pereira TV, Saadat P, et al. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. BMJ 2021;375:n2321.
3. Rokkas T, Gisbert JP, Malfertheiner P, et al. Comparative effectiveness of multiple different first-line treatment regimens for *Helicobacter pylori* infection: a network meta-analysis. Gastroenterology 2021;161(2):495–507.e4.
4. Indrayan A, Malhotra RK. Medical Biostatistics, 4th edition. Boca Raton: CRC Press; 2017. p. 8.
5. Samajdar SS, Joshi SR, Tripathi R, et al. Spiritual lessons from Shrimad Bhagavad Gita for healthcare providers: a few COVID-19 cases. J Mod Med 2024;2(1):38–41.
6. Samajdar SS, Joshi SR, Pal J. Balancing faith and medicine: integrating spiritual care in diabetes management and recovery from ketoacidosis. Int J Diabetes Dev Ctries 2024.
7. Sen K, Samajdar SS, Joshi SR. Bridging science, skills, and spirituality in medical education: a path toward holistic healthcare. J Indian Med Assoc 2025;123(1):11–14.

Stasis Ulcer and Its Possible Etiologies

Vivek Soni[1], Tanvi Batra[2*], Atul Kakar[3]

Received: 02 September 2024; *Accepted:* 08 July 2025

A 62-year-old female, a known case of hypothyroidism, diabetes mellitus, and varicose veins, presented with a complaint of swelling of both lower limbs and ulceration on the left leg for 2 months. She also complained of dyspnea on exertion. As per the history, ulcer began as a pea-sized blackish discoloration on the left lower limb just above the ankle joint on medial aspect (Fig. 1) and increased to 6 × 8 cm, with irregular and raised margins (Fig. 2). The base of ulcer had whitish-yellow exudate with no healthy granulation tissue. The surrounding skin revealed hyperpigmentation. On examination, she had bilateral lower limb pitting edema—grade IV (Fig. 3), extending from above ankle to mid-calf region. The skin appeared to be shiny. Investigations revealed microcytic hypochromic anemia and high fructosamine levels. There was no history of trauma. Anti-HIV was negative. A biopsy was taken, thus revealing it to be a stasis ulcer. Our initial assessment for the causes of this ulcer included anemia resulting in poor perfusion, venous insufficiency exacerbated by varicose veins, and hypothyroidism or diabetes mellitus contributing to poor wound healing.

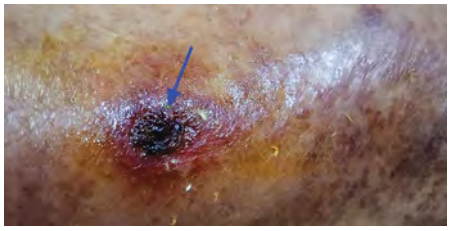


Fig. 1: Pea-sized blackish discoloration on the left lower limb just above the ankle joint on medial aspect

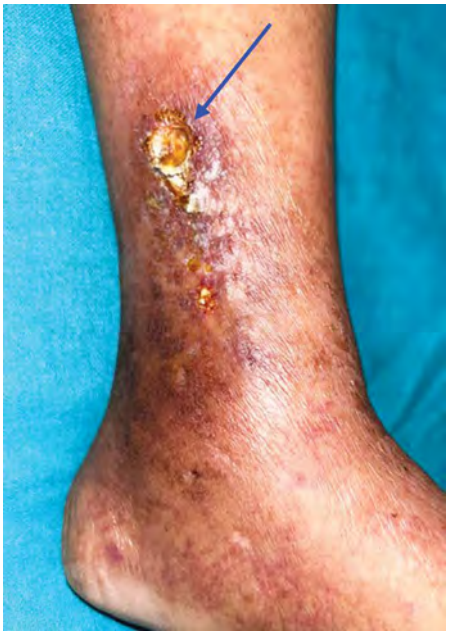


Fig. 2: Ulcer progressively increased in size with irregular and raised margins

In such cases of nonhealing ulcer, the differential diagnosis can include various conditions such as:

- Venous ulcers due to chronic venous insufficiency—typically seen on medial aspect of lower leg just above the ankle.
- Arterial ulcer due to underlying peripheral arterial disease—preferentially seen on lateral aspect of lower leg.
- Neuropathic ulcers—generally seen on plantar surface of foot, metatarsal heads, tip of the toes, and usually painless.
- Decubitus ulcers—typically seen in bedridden patients over bony prominences such as sacrum, heels, and ankles.

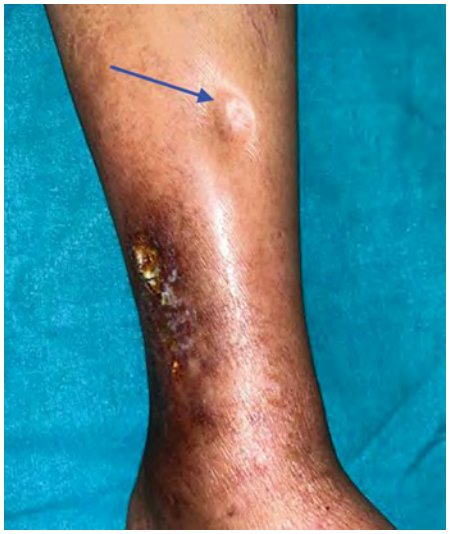


Fig. 3: Lower limb showing grade IV pitting pedal edema

Other causes may also include pyoderma gangrenosum, chronic infection, trauma, and skin cancers (squamous cell carcinoma or melanoma).

Severe anemia, specifically microcytic hypochromic anemia, impairs wound healing due to poor tissue perfusion and oxygenation.[1] Hypothyroidism is also an important factor in delaying wound healing by affecting skin integrity and overall metabolism. It may contribute to peripheral edema as well, thereby complicating venous insufficiency and ulceration.[2] Diabetes mellitus is also known for its notorious role in causing delay in wound healing. The combination of hypothyroidism, diabetes mellitus, varicose veins, and severe anemia creates a challenging environment in such a situation.

The patient was advised for oral iron therapy, leg elevation, compression stockings, adequate sugar control, and thyroid hormone replacement on discharge. She is currently doing well on follow-up.

Orcid

Tanvi Batra https://orcid.org/0009-0007-8215-5792

References

1. Ferris AE, Harding KG. An overview of the relationship between anaemia, iron, and venous leg ulcers. Int Wound J 2019;16:1323–1329.
2. Raffetto JD, Ligi D, Maniscalco R, et al. Why venous leg ulcers have difficulty healing: overview on pathophysiology, clinical consequences, and treatment. J Clin Med 2020;10:29.

[1]DNB Trainee, Department of Family Medicine; [2]Associate Consultant, Department of Internal Medicine; [3]Senior Consultant, Department of Medicine, Sir Ganga Ram Hospital, New Delhi, India; *Corresponding Author

How to cite this article: Soni V, Batra T, Kakar A. Stasis Ulcer and Its Possible Etiologies. J Assoc Physicians India 2025;73(8):100–100.

Caput Medusae Mimicking Umbilical Hernia

Rahul Kumar[1*], Tanvi Batra[2], Atul Kakar[3]

Received: 26 April 2024; *Accepted:* 07 April 2025

A 34-year-old female, a diagnosed case of chronic liver disease, presented to the emergency department with yellowish discoloration of the skin, abdominal distension, and bilateral lower limb swelling for 1 week. She also complained of painless swelling over her umbilicus for the last 6 months. On examination, she was conscious, oriented, and hemodynamically stable. General physical examination revealed icterus and bilateral pitting pedal edema up to the knees. On abdominal examination, the abdomen was distended and shifting dullness was present. A large swelling of approximately 7 × 5 cm was present over the anterior abdominal wall with a palpable thrill and an audible Cruveilhier–Baumgarten murmur (Figs 1A and B). The swelling was not reducible and had no signs of inflammation. The rest of the systemic examination was normal.

Abdominal computed tomography (CT) angiography revealed chronic liver disease, splenomegaly, ascites with multiple perisplenic collaterals coursing along the anterior abdominal wall with a bunch of dilated collaterals in the paraumbilical region which drained into the systemic veins (Fig. 2).

Based on the clinical examination and imaging, this swelling was diagnosed as caput medusae. The patient was managed conservatively.

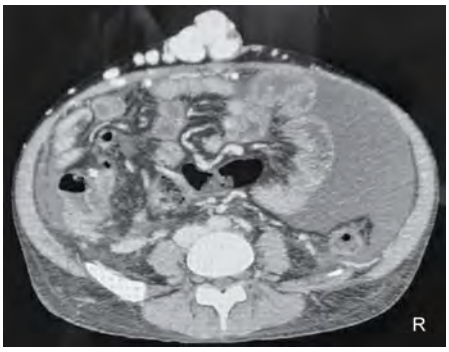
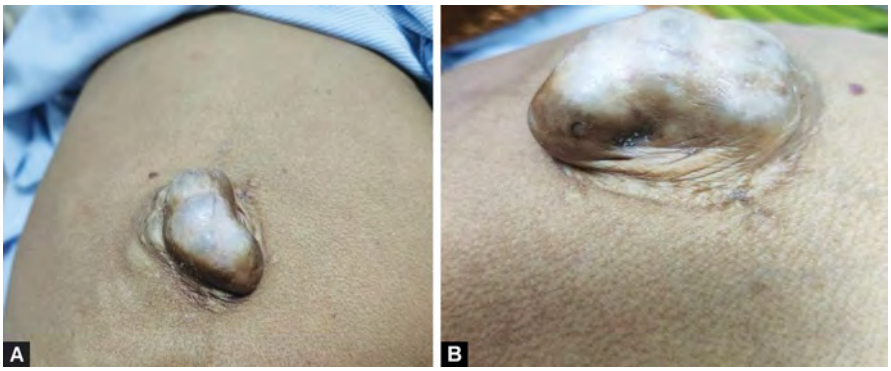


Fig. 2: Computed tomography angiography showing dilated collaterals in the paraumbilical region draining into the systemic veins (caput medusae appearance)



Figs 1A and B: Grossly dilated tortuous venous swelling over the anterior abdominal walls in the umbilical region

The term "caput" is the Latin derivation for "head." "Medusae" comes from the Greek mythology and depicts an ancient monster who had hair made of snakes, moving in all directions.[1] Caput medusae is a cardinal feature of portal hypertension. The appearance of the same can be attributed to portosystemic collateral formation with portal vein blood shunted through umbilical veins into the abdominal wall systemic veins. The umbilical vein usually carries oxygenated blood from mother to fetus and is closed off within 1 week of birth. In cases of portal hypertension, it gets recanalized.[2,3] It is a rare phenomenon these days due to timely diagnosis and treatment of portal hypertension.

Orcid

Rahul Kumar https://orcid.org/0009-0005-5247-0113
Tanvi Batra https://orcid.org/0009-0007-8215-5792

References

1. Soni N, Israrahmed A, Singh P, et al. Caput medusa: a sign of portal hypertension in case of chronic Budd-Chiari syndrome. BMJ Case Rep 2021;14:e242076.
2. Hari Kumar KV, Rastogi SK. Caput medusae in alcoholic liver disease. Niger J Clin Pract 2011;14:508–509.
3. Singh NK, Cheema U, Khalil A. Caput medusae. BMJ Case Rep 2010;2010:bcr0320102795.

[1]DNB Trainee; [2]Associate Consultant, Department of Internal Medicine; [3]Senior Consultant, Department of Medicine, Sir Ganga Ram Hospital, New Delhi, India; *Corresponding Author

How to cite this article: Kumar R, Batra T, Kakar A. Caput Medusae Mimicking Umbilical Hernia. J Assoc Physicians India 2025;73(8):102–102.

Letter to the Editor: Human Metapneumovirus—How It Affects and Whom?

Prachee Ratre[1], Rahul Khera[2], Deepak Prajapat[3], Kanishka Kumar Singh[4], Deepak Talwar[5]

[1]DNB Resident; [2]Associate Consultant; [3,4]Senior Consultant; [5]Director and Chairman, Department of Pulmonary, Critical Care and Sleep Medicine, Metro Center for Respiratory Diseases, Noida, Uttar Pradesh, India

Dear Editor,

We would like to highlight the clinical spectrum of human metapneumovirus (hMPV) infection in 11 patients diagnosed in the year 2024 at our center, clarifying that it is neither new nor does it resemble COVID-19. Our observations aim to provide insights and contribute to a clearer understanding of its role in respiratory diseases.

Recent reports of hMPV infections have sparked concerns and anxiety, partly due to speculations regarding its potential origin from Wuhan, the city associated with the COVID-19 outbreak. hMPV is an RNA virus that primarily infects respiratory epithelial cells by attaching to the integrin alpha-V-beta-1 receptor.[1] It is a seasonal virus, typically seen during the winter months.[2] In our study, 145 tests were conducted throughout 2024, and all hMPV-positive cases occurred between January and March 2024. hMPV is transmitted through direct or close contact with contaminated secretions and can affect individuals of all ages, but it is particularly symptomatic in young children and older adults.[3]

We conducted a retrospective study of patients diagnosed with hMPV between January and December 2024 at our center. We analyzed clinical data from medical records, including demographic details, symptoms, comorbidities, diagnostic tests, treatments, and outcomes. The diagnosis of hMPV was confirmed using the BioFire FilmArray respiratory panel, a multiplex polymerase chain reaction (PCR) test.[4]

Our study included 11 patients with a mean age of 69.9 years (range: 50–85 years), with no sex predilection (six males and five females). All patients presented with shortness of breath and cough with expectoration. Additionally, seven patients (63.6%) reported fever, and six patients (54.5%) exhibited other symptoms, including wheezing (18.2%), rhinorrhea (18.2%), body aches (18.2%), and sore throat (9.1%). The duration of symptoms before hospitalization ranged from 2 to 7 days. Patients in this cohort had significant comorbidities such as hypertension (63.6%), type 2 diabetes mellitus (54.5%), coronary artery disease and heart disease (27.3%), chronic kidney disease (9.1%), and a history of cerebrovascular accidents (18.2%).[5] All patients required respiratory support: six patients received noninvasive mechanical ventilation (NIMV), two patients were on high-flow nasal cannula, and three patients required oxygen support *via* nasal prongs. Seven patients had bacterial infections, and three had both bacterial and viral coinfections. The bacterial infections included *Klebsiella pneumoniae*, which was isolated in all cases; two had *Pseudomonas aeruginosa* and *Haemophilus influenza* each; one had *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Acinetobacter baumannii* complex, and *Moraxella catarrhalis* each. Viral coinfections, such as influenza, parainfluenza, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), were seen in one case each.[6]

Nine patients survived and were discharged from the hospital: five patients were discharged on room air, two patients remained on oxygen support, and two patients were discharged on NIMV support. Unfortunately, two patients died, including one with interstitial lung disease (ILD). Both deaths were attributed to multidrug-resistant bacterial infections and septic shock with multiorgan dysfunction.[7]

The clinical symptoms of hMPV are primarily respiratory, including shortness of breath, cough with expectoration, wheezing, and rhinorrhea, with or without fever (one-third of cases had no fever). Although it commonly leads to mild respiratory infections, it can also cause bronchiolitis or exacerbate asthma and chronic obstructive pulmonary disease (COPD).[1] There is partial cross-immunity between hMPV and respiratory syncytial virus (RSV).[2] Diagnosis is confirmed through reverse transcriptase PCR (RT-PCR). Management is primarily supportive, focusing on infection control and the medical management of underlying conditions. Our study suggests that patients with multiple comorbidities require prolonged intensive care unit (ICU) care and longer hospital stays.

Human metapneumovirus infections often mimic other bacterial and viral infections. In our study, none of the patients had isolated hMPV infections; all cases were complicated by coexisting bacterial and viral infections. Although hMPV itself is not directly associated with mortality, patients with multiple comorbidities are at higher risk of severe outcomes, including mortality, longer hospital stays, and the need for respiratory support due to the severe deterioration of underlying respiratory conditions. General comorbidities such as diabetes mellitus, chronic kidney disease, coronary artery disease, and cerebrovascular accidents further complicate hMPV infections by making patients more susceptible to secondary infections, suppressing immunity in elderly multimorbid individuals. Since there is no vaccine or specific treatment available, prevention should focus on shielding vulnerable patients who are at risk of complications from this viral infection.[3]

This study provides valuable insights that may aid in the planning and optimization of treatment strategies during disease outbreaks. We hope this information will be valuable to your readership and contribute to ongoing discussions about hMPV.

Orcid

Deepak Prajapat https://orcid.org/0000-0002-8362-055X
Kanishka Kumar Singh https://orcid.org/0009-0001-8420-5075

References

1. Falsey AR, Erdman D, Anderson LJ, et al. Human metapneumovirus infections in young and elderly adults. J Infect Dis 2003;187(5):785–790.
2. Feuillet F, Lina B, Rosa-Calatrava M, et al. Ten years of human metapneumovirus research. J Clin Virol 2012;53(2):97–105.
3. Falsey AR. Human metapneumovirus infection in adults. Pediatr Infect Dis J 2008;27(10):S80–S83.
4. van den Hoogen BG, van Doornum GJ, Fockens JC, et al. Prevalence and clinical symptoms of human metapneumovirus infection in hospitalized patients. J Infect Dis 2003;188(10):1571–1577.
5. Shafagati N, Williams J. Human metapneumovirus - what we know now. F1000Research 2018;7:135.
6. Williams JV, Martino R, Rabella N, et al. Human metapneumovirus pneumonia in adults: the role of co-infections. Clin Infect Dis 2005;41(5):617–624.
7. Boivin G, De Serres G, Cote S, et al. Human metapneumovirus infections in hospitalized children. Emerg Infect Dis 2003;9(6):634–640.

Letter to Editor in Response to Article "Estimation of Predictors of Mortality in Patients with Acute Respiratory Failure Secondary to Chronic Obstructive Pulmonary Disease Admitted in Tertiary Care Center" J Assoc Physicians India 2025;73(2):35–38

Madhusudan Barthwal[1], Sachinkumar S Dole[2]

[1]Professor and Head; [2]Professor, Department of Respiratory Medicine, Dr. D. Y. Patil Medical College, Hospital & Research Centre, Pune, Maharashtra, India

We read with interest an article titled "Estimation of Predictors of Mortality in Patients with Acute Respiratory Failure Secondary to Chronic Obstructive Pulmonary Disease Admitted in Tertiary Care Center" published in the Journal of the Association of Physicians of India.[1] We have the following comments to offer:

- The title of the study suggests patients with acute respiratory failure secondary to chronic obstructive pulmonary disease (COPD). The authors have included patients with COPD exacerbations within 72 hours and patients with an established diagnosis of COPD with respiratory failure (type I/II). First, COPD exacerbations leading to acute respiratory failure are mostly severe exacerbations of duration <14 days as per the GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines.[2] However, the same has not been defined in the methodology. Second, in COPD, there is always type II respiratory failure, and these patients require admission to the hospital when presenting with acute-on-chronic respiratory failure. The authors have not clarified the above point in the methodology.
- In the methodology, the authors mentioned that COPD without respiratory failure was not included in the study, while in the limitations of the study it was mentioned that stable COPD patients were taken as controls. These statements are contradictory and need elaboration.
- The predictors such as C-reactive protein (CRP), D-dimer, and hypoalbuminemia used in the present study for predicting mortality in patients with acute respiratory failure have already been well proven in various recent studies[3–5] including those mentioned by the authors in the discussion. The novelty in the present study needs to be elaborated by the authors.

Orcid

Madhusudan Barthwal https://orcid.org/0000-0001-8069-6084
Sachinkumar S Dole https://orcid.org/0000-0002-1805-1725

References

1. Jain H, Chejara RS, Agarwal M, et al. Estimation of predictors of mortality in patients with acute respiratory failure secondary to chronic obstructive pulmonary disease admitted in tertiary care center. J Assoc Physicians India 2025;73(2):35–38.
2. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2024 Report). Available from https://goldcopd.org/2024-gold-report/
3. Akbaş T, Güneş H. Characteristics and outcomes of patients with chronic obstructive pulmonary disease admitted to the intensive care unit due to acute hypercapnic respiratory failure. Acute Crit Care 2023;38(1):49–56.
4. Shen S, Xiao Y. Association between C-reactive protein and albumin ratios and risk of mortality in patients with chronic obstructive pulmonary disease. Int J Chronic Obstruct Pulmon Dis 2023 31:2289–2303.
5. Han H, Hu S, Du J. Predictive value of the hemoglobin–albumin–lymphocyte–platelet (HALP) index for ICU mortality in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD). Intern Emerg Med 2023;18:85–96.

Anagen Effluvium as an Early Sign of Azathioprine Toxicity

Sehtaj Kaur[1], Asit Kumar Mittal[2], Shaifali Jain[3], Laxman Kumar[4]

[1]Postgraduate Junior Resident; [2]Senior Professor and HOD; [3]Second Year Resident; [4]Third Year Resident, Department of Dermatology, RNT Medical College, Udaipur, Rajasthan, India

Dear Sir,

Azathioprine is a purine analog which is Food and Drug Administration (FDA) approved for organ transplant and severe rheumatoid arthritis (RA). Off-label use in dermatological diseases like immunobullous diseases, atopic dermatitis, autoimmune connective tissue disorders like systemic lupus erythematosus (SLE) and dermatomyositis, and other medical conditions like Crohn's disease, Churg–Strauss syndrome, and myasthenia gravis has long been in the picture.[1–3] The active metabolite of this prodrug is 6-thioguanine (6-TG), which gets incorporated into DNA/RNA structure, causing decreased purine metabolism resulting in its immunosuppressive effect. Thiopurine methyltransferase (TPMT) converts 6-mercaptopurine (6-MP) to an inactive metabolite. TPMT deficiency will cause increased conversion of 6-MP to active metabolite 6-TG, which increases the risk of myelosuppression, one of the life-threatening side effects of the drug.[1,2]

A 29-year-old female, a known case of pemphigus vulgaris, was started on oral prednisolone and azathioprine 100 mg/day. Her blood counts were normal when starting azathioprine, but the counts were not repeated after 1 week of starting the drug. After 20 days, she presented to the hospital with upper respiratory tract infection (URTI), body ache, and a history of acute hair fall since 5 days, but was otherwise in good general health. The hair pull test was strongly positive (Fig. 1). Hair microscopy showed dystrophic anagen hair (Fig. 2). Her blood counts showed significant neutropenia. Total leukocyte count (TLC)—1100/µL, neutrophils—3.6%, lymphocytes—93.6%, monocytes—2.8%, and platelets—39000/µL. Azathioprine was stopped immediately, and she was given

Fig. 1: Positive hair pull test

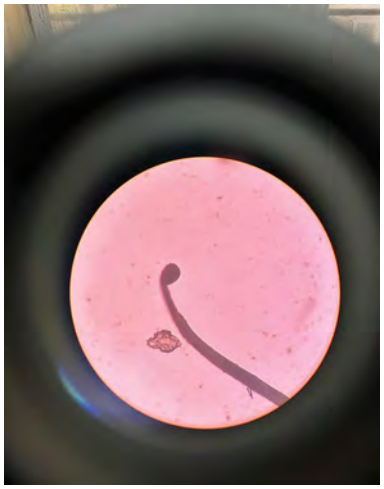


Fig. 2: Anagen hair on microscopy

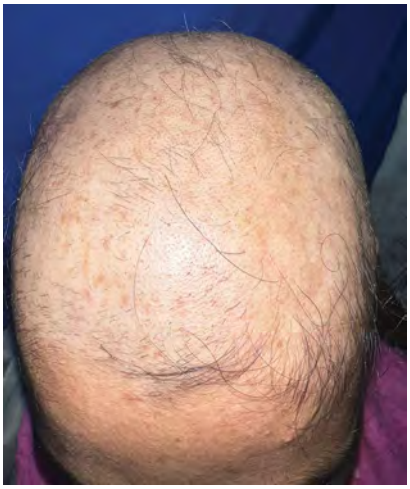


Fig. 3: Alopecia totalis

intravenous broad-spectrum antibiotics. She was also put on injection filgrastim [granulocyte colony-stimulating factor (GCSF)] 300 µg for 5 days, after transfusion of 4 units of platelets. Within the next 1 week, she presented with total loss of scalp hair (alopecia totalis—Fig. 3), though her blood counts had come back to normal. Azathioprine suppresses bone marrow, especially in TPMT-deficient patients or in patients who are on febuxostat or allopurinol.[3] Regular monitoring of blood counts is recommended. Ideally, TPMT levels should be done in all patients receiving azathioprine therapy, but since it is an expensive test, in resource-poor countries, regular measurements of blood counts remain the most practical way to detect myelosuppression.[2] Anagen effluvium refers to abrupt shedding of hair in the anagen phase due to impaired follicular mitotic activity.[1] Azathioprine is theoretically known to inhibit mitosis of hair matrix, resulting in anagen effluvium. Two authors have reported hair loss after 1 month of initiating azathioprine, while Sonthalia and Daulatabad noted its occurrence after 48 hours only.[3,4] In our case, the shedding of hair started after 10–15 days, and it correlates with the decreased blood counts, which suggests that this hair loss can be a marker of myelosuppression.

Hence, from this case report, we understand that anagen effluvium is an uncommon but early side effect of azathioprine that may indicate life-threatening myelosuppression.

References

1. Sharma R, Poddar S, Podder I. Azathioprine induced anagen effluvium- an uncommon adverse effect of a commonly used drug. Indian J Dermatol 2022;67(6):815–817.
2. Balasubramanian P, Jagadeesan S, Anjaneyan G, et al. An interesting case report of azathioprine-induced anagen effluvium. Indian J Dermatol 2015;60(3):324.
3. Wolverton SE. Comprehensive Dermatologic Drug Therapy, 4th edition. Amsterdam: Elsevier; 2020 [chapter 15].
4. Sonthalia S, Daulatabad D. Azathioprine-associated anagen effluvium. Indian J Dermatol Venereol Leprol 2016;82:322–324.

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