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Telmisartan plus Metoprolol Succinate is contraindicated in severe bradycardia, second or third degree heart block, cardiogenic shock, decompensated cardiacfailure, and sick sinus syndrome (unless a permanent pacemaker is in place). **Warnings and Precautions:** Telmisartan: Fetal Toxicity Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Telmisartan as soon as possible. Hypotension In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with Telmisartan. Either correct this condition prior to administration of Telmisartan, or start treatment under close medical supervision with a reduced dose. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized. Hyperkalemia Hyperkalemia may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk. Impaired Hepatic Function As the majority of Telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Initiate Telmisartan at low doses and titrate slowly in these patients. Impaired Renal Function As a consequence of inhibiting the renin-angiotensin-aldosterone system, anticipate changes in renal function in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results have been reported with Telmisartan. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of Telmisartan in patients with unilateral or bilateral renal artery stenosis, but anticipate an effect similar to that seen withACE inhibitors. Dual Blockade of the Renin-Angiotensin-Aidosterone System (RAS) Dual blockade of the RAS with angiotensin-receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. In most patients no benefit has been associated with using two RAS inhibitors concomitantly. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function, and electrolytes in patients on Telmisartan and other agents that affect the RAS. Do not co-administer aliskiren with Telmisartan in patients with diabetes. Avoid concomitant use of aliskiren with Telmisartan in patients with renal impairment (GFR <60 mL/min/1.73 m^2). Metoprolol Ischemic Heart Disease Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Metoprolol succinate, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of 1 to 2 weeks and monitor the patient. If angina markedly worsens or acute coronary ischemia develops, promptly reinstate Metoprolol succinate, and take measures appropriate for the management of unstable angina. Warn patients not to interrupt therapy without their physician's advice. Because coronary artery disease is common and may be unrecognized, avoid abruptly discontinuing Metoprolol succinate in patients treated only for hypertension. Heart Failure Worsening cardiac failure may occur during up-titration of Metoprolol succinate. If such symptoms occur, increase diuretics and restore clinical stability before advancing the dose of Metoprolol succinate. It may be necessary to lower the dose of Metoprolol succinate or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of Metoprolol succinate. Bronchospastic Disease PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative beta, cardio-selectivity, however, Metoprolol succinate may be used in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Because beta, -selectivity is not absolute, use the lowest possible dose of Metoprolol succinate. Bronchodilators, including beta,- agonists, should be readily available or administered concomitantly. Pheochromocytoma If Metoprolol succinate is used in the setting of pheochromocytoma, it should be given in combination with an alpha blocker, and only after the alpha blocker has been initiated. Administration of beta-blockers alone in the setting of pheochromocytoma has been associated with a paradoxical increase in blood pressure due to the attenuation of beta-mediated vasodilatation in skeletal muscle. Major Surgery Avoid initiation of a high-dose regimen of extended-release Metoprolol in patients undergoing noncardiac surgery, since such use in patients with cardiovascular risk factors has been associated with bradycardia, hypotension, stroke and death. Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery, however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures. Diabetes and Hypoglycemia Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. Hepatic impairment Consider initiating Metoprolol succinate therapy at doses lower than those recommended for a given indication; gradually increase dosage to optimize therapy, while monitoring closely for adverse events. Thyrotoxicosis Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of beta-blockade may precipitate a thyroid storm. Anaphylactic Reaction While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge and may be unresponsive to the usual doses of epinephrine used to treat an allergic reaction. Peripheral Vascular Disease Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Calcium Channel Blockers Because of significant inotropic and chronotropic effects in patients treated with beta-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be exercised in patients treated with these agents concomitantly. **Use in Pregnancy and lactation:** Pregnancy: Telmisartan can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. There are no adequate and well-controlled studies of Metoprolol in pregnant women. Therefore, when pregnancy is detected, discontinue the combination of Telmisartan plus Metoprolol as soon as possible. Lactation: There is no information regarding the presence of Telmisartan in human milk, the effects on the breastfed infant, or the effects on milk production. Telmisartan is present in the milk of lactating rats. Metoprolol is excreted in breast milk in very small quantities. Because of the potential for serious adverse reactions in the breastfed infant including hypotension, hyperkalemia and renal impairment, advise a nursing woman not to breastfeed during treatment with the combination of Telmisartan plus Metoprolol.

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Canagliflozin/metformin Fixed-dose Combination: National Evidence, Global Relevance

Sanjay Kalra[1*], Nitin Kapoor[2]

Diabetes is a multifactorial and multifaceted syndrome, which needs a multipronged approach to management.[1] Judicious use of rational drug combinations assists in the timely achievement of glycemic targets in persons with type 2 diabetes.[2] Fixed-dose combinations (FDCs) offer a person-friendly means of taking multiple drugs. Not only that, FDCs are physician-friendly but pharmacist-friendly as well, as they ease both prescription writing and dispensing.

In recent years, sodium-glucose transporter 2 inhibitors (SGLT2i) have created a paradigm shift in the management of type 2 diabetes.[3] Apart from good glucose control, these drugs also ensure cardiovascular and renal benefits. This has made them a preferred choice in modern algorithms. Certain guidelines suggest the use of SGLT2i, with metformin, as first-line therapy.[4] This move is welcome, as it allows persons living with type 2 diabetes to benefit from the pleiotropic advantages of SGLT2i.[5]

While randomized controlled trials (RCTs) have always provided robust evidence for the efficacy, safety, and tolerability of drugs, their applicability to large populations can be questioned. Real-world evidence (RWE),[6] therefore, is required to explore the utility of newly introduced medications. One way of doing this is to perform phase 4, or postmarketing trials. Phase 4 trials, conducted in India, allow medicines to be tested in Indian participants, with appropriate trial methodology, using clinically relevant endpoints under the robust controls associated with clinical trials. Thus, phase 4 trials offer the advantages of both phase 3 RCTs and RWE and study the safety as well as efficacy of the concerned drug.

Magdum et al. report the findings of such a prospective, multicentric, open-label, single-arm study, conducted on 276 Indian adults living with type 2 diabetes.[7] These participants, aged 18–65, were inadequately controlled on diet and exercise. They were initiated on an FDC of canagliflozin and metformin (50/500 and 50/1000 mg) twice daily. Unlike most other studies safety assessment was taken as the primary endpoint, and change in glycated hemoglobin (HbA1c) as the secondary endpoint. This methodology highlights the need to focus on the safety and tolerability of newer drugs. The inclusion criteria allowed initiation of canagliflozin + metformin in persons on glucose-lowering pharmacotherapy, as well as those who were treatment-naive. This is concordant with guidance from European as well as American professional organizations.[4]

The demographics of the study cohort are representative of patients seen in Indian diabetes practice, with a majority of relatively elder male participants. Central obesity, as well as obesity, is common and so is impaired renal function. Dyslipidemia and hypertension are the commonly reported comorbidities, followed by hypothyroidism and diabetic neuropathy.

The results reveal good tolerability of the canagliflozin + metformin FDC. As 41.6% of participants reported a treatment-emergent adverse event (TEAE), this reflects the attentiveness of the investigators. Only 10.6% of participants; however, experienced a TEAE related to the study treatment. Serious TEAEs were uncommon (1.1%), with only two persons (0.7%) reporting serious TEAE related to the study treatment. Adverse events that are commonly linked to SGLT2i include genital infection, urinary tract infection, and diabetic ketoacidosis. These were noted in 3.3, 2.6, and 0.4% of participants, respectively. Counseling regarding genital hygiene and hydration can further minimize the risk of these complications. Hypoglycemia, rarely encountered with SGLT2i and metformin, was reported by 3.3% of participants. It must be noted that these persons were those who were taking other glucose-lowering therapy as well.

Efficacy was a secondary endpoint in this study. Starting from a baseline of 8.5 ± 0.83%. Around 27.8 and 34.3% of persons were able to achieve target HBA1 c <7% at 12 and 24 weeks, respectively. A weight loss of 2.1 kg and a reduction in waist circumference of 1.73 cm were documented at week 24, along with a fall in blood pressure of 2.6/0.1 mmHg.

Canagliflozin was approved for medical use in 2013. The Canagliflozin Cardiovascular Assessment Study trial proved the cardiovascular and renal safety and benefits of canagliflozin in 2017. Along with similar findings from other cardiovascular outcome trials, these have brought about a paradigm shift in the management of diabetes SGLT2i are now used as preferred therapy not only to achieve euglycemia, but also to protect the heart and kidney, and prevent vascular and renal complications.

The pan India by Magdum et al. describes the safety and efficacy of providing reassurance that canagliflozin + metformin FDC can be used safely in a wide spectrum of patients, as monotherapy, or along with other glucose-lowering drugs. At the same time, the results caution us to practice pharmacovigilance and keep a close watch on possible adverse events. The study also adds weight to the growing data on diabetes care from India and showcases the ability of Indian investigators to conduct, and publish, good-quality RWE. We commend the authors, as well as the editor of the Journal of Physicians of India for sharing their knowledge, and for contributing to the growth of Indian diabetology.

The data, collected from across India, has not only national but international relevance.

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ORIGINAL ARTICLE

Fixed-Dose Combination of Canagliflozin and Metformin as an Adjunct to Diet and Exercise in Indian Adults with Type 2 Diabetes Mellitus: Results from a Multicentric, Open-Label, Single-Arm, Phase IV Study

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Abstract

Background: Canagliflozin and metformin fixed-dose combination (CANA/MET FDC), an approved treatment for type 2 diabetes mellitus (T2DM) in India, effectively lowers glycated hemoglobin (HbA1c), promotes weight loss, and improves patient adherence. As a regulatory requirement, we aimed to evaluate the safety and efficacy of CANA/MET FDC in Indian patients with T2DM.

Research design and methods: This prospective, multicenter, open-label, single-arm, phase IV study included Indian patients with T2DM (aged 18–65 years) inadequately controlled on diet and exercise. Patients received CANA/MET (50/500 and 50/1000 mg) immediate-release (IR) FDC twice daily for 24 weeks. The primary endpoint was safety assessment, including adverse events (AEs) and serious AEs (SAEs). The secondary endpoint included a change in HbA1c from baseline to weeks 12 and 24. Descriptive statistics were used for all continuous safety variables and efficacy parameters.

Results: Of the 310 patients screened, 276 were enrolled. 114/274 (41.6%) patients had ≥1 treatment-emergent AE [treatment-emergent AEs (TEAEs), among which 29 (10.6%) were related to study intervention]. The most common TEAEs were dyslipidemia (4.7%), pyrexia (4.7%), genital infections (3.3%), hypoglycemia (3.3%), and urinary tract infections (2.6%). Three (1.1%) patients had serious TEAEs, and all cases were resolved. No deaths were reported. The mean change in HbA1c from baseline was −0.92 and −0.93% at weeks 12 and 24, respectively.

Conclusion: The study demonstrates the safety and efficacy of CANA/MET FDC in Indian patients with T2DM, presenting a safe therapeutic option for diabetes management in India.

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Introduction

The prevalence of type 2 diabetes mellitus (T2DM) has been steadily rising, with an estimated 537 million adults (20–79 years) living with T2DM across the globe.[1] The trend remains similar in India, wherein 101 million people currently live with T2DM; the number is projected to reach 134 million by 2045, making India the diabetes capital of the world.[1–3]

Clinical and biochemical characteristics unique to the Indian population include high abdominal fat despite low body mass index (BMI), as well as high insulin resistance and triglycerides, resulting in a predisposition to T2DM.[4] These characteristics together give rise to what is known as the "Asian Indian phenotype." Along with urbanization and lifestyle changes, it is responsible for the rise of T2DM cases in India.[4–6] Available data also suggest that the susceptibility of Asian Indians to the complications of DM differs from that of white populations.[7] Asian Indians are at a higher risk of T2DM than individuals from other major ethnic groups.[7,8] The younger age of onset, along with all the other factors associated with this phenotype, increases the probability of developing microvascular and macrovascular complications, which may lead to heart disease, kidney failure, blindness, and lower-limb amputations.[6,9–11]

Impaired glucose metabolism, the major pathophysiology of T2DM, is impacted by metabolic processes, including decreased insulin secretion, decreased incretin effect, increased lipolysis, increased glucagon secretion, and increased glucose absorption. Thus, combining therapies with varying and complementaryw mechanisms of action might be beneficial in preventing complications, along with achieving glycemic control in patients with T2DM.[12] Moreover, literature advocates that monotherapy cannot address the multiple defects of T2DM and often leads to failure to maintain glycemic control over time.[13]

The mainstay of T2DM treatment in India has been metformin (MET), which is known to reduce hepatic glucose production and intestinal glucose absorption, thereby reducing plasma glucose.[13–15] Metformin is associated with a low risk of hypoglycemia and is weight-neutral or leads to weight loss.[16,17] However, in the case of disease progression and unmet needs of glycemic control, additional antihyperglycemic agents are recommended.[13,18,19] The combination of antihyperglycemic agents (AHA) with complementary mechanism of action may provide a more robust and durable glucose-lowering efficacy compared to a single agent.[20]

Canagliflozin (CANA), an active inhibitor of sodium-glucose cotransporter 2 (SGLT2i),

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lowers the renal threshold for glucose and leads to an increase in urinary glucose excretion, thereby lowering plasma glucose in patients with T2DM.[21] Previous studies have demonstrated that the addition of CANA to MET monotherapy significantly reduced glycated hemoglobin (HbA1c), along with weight loss in patients with T2DM.[21–24] The American Diabetes Association (ADA) 2023 guideline recommends SGLT2i as first-line therapy with and without MET in high-risk patients with T2DM, including cardiovascular and renal diseases. The European Society of Cardiology 2023 guideline also suggested frontline SGLT2i alone or in combination with MET in patients with cardiovascular disease and T2DM.[25,26] In August 2014, the United States Food and Drug Administration approved the CANA MET immediate-release fixed-dose combination (CANA/MET IR FDC) for the treatment of T2DM.[27] The bioequivalence of CANA/MET IR FDC vs the individual components was established in pharmacokinetic studies in healthy participants.[14] In general, FDCs have been shown to reduce noncompliance and improve adherence in T2DM compared to the monotherapies.[28,29] The CANA/MET FDC was shown to simplify treatment regimens, thereby improving treatment adherence.[30]

The present study evaluated the safety and efficacy of the CANA/MET IR FDC marketed formulations (50/500 and 50/1000 mg) in Indian patients with T2DM to fulfill the postmarketing regulatory commitment in India.

Research Design and Methods

Study Design and Patients

This was a prospective, multicenter, open-label, single-arm, phase IV study conducted across 10 sites in different cities of India (Pune, Guwahati, Mohali, Trivandrum, Coimbatore, Bengaluru, Surat, Chandigarh, and Hyderabad) from December 2020 to July 2022. Patients with T2DM aged 18–65 years, following an inadequately controlled diet and exercise (as per investigator's opinion), and able to receive the study drug as per prescribing information were included. Additionally, patients who were on stable AHA therapy for at least 12 weeks before screening and had HbA1c of ≥7.0 and ≤10.0% at screening were included.

Patients having a history of liver or renal insufficiency (estimated creatinine clearance <45 mL/minute); significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances, hereditary glucose-galactose malabsorption or primary renal glucosuria, history of diabetic ketoacidosis, type 1 DM, pancreas or β-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy, were excluded from the study. Patients were also deemed ineligible if they had a contraindication, any known allergies, hypersensitivity, or intolerance to CANA, MET, or CANA/MET IR FDC, or its excipients, or if they had used any other SGLT2i within 12 weeks before the screening visit. The study was carried out in three phases: a 7-day screening phase, a 24-week treatment phase, and a 28-day post-treatment phase. The study design is presented in Figure 1.

Patients received CANA/MET IR FDC (50/500 and 50/1000 mg) orally twice daily with meals, approximately at the same time each day. Wash-out from the previous treatment was not required. The study protocol was approved by local institutional review boards/ethics committees, and all the patients provided written informed consent prior to any study-related procedures. The study was conducted in compliance with the Declaration of Helsinki and the International Committee on Harmonization Good Clinical Practices and as per the New Drugs and Clinical Trials Rules, 2019—India and the Drug and Cosmetics Act and applicable regulatory requirements (Clinical Trials Registry CTRI/2020/07/026539).

Study Assessment

The primary endpoint was the determination of the incidence of adverse events (AEs), serious AEs (SAEs), unexpected AEs, or adverse drug reactions (ADRs) over the study period. Other safety assessments were also evaluated, including hypoglycemic episodes, safety laboratory parameters (including chemistry, hematology, and urinalysis), vital signs [systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse], and physical examinations.

All AEs were classified as per the Medical Dictionary for Regulatory Activities. Treatment-emergent AEs (TEAEs) were the AEs with onset during the treatment period that developed, worsened, or became serious from the initial administration of the study drug through the day of the last dose plus 28 days. The TEAEs that were not resolved or recovered, resolving, or recovering, or had an unknown status, were considered persistent TEAEs.

The secondary endpoint was the change in HbA1c from baseline to weeks 12 and 24. The exploratory endpoints were changes in fasting plasma glucose (FPG), 2-hour postprandial glucose (PPG), body weight, waist circumference, blood pressure (systolic and diastolic), and proportion of patients achieving HbA1c of <7.0% from baseline to weeks 12 and 24.

Statistical Analysis

All the safety endpoints were assessed in the safety analysis set, comprising patients who received ≥1 dose of the study drug. Descriptive statistics were used for all continuous safety variables; categorical variables were summarized using frequency counts and percentages. All chemistry, hematology, and urinalysis laboratory tests were summarized using descriptive statistics. All the efficacy endpoints were assessed in the efficacy analysis set, comprising patients who had taken ≥1 dose of study intervention

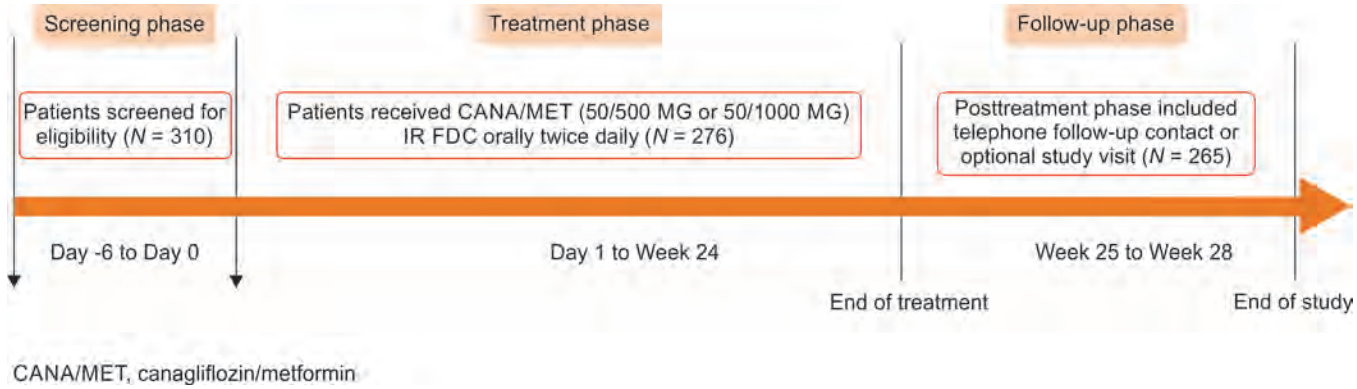


Fig. 1: Schematic representation of the study design; CANA, canagliflozin; FDC, fixed-dose combination; MET, metformin; IR, immediate-release

and had both baseline and at least 1 post-baseline efficacy assessment of HbA1c. All efficacy parameters were summarized using descriptive statistics.

Results

Patient Demographics and Disposition

Of the 310 patients screened, 276 were enrolled in this study as per inclusion and exclusion criteria and were treated with CANA/MET IR FDC. Two patients did not receive any dose of the study medication, resulting in 274 patients in the safety analysis set. The efficacy analysis set comprised 266 patients. The median age of the patients was 54 years, and the proportion of males (*n* = 169, 61.2%) was higher compared to females (*n* = 107, 38.8%). The mean ± standard deviation (SD) baseline weight, BMI, and waist circumference were 72.3 ± 11.67 kg, 26.6 ± 4.17 kg/m^2, and 98.4 ± 10.92 cm, respectively. The mean ± SD baseline FPG, PPG, and HbA1c values were 151.2 ± 50.67, 229.4 ± 67.46, and 8.5 ± 0.83% mg/dL, respectively (Table 1).

Overall, 180 (65.7%) and 94 (34.3%) patients received CANA/MET IR FDC with doses of 50/500 and 50/1000 mg, respectively. Two patients (0.7%) required modification of the study drug dose. The median duration of exposure to the study drug was 24.29 weeks (0.6–28.1 weeks). Overall, 265/274 (96.7%) patients showed ≥80% compliance to the study medication. In total, 263/274 (96%) patients used ≥1 concomitant medication; the most commonly used were for diabetes (71.2%), general nutrients (48.2%), and lipid-modifying agents (45.6%). Of the 274 patients, 41 (15%) required rescue medications during the study. Rescue medication was defined as the new antidiabetic medication following the initiation of the study drug.

Safety

Overall, 41.6% (114/274) of the patients had ≥1 TEAE. Of these, 29 (10.6%) patients had TEAEs related to the study intervention. The most common TEAEs were dyslipidemia in 13/274 (4.7%), pyrexia in 13/274 (4.7%), genital infection in 9/274 (3.3%), and hypoglycemia in 9/274 (3.3%) patients. A total of 35 (12.8%) patients reported persistent TEAEs by the end of the study. Most of the TEAEs were mild or moderate in severity. The details of the TEAEs are presented in Table 2.

Overall, three (1.1%) patients reported ≥1 SAE during the study. Two (0.7%) patients reported SAE of severe urinary tract infection and were considered by the investigator to be possibly related to the study intervention. Of these two patients, one (0.4%) patient also had an SAE of diabetic ketoacidosis, which was assessed by the investigator as possibly related to study intervention. The same patient also had an SAE of prostatomegaly, which was severe and assessed by an investigator not related to the study intervention. One (0.4%) patient was hospitalized due to coronavirus disease of 2019 (COVID-19) infection with mild severity, which was assessed by the investigator as not related to study intervention. All the SAEs were resolved, and the patients recovered. Approximately, 262 (94.9%) patients had no hypoglycemic episodes, and eight (2.9%) patients had one hypoglycemic episode during the study. Two (0.7%) patients each had two, three, and four episodes of hypoglycemia, respectively. Of these 14 patients who had ≥1 hypoglycemic episode, the hypoglycemic events in five patients were not deemed clinically significant as per the investigator's discretion. Overall, TEAEs leading to treatment discontinuation were low, that is, 6/274 (2.2%), asthenia (3 [1.1%] patients) being the most common (≥1.0%). Other TEAEs leading to study discontinuation were pyrexia, gastroenteritis, urinary tract infection, decreased appetite, limb injury, diabetic ketoacidosis, and prostatomegaly reported in one patient each. No deaths were reported during the study.

In general, no clinically significant changes were observed in safety laboratory parameters at weeks 12 and 24. Clinically significant abnormal values for creatinine, potassium, and total cholesterol were reported in one (0.4%) patient each, whereas triglycerides and low-density lipoprotein (LDL) cholesterol were clinically abnormal in two (0.8%) and

Table 1: Summary of demographics and baseline characteristics (all enrolled analysis set)

Patient characteristics	*CANA/MET IR FDC*
Age, years	
Mean (SD)	52.2 (8.3)
Sex, *n* (%)	
Male	169 (61.2)
Female	107 (38.8)
Weight (kg)*	
Mean (SD)	72.3 (11.7)
BMI, kg/m^2, *n* (%)*	
Mean (SD)	26.6 (4.2)
<25	92 (33.6)
25–30	138 (50.4)
>30	44 (16.1)
Waist circumference (cm)*	
Mean (SD)	98.4 (10.9)
FPG (mg/dL)	
Mean (SD)	151.2 (50.7)
PPG (mg/dL)*	
Mean (SD)	229.4 (67.5)
HbA1c (%)*	
Mean (SD)	8.5 (0.83)
eGFR (mL/minute/1.73 m^2), *n* (%)	
Mean (SD)	95.9 (15.3)
<60	9 (3.3)
60–<90	65 (23.7)
≥90	200 (73.0)
Comorbidities, *n* (%)	
Dyslipidemia	94 (34.1)
Hypertension	130 (47.1)
Blood cholesterol increased	28 (10.1)
Hypothyroidism	22 (8.0)
Diabetic neuropathy	16 (5.8)

N = 276, the total number of patients enrolled in the study; **N* = 274; safety analysis set; patients who received at least one dose of the intervention; BMI, body mass index; CANA, canagliflozin; cm, centimeter; eGFR, estimated glomerular filtration rate; FDC, fixed-dose combination; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; IR, immediate release; MET, metformin hydrochloride; PPG, postprandial plasma glucose; SD, standard deviation.

four (1.5%) patients, respectively at week 12. Clinically significant abnormal values for creatinine persisted in one (0.4%) and two (0.8%) patients each for LDL cholesterol and triglycerides at week 24, respectively (Table 3).

None of the patients had clinically significantly abnormal values for any hematology parameter at week 24. For urinalysis, at week 12, one (0.4%) patient each had clinically significant abnormal values of urine albumin and urine creatinine, and two (0.8%) patients had a clinically abnormal urine albumin/creatinine ratio. At week 24, four (1.5%) patients had clinically significant abnormal urine albumin/creatinine ratio values (Table 3).

Table 2: Summary of TEAEs (safety analysis set)

Safety analysis	*CANA/MET IR FDC (N = 274), n (%)*
Subjects with one or more TEAEs	114 (41.6)
Related to the study treatment	29 (10.6)
TEAEs leading to death	0
Serious TEAEs	3 (1.1)
Related to the study treatment	2 (0.7)
TEAEs leading to discontinuation of study agent	6 (2.2)
TEAEs leading to termination of study participation	5 (1.8)
COVID-19 related TEAEs	5 (1.8)
Most common TEAEs	
Infections and infestations	33 (12.0)
Genital infection	9 (3.3)
Urinary tract infection	7 (2.6)
Metabolism and nutrition disorders	31 (11.3)
Dyslipidemia	13 (4.7)
Hypoglycemia	9 (3.3)
General disorders and administration site conditions	22 (8.0)
Pyrexia	13 (4.7)
One or more serious TEAEs	
Urinary tract infection	2 (0.7)
COVID-19	1 (0.4)
Diabetic ketoacidosis	1 (0.4)
Prostatomegaly	1 (0.4)

Safety analysis set, patients who received at least one dose of the intervention; CANA, canagliflozin; COVID, coronavirus disease; FDC, fixed-dose combination; IR, immediate-release; MET, metformin hydrochloride; TEAE; treatment-emergent AE

Table 3: Summary of patients with clinically significant abnormal laboratory parameters (safety analysis set)

Parameter	*Baseline, n (%)*	*Week 12, n (%)*	*Week 24, n (%)*
FPG (mg/dL)	75 (27.4)	46 (17.4)	35 (13.2)
PPG (mg/dL)	91 (33.2)	53 (20.2)	48 (18.3)
HbA1c (%)	57 (20.8)	28 (10.6)	23 (8.7)
HDL cholesterol (mg/dL)	3 (1.1)	0	0
LDL cholesterol (mg/dL)	5 (1.8)	4 (1.5)	2 (0.8)
Total cholesterol (mg/dL)	2 (0.7)	1 (0.4)	0
Triglycerides (mg/dL)	4 (1.5)	2 (0.8)	2 (0.8)
Urine albumin (mg/dL)	2 (0.7)	1 (0.4)	0
Urine creatinine (gm/dL)	1 (0.4)	1 (0.4)	0
UACR (mg/gm)	4 (1.5)	2 (0.8)	4 (1.5)
SBP (mm Hg)	2 (0.7)	1 (0.4)	0
DBP (mm Hg)	2 (0.7)	2 (0.8)	0

Safety analysis set, patients who received at least one dose of the intervention; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PPG, postprandial plasma glucose; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio

At week 12, very few patients had clinically significant abnormal vital signs for SBP, pulse (1 [0.4%] patient each), and DBP [two (0.8%) patients]. None of the patients had clinically significant abnormal vital signs at week 24. Overall incidences of abnormal flagged electrocardiogram values were low ($n = 2$).

Efficacy

The change in mean HbA1c levels from baseline was −0.92 (95% confidence interval [CI]: −1.055; −0.780) and −0.93% (95% CI: −1.084; −0.768) (at weeks 12 and 24, respectively (Fig. 2). Overall, 27.8% of the patients achieved an HbA1c <7% at week 12, which was increased to 34.2% at week 24 (Fig. 3).

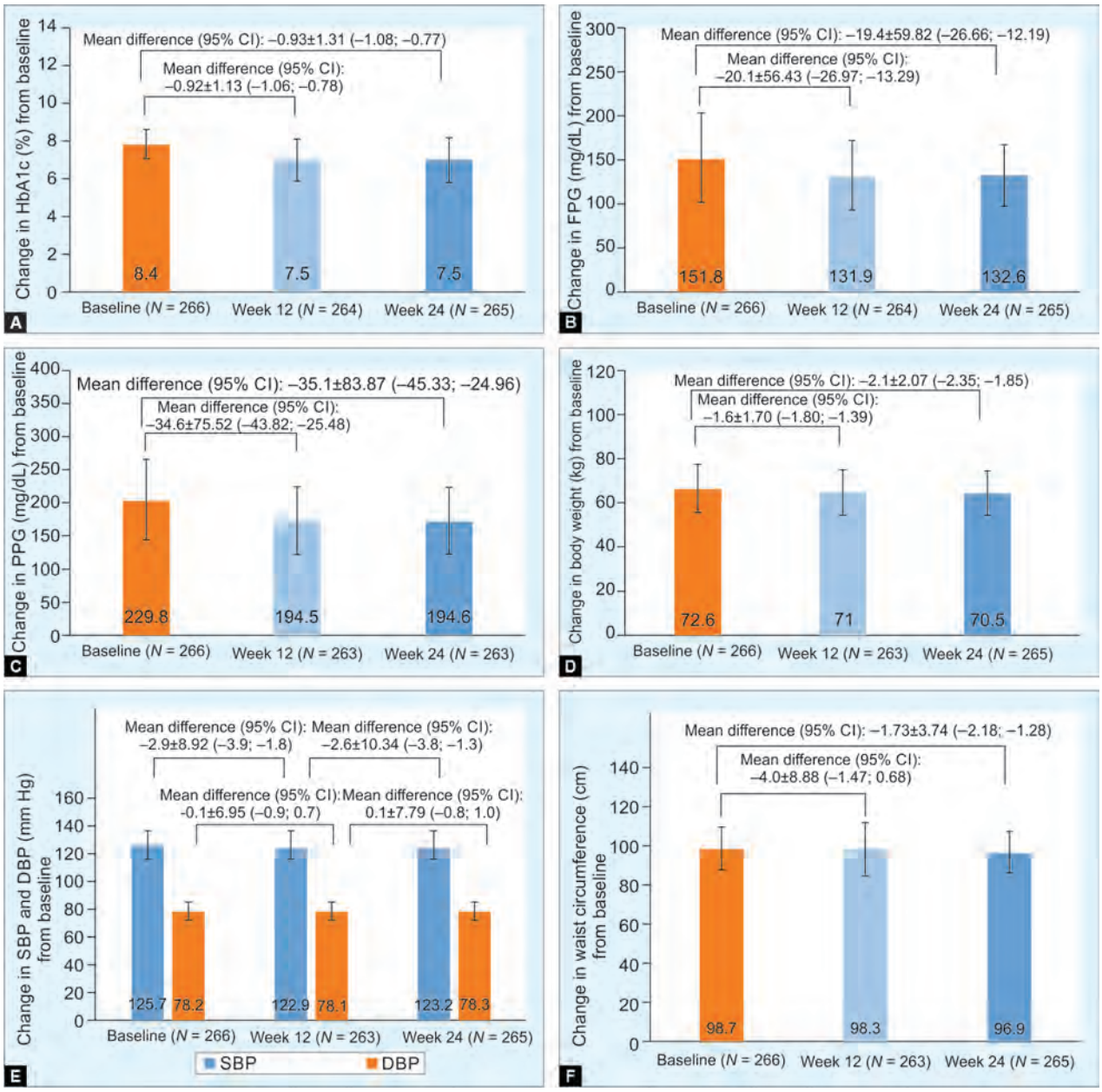
The changes in the mean FPG from baseline were −20.13 mg/dL (95% CI: −26.97; −13.29) and −19.42 mg/dL (95% CI: −26.66; −12.19) at weeks 12 and 24, respectively. The changes in the mean 2-hour PPG from baseline were −34.65 mg/dL (95% CI: −43.82; −25.48) and −35.14 mg/dL (95% CI: −45.33; −24.96) at weeks 12 and 24, respectively (Fig. 2).

Mean changes in SBP and DBP from the baseline were −2.6 and −0.1 mm Hg at week 24, respectively. The mean body weight reduction was 2.10 kg, and the mean waist circumference reduction was 1.73 cm at the end of week 24. The results are presented in Figure 2.

Discussion

The present study evaluated the safety and efficacy of CANA/MET IR FDC (50/500 and 50/1000 mg) in Indian patients with T2DM who were inadequately controlled with diet and exercise and were eligible to receive the study drug as per prescribing information. It was also the first study conducted to evaluate the safety and efficacy of CANA/MET FDC in Indian patients with T2DM.

Safety assessments, including the determination of AEs, SAEs, and unexpected AEs, or ADRs over the study period was the primary endpoint of the study, and the safety profiles of CANA/MET IR FDC were found to be consistent with those reported in previous studies.[23,24] Dyslipidemia, pyrexia, hypoglycemia, genital infection, and urinary tract infection were the most common TEAEs. No deaths were reported during the study. Improvements in HbA1c and FPG levels from the baseline were observed after 12 and 24 weeks of treatment with CANA/MET IR FDC. Overall, the study demonstrates the safety and efficacy of CANA/MET IR FDC and offers a safe therapeutic regimen in Indian patients with inadequately controlled T2DM.



Figs 2A to F: Changes in the secondary endpoints from baseline through weeks 12 and 24; (A) Changes in HbA1c; (B) Changes in FPG; (C) Changes in PPG; (D) Changes in weight; (E) Changes in SBP and DBP; (F) Change in waist circumference; CI, confidence interval; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; PPG, postprandial plasma glucose; SBP, systolic blood pressure

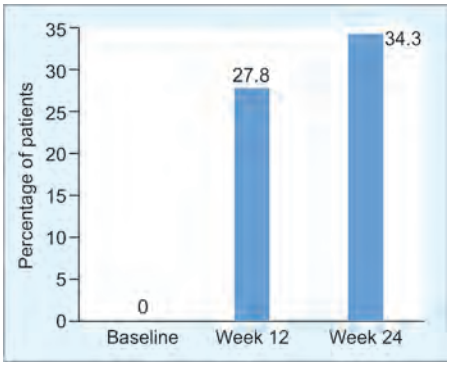


Fig. 3: Percentage of patients achieving glycated hemoglobin HbA1c goal of <7% at baseline, weeks 12 and 24

The baseline demographics of the included patients (older adult age, overweight mean BMI, male dominance) were consistent with a phase IV study evaluating the safety and efficacy of SGLT2i in patients with T2DM.[31] In the current analysis, the majority (96%) of patients were using one or more concomitant medications for comorbidities associated with diabetes. These findings concur with a cross-sectional survey from India, which reported that around 84% of patients with T2DM were suffering from one or more comorbid conditions associated with diabetes.[32]

In this study, 41.6% of patients reported TEAEs, of which only 10.6% were related to the study drug, as assessed by the investigators. These results are in line with a phase II study in which treatment with CANA 50 mg twice daily wherein 35.5% of AE (11.8% related to the study drug) were reported.[22] Additionally, in a dose-ranging study, 50% of patients reported at least one AE, with CANA 50 mg once daily added to background MET in patients with T2DM.[23,24] Overall, only three (1.1%) patients reported SAEs in the current study, and most of the TEAEs were mild or moderate in severity, with minimal patient discontinuation (2.2%) in line with the previous CANA 50 mg study.[22] Safety data from six phase III studies[33–38] on CANA showed 41.82% (CANA 100 mg) and

40.95% (CANA 300 mg) of patients reporting any AEs at week 26. Frequently occurring AEs were osmotic diuresis-related AEs, volume depletion AEs, urinary tract infections, and genital mycotic infections.[39]

As per the System Organ Class, infections and infestations were the most common AEs reported in 33 (12%) patients, including nine patients with genital infections (3.3%) and seven patients with urinary tract infections (2.6%). Not surprisingly, owing to its mechanism of action (SGLT2 inhibition), CANA is associated with a higher incidence of genital mycotic infections and urinary tract infections, as reported in the literature.[5,22,23] The SGLT2 inhibitors increase urinary glucose concentration pharmacologically and provide favorable conditions for microbial growth, which results in an increased incidence of genital infections.[40] Hence, clinicians should pay careful attention to the infections associated with SGLT2 inhibitors and personalize the treatment accordingly for patients with T2DM. Rosenstock et al. have reported genital infections in 4–6% of patients in the CANA/MET combination group, whereas 5–10% of patients in CANA alone.[24] Similarly, 6% of patients suffered from genital infections, as reported in the *post hoc* analysis of pooled phase 3 studies of patients with T2DM from India treated with CANA (100 mg) on a range of background therapies.[5]

In the present study, hypoglycemia was recorded in nine (3.3%) patients, consistent with the global study where 4.2 and 5.5% of patients had hypoglycemia in the CANA100/MET and CANA300/MET groups, respectively.[24] In the *post hoc* analysis of Indian patients, fewer cases of hypoglycemia were reported in patients on CANA, not on a background AHA, compared to those on a background AHA.[5] In general, fewer hypoglycemic episodes have been one of the key advantages associated with the use of SGLT2i.[41,42] In studies wherein the patients were not on background AHAs, the low risk of hypoglycemia observed with CANA, is by virtue of its mechanism of action, as the renal threshold for glucose is typically reduced to −80–90 mg/dL above the hypoglycemia threshold in patients with T2DM.[23,43–45] Incidences of hypoglycemia in our study might be associated with the concomitant AHAs taken, along with the study medication. A phase II pooled analysis showed a higher incidence of documented hypoglycemia episodes in patients on a background of sulfonylurea compared to placebo, and this incidence was a dose-related increase as seen with CANA 100 and 300 mg.[45] Our results are substantiated with other large trials, which have reported a safe and well-tolerated profile of CANA both alone and in combination of other AHAs, including MET.[36,37,43]

Approximately, 12.8% of patients reported persistent TEAEs that were not resolved or recovered or status unknown. Only one (0.4%) patient reported both severe DKA and prostatomegaly. This is in line with the published studies where the incidence of DKA was reported to be very low with the use of SGLT2 inhibitors.[46,47] Dyslipidemia (4.7%) and pyrexia (4.7%) were the most common AE as per the preferred term reported in this study. A considerable number of patients (34.1%) had dyslipidemia at the time of study initiation, and this may have resulted in a higher incidence of AEs of dyslipidemia. Literature supports the potential beneficial effect of SGLT2 inhibitors on lipid metabolism at the cellular level to regulate lipoprotein concentration, fat storage, and substrate utilization.[48] In this study, the abnormal values for creatinine, potassium, triglycerides, and LDL cholesterol were reported only in a small number of patients (–1%), which is consistent with published studies.[5,22–24,41] Although the incidence of fever is reported to be very low in patients continuing CANA,[22,24] the increase in the incidence of fever in this study might result from the higher incidence of infections.

The change in HbA1c levels from baseline were −0.92 and −0.93% at weeks 12 and 24, respectively. In a double-blind, placebo-controlled, parallel-group, multicenter, dose-ranging study including 451 subjects, CANA 50 mg once daily added to background MET therapy reduced HbA1c level by 0.79% at 12 weeks.[23] However, another randomized, double-blind placebo-controlled study (N = 271) reported a decrease of 0.45% in HbA1c at 18 weeks with treatment of CANA 50 mg twice daily added to MET monotherapy. Rosenstock et al. reported HbA1c reductions of 1.77% for CANA100/MET and 1.78% for CANA300/MET at 26 weeks.[24] As per the ADA and the European Association for the Study of Diabetes, the recommended target level of HbA1c is 7%.[49] Nearly one-third of the patients (34%) achieved the target HbA1c level in our study compared with 43% of patients in a previous phase III study, evaluating the safety and efficacy of CANA/MET FDC.[24] This difference might be due to the slight difference in the study duration. As SGLT2i acts by increasing the urinary glucose excretion, the differences in the baseline estimated glomerular filtration rate (eGFR) and potentially some other characteristics could influence the HbA1c responses across different ethnicities.[50] In a phase II study of 279 patients evaluating 50 and 150 mg of CANA, significantly higher proportions of patients achieved HbA1c <7.0% at week 18 with 50 (47.8%) and 150 mg (57.1%) compared with placebo.[22]

The FPG reductions (–20.13 mg/dL) in this study are nearly consistent with the findings of the previous CANA studies. Rosenstock et al. reported a decline of –65.77, 66.37, and –52.32 mg/dL in CANA 100/MET vs CANA 300/MET vs MET at week 26.[24] Similarly, in a real-world study, there was a significant reduction in the FPG (–35.8 mg/dL; $p < 0.005$) at week 26 after switching from sitagliptin to CANA (100 mg).[39] The mean PPG levels also showed a decline from the baseline at weeks 12 and 24, in line with CANA studies.[32] Moreover, the changes in body weight, waist circumference, SBP, and DBP reported in this study are consistent with the published studies.[22,24,32]

The main strengths of our study were the low dropout rates and the inclusion of a considerable number of patients in the real-world setting. Among the 276 patients enrolled, 265 (96.7%) patients completed the study. This might be due to the adherence and compliance associated with FDC.[28,51] The limitation of the current study is that it is a single-arm, real-world, postmarketing study without a comparator arm as this was a real-world, post-marketing study with safety assessment as the primary endpoint. Further, efficacy endpoints could have been impacted by concomitant medications and comorbidities. The efficacy endpoints assessed changes from the baseline, and there was no direct comparison with a comparator arm.

Overall, results from this study have demonstrated that CANA/MET IR FDC (50/500 and 50/1000 mg) have an acceptable safety profile to be prescribed in Indian patients since all reported AEs were manageable without any new safety signals, and no deaths were reported. The CANA/MET FDC could effectively reduce the HbA1c, FPG, and PPG levels in Indian patients with T2DM. Additionally, the reduction in body weight, waist circumference, and vital parameters was consistent with previous studies. Thus, CANA/MET IR FDC could be an acceptable and effective therapeutic option in Indian patients with T2DM.

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Disclosures

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Author Contributions

All authors contributed to data analysis, drafting, or revising of the article, provided final approval for the version to be published, and agreed to be accountable for all aspects of the work.

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ORIGINAL ARTICLE

Effect of α-blockers on Handgrip Test Response of Diastolic Blood Pressure in Hypertensive, Benign Hypertrophy of Prostate Patients in a Therapeutics Clinic, Kolkata: A Cross-sectional Study

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Abstract

Background: The isometric handgrip (IHG) test is commonly used to detect sympathetic autonomic dysfunction. Tamsulosin, approved for the management of symptomatic benign prostatic hyperplasia (BPH), acts as an antagonist for α_1-adrenergic receptors (α_1-AR), whereas prazosin, an α_1 receptor blocker, being less selective than tamsulosin, is used as an antihypertensive agent clinically. Our objective was to investigate if there is a distinction in blood pressure (BP) increase during IHG exercise between individuals with essential hypertension taking tamsulosin compared to those taking prazosin.

Materials and methods: A cross-sectional observational study was performed on 50 subjects receiving tablet prazosin and 47 subjects receiving tamsulosin, who were asked to undergo an IHG test. Pre- and posttest BP was recorded for both the groups, and the difference in diastolic BP (DBP) (delta DBP) was compared between the groups and to their respective baseline values.

Results: Post-IHG test, mean DBP was found to be 93.98 ± 9.13 mm Hg in the prazosin group and 101.00 ± 12.05 mm Hg in the tamsulosin group, respectively. The change of delta DBP in the tamsulosin group was significant, but the prazosin group showed an insignificant rise in DBP.

Conclusion: Prazosin, being less selective than tamsulosin in terms of α_1 receptor antagonism, showed suppression of BP during IHG. Tamsulosin demonstrates high selectivity for prostatic receptors while showing minimal affinity for vascular receptors. As a result, its impact on BP is expected to be minimal.

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Introduction

Benign prostatic hyperplasia (BPH) denotes the nonmalignant enlargement of the prostate gland, commonly observed in men during the latter stages of their lives. The actual hyperplasia of the prostate gland, constituting BPH, arises primarily as a consequence of aging and is prevalent in nearly all men, typically beginning around the ages of 40–45. Various autopsy studies conducted worldwide have examined the histologic prevalence of BPH, revealing approximately 10% of men in their 30s affected, increasing to 20% in their 40s and reaching levels of 50–60% in their 60s.[1] Clinically, BPH presents with lower urinary tract symptoms, which include irritative symptoms such as urgency, frequency, and nocturia, along with obstructive symptoms like hesitancy, 1 weak and interrupted urinary stream, difficulty initiating urination, and a sense of incomplete bladder emptying.[2] α-adrenergic blockers are a commonly used class of drugs to relieve the symptoms associated with it. The rationale behind the utilization of α-adrenergic blockers stems from the action of noradrenaline on α_1-adrenergic receptors (α_1-AR) located in the neck and sphincter of the urinary bladder, which promotes contraction and urinary retention. Additionally, noradrenaline regulates the smooth muscles in the prostate capsule and prostate urethra.[3] Prazosin was the pioneer selective α_1-AR antagonist explored for the treatment of BPH. It features a piperazinyl quinazoline nucleus and acts as a selective α_1-adrenergic antagonist, with an affinity 1000-fold higher than that for α_2-receptors. Tamsulosin, the third uroselective α_1-AR antagonist, exhibits 10-fold greater selectivity for the α_1A-receptor subtype compared to the α_1B-receptor subtype and has been approved for treating symptomatic BPH. Notably, a considerable decrease in urinary flow has been noted following the administration of a single dose (0.4 or 0.8 mg) of tamsulosin in comparison to placebo.[4] As an α_1-receptor antagonist, prazosin has the potential to competitively interact with α_1-receptor autoantibodies. Its primary function is to selectively inhibit the α_1-receptor on the postsynaptic membrane of vascular smooth muscle, inducing relaxation in small arteries and veins. This action reduces peripheral resistance, consequently lowering BP. This is the reason why prazosin is clinically widely used in the management of hypertension, especially in those with chronic kidney disease.[5] Handgrip strength is good.

Tool to evaluate an individual's autonomic function, precisely the sympathetic function, and when reduced, is associated with adverse health consequences. Few studies have described the association between conditions like diabetes and commonly prescribed antihypertensive drugs and diminished handgrip test response. Thus, in our study, we tried to evaluate the effect of the α-blocker class of agents on the result of the handgrip test.

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Materials and Methods

A total of 97 male subjects of essential hypertension with radiologically and clinically diagnosed benign prostatic hyperplasia aged between 50 and 70 years, attending the clinical pharmacology outpatient department, were part of this cross-sectional study. Informed consent was obtained from each participant prior to the initiation of the study. Subjects with diagnosed autonomic neuropathy, or any condition like diabetes mellitus that can have an impact on their autonomic nervous system or taking any drug that can alter autonomic neuronal function, were excluded from the study. Subjects were on angiotensin receptor blockers (ARB) for at least the last 1 year. Around 50 subjects were receiving tablet prazosin in optimum dosage according to their body weight and clinical status as an add-on therapy to ARB for hypertension and/or BPH for at least the last 6 months but not >2 years. Around 47 subjects were on tablet tamsulosin in optimum dosage as a part of their treatment for BPH. We evaluated the BP of all the subjects prior to doing the isometric handgrip (IHG) test at the baseline. All the subjects in both the prazosin and tamsulosin groups underwent an isometric exercise test in the form of a handgrip test for 3 minutes. IHG was conducted at 30% of the maximum voluntary contraction of the right hand, maintained for a duration of 3 minutes. Participants were directed to exert their maximum brief compressive force with their right hand on three separate occasions to establish their maximal voluntary contraction. The greatest tension reached during these trials was recorded as the maximal force at the end of the test; that is, after 3 minutes, the BP of all the subjects was recorded using an Omron HEM-7600T BP monitor. After completion of the test, the BP of all the subjects in both the prazosin and tamsulosin groups was measured, the mean BP was compared with the mean baseline BP value, and changes were recorded. The change in mean DBP was measured and compared between the prazosin and tamsulosin groups.

Table 1: Basic demographics

	Observed values [mean ± SD (range)]
Mean age (years)	70.03 ± 4.19 (61–80)
Mean BMI (kg/m^2)	24.71 ± 3.01 (18.3–26.1)
Mean baseline SBP (mm Hg)	136.32 ± 10.73 (116–156)
Mean baseline DBP (mm Hg)	83.71 ± 9.41(60–94)

Results

The mean age of the study population was 70 years, with a standard deviation of 4.19. The mean body mass index (BMI) was 24.71. The DBP value (mean) was 83.71 ± 9.41 mm Hg at the baseline (Table 1). Subjects on the prazosin arm had a baseline mean DBP of 83.62 ± 9.01 mm Hg, whereas in the tamsulosin group, it was 83.81 ± 9.91 mm Hg at the baseline. After completion of the IHG test, the mean DBP was found to be 93.98 ± 9.13 in the prazosin group (*p*-value of 0.92), and 101.00 ± 12.05 was in the tamsulosin group ($p < 0.001$) (Table 2). Post-IHG, four subjects in the prazosin group showed an increment of DBP >16 mm Hg, whereas Figure 1 was 16 in the tamsulosin group. A 10–15 mm Hg rise in DBP was observed in 26 and 10 subjects in the prazosin and tamsulosin groups, respectively (Table 3).

Discussion

The involvement of catecholamine neurotransmitters in circulatory regulation, both in the brain and the periphery, occurs through specific receptors. Ahlquist was the first to propose categorizing catecholamine receptors into α and β subtypes in the late 1940s. The mechanisms of both α_1 and α_2 receptors play roles in regulating circulation and maintaining BP, exerting cardiovascular control at various peripheral and central locations. In the peripheral nervous system, α_1 receptors, or classic postsynaptic α receptors found on smooth muscle, mediate responses to noradrenaline released by neurons at vascular neuroeffector junctions and likely contribute to responses to circulating catecholamines as well.[6] Several classes of drugs influence BP regulation through their interactions with peripheral α_1 receptors. The haloalkylamine α-adrenergic receptor antagonists were initially investigated during the 1940s.[7] Prazosin was later examined as a potential therapy for BPH in numerous placebo-controlled clinical trials. It demonstrated better effectiveness compared to placebo and exhibited a reduced occurrence of unwanted α blockade side effects when compared to older drugs such as phenoxybenzamine. This suggests that α_1 selectivity provides advantages in terms of clinical tolerability.[8] Three subtypes of the α_1-adrenoceptor (α_1a) (α_1b, and α_1d) have been cloned and thoroughly characterized pharmacologically. Lepor et al. demonstrated that α_1a is the predominant subtype of α_1-adrenoceptor in the human prostate.[9] Recently, α_1-blockers that exhibit a preference for acting on the prostate region rather than vascular smooth muscle, such as alfuzosin and tamsulosin, have been developed. Both medications are exclusively marketed for the treatment of BPH. Their efficacy is comparable to that observed with other α_1-blockers, and they are associated with a lower incidence of adverse events, particularly postural symptoms.[10]

Numerous studies have indicated that individuals with a family history of hypertension are at an increased risk of developing hypertension. Additionally, there is a significant increase in systolic, diastolic, and mean BP observed during isometric exercise in individuals with hypertension,[11] a finding consistent with our own observations. Typically, during exercise, there is a rise in the concentrations of metabolites such as lactic acid and adenosine, which are detected by metabolite-sensitive nerve endings within the skeletal muscle interstitium. These substances stimulate the discharge of group IV (metaboreceptor) afferent fibers, thereby

Table 2: Changes post handgrip test

	Prazosin arm (n = 50)	*Tamsulosin arm (n = 47)*
Mean baseline DBP (mm Hg)	83.62 ± 9.01 (60–94)	83.81 ± 9.91 (60–93)
Mean DBP posttest (mm Hg)	93.98 ± 9.13 (73–107)	101.00 ±12.05 (68–116)
p-values	0.92	<0.001

Values expressed as mean ± SD (range)

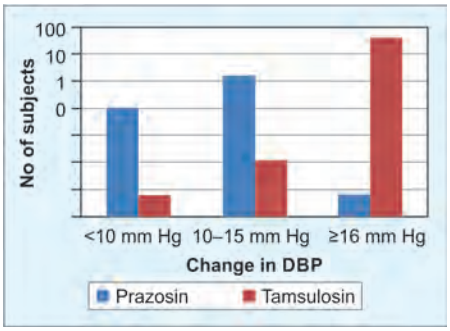

Fig. 1: Changes in DBP in prazosin and tamsulosin group

Table 3: Changes in DBP

	Changes in DBP [n (%)]			
	<10 mm Hg	*10–15 mm Hg*	*>16 mm Hg*	
Prazosin arm (*n* = 50)	20 (20.62)	26 (26.80)	4 (4.12)	$\chi^2 = 40.4534$. *p*-value < 0.00001
Tamsulosin arm (*n* = 47)	4 (4.12)	10 (10.31)	33 (34.02)	

initiating a potent reflex that augments sympathetic nerve activity. This ultimately leads to vasoconstriction, contributing to an elevation in BP.[12] Our findings were consistent with these results.

A study conducted in Japan[13] showed a greater increment in DBP after conducting the IHG test was observed among subjects with essential hypertension compared to normotensive subjects. The study also showed that BP changes during IHG were significantly less in subjects taking prazosin than in subjects with no treatment. They further suggested BP elevation with prazosin was markedly suppressed due to the blockade of postjunctional α adrenoreceptor by the drug. Such a response is less likely with tamsulosin because it is a more selective α_1a receptor blocker, which is predominantly present in prostatic tissue. It is also proposed that due to its higher selectivity, tamsulosin is expected to minimally affect BP and is unlikely to enhance the antihypertensive effects of other agents.[14]

Conclusion

Tamsulosin exhibits high selectivity for prostatic receptors and has minimal affinity for vascular receptors. Consequently, it is expected to have minimal impact on BP and is unlikely to enhance the antihypertensive effects of other agents.

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ORIGINAL ARTICLE

Comparison of Insulin Sensitivity in Subclinical and Overt Hypothyroidism

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Abstract

Objective: To assess the association of thyroid hormone levels with insulin sensitivity in patients with subclinical (SCH) and overt hypothyroidism (OH).

Materials and methods: The present cross-sectional case-control study observed the association of thyroid hormone levels with insulin sensitivity in patients with SCH and OH as compared to their age-matched controls with euthyroidism (ET). Thyroid profile status, fasting blood sugar and triglyceride level, and basic anthropometric measurements were noted. Fasting insulin level (FIL) was analyzed using serum. Body mass index (BMI) and quantitative insulin sensitivity check index (QUICKI) were calculated.

Results: Insulin levels were found to be significantly increased ($p = 0.038$) in patients with SCH as well as those with OH when compared with compared with age-matched ET controls. insulin sensitivity index (ISI) was comparable among the subjects of the three groups.

Conclusion: Subclinical hypothyroidism (SCH) and OH had high insulin levels but without statistically significant association between thyroid-stimulating hormone (TSH) levels and QUICKI.

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Introduction

Insulin resistance (IR) and dyslipidemia are key to the pathological health complications associated with thyroid disorders.[1–6] It is established that clinical hypothyroidism is considered an insulin-resistant state,[7,8] but the exact mechanism connecting hypothyroidism to IR and dyslipidemia is a matter of research.[9]

Thyroid hormonal dysregulation influences glucose metabolism by furthering the progress of IR or blunting insulin sensitivity. In hyperthyroidism, IR affecting the liver results in impaired glucose tolerance, whereas influencing the peripheral tissues prevails in hypothyroidism.[10,11]

Finding a correlation of thyroid profile parameters with insulin sensitivity in patients with SCH and overt hypothyroidism (OH) was the aim of this study (Fig. 1). Fasting insulin level (FIL) and quantitative insulin sensitivity check index (QUICKI) were used as surrogate indices for assessing insulin sensitivity.

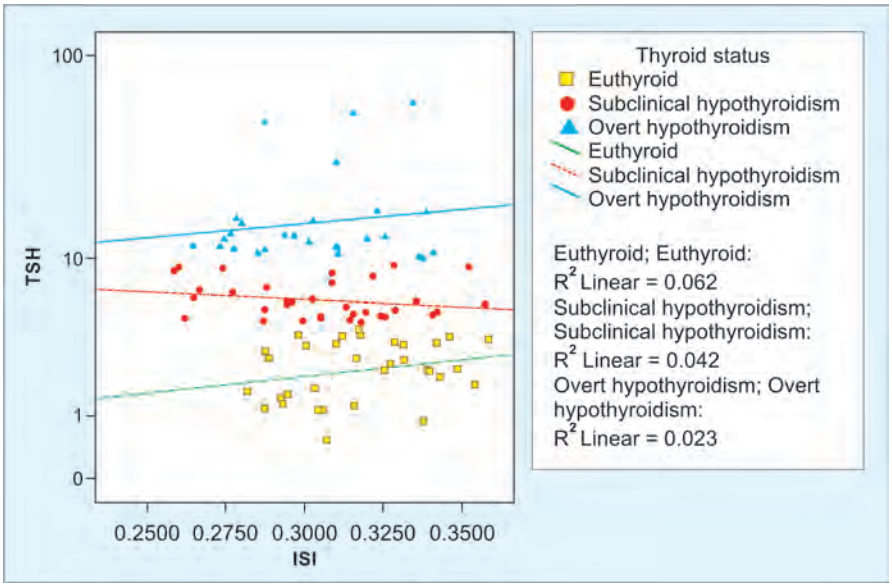

Fig. 1: Correlation of TSH with ISI

Materials and Methods

Study Design

This observational cross-sectional case-control study was conducted at the Center of Basic Sciences, Biochemistry and Department of Medicine, KMC Hospitals, Mangaluru, Karnataka, India, over 4 months duration. Institutional ethical clearance was obtained. Fasting glucose, lipid profile, and thyroid function levels of patients aged between 20 and 60 years who came for routine biochemical tests were noted. Leftover fasting serum samples collected for the routine biochemical tests were preserved suitably and used for insulin assay only after obtaining informed consent. QUICKI was calculated from fasting plasma glucose (FPG) and insulin.

Relevant demographic patient data and history details were recorded. Waist circumference (WC), weight, and height were noted. On the basis of thyroid profile values and inclusion criteria, subjects were assigned to euthyroid, SCH, and OH groups.

This study involved 105 study subjects with the following thyroid status: euthyroid ($n = 35$), SCH ($n = 35$), and OH ($n = 27$).

Patients on lipid-lowering drugs/antihypertensives/being treated for endocrinopathies/diabetes mellitus/past thyroid disorder, on treatment altering thyroid function were excluded, including pregnant/lactating women.

Sample Collection and Analysis

Fasting glucose, triglyceride, and thyroid function tests [thyroid-stimulating hormone

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(TSH), thyroxine (T4), and triiodothyronine (T3)] levels analyzed for routine biochemical tests on Roche COBAS 6000 by hexokinase, enzymatic colorimetric, and electrochemiluminescence immunoassay methods, respectively, were noted from electronic laboratory reports. Serum samples were stored at –20°C in a refrigerator, and fasting serum insulin was estimated by enzyme-linked immunosorbent assay (DRG kit, solid phase).

Anthropometric Measurements

Height, weight, and WC were measured. Body mass index (BMI) was calculated using the formula—weight in kilograms/(height in meters)^2.

Insulin sensitivity was calculated using QUICKI method with the following formula:

$$QUICKI = 1/\left[log\ I_0(\mu U/mL) + log\ G_0(mg/dL)\right]$$

Where I_0 is fasting insulin, and G_0 is fasting glucose.[12]

A QUICKI of >0.4 is treated as normal, and a decline in values indicates a decline in insulin sensitivity or the presence of IR.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences version 17.0 software. Normally, distributed data are presented as mean ± standard deviation (SD). Differences between the means were analyzed by one-way analysis of variance. Tukey's test analyzes differences in baseline characteristics between the study groups and the control group. $p < 0.05$ was considered statistically significant.

Results

Both T3 and T4 were significantly decreased ($p \leq 0.05$) in OH. TSH was significantly higher ($p \leq 0.005$) in OH and SCH groups. A statistically significant increase was observed in insulin values of OH (Tables 1 and 2).

Bivariate correlation across different categories of thyroid status [euthyroidism (ET), SCH, OH] was done between thyroid hormones (T3, T4, and TSH) and with insulin sensitivity and triglycerides (TG). In the OH group, T3 was significantly negatively correlated with TG ($r = -0.386$, $p = 0.047$). In ET, TSH showed a significant negative correlation with TG ($r = -0.383$, $p = 0.023$).

Discussion

In the present study, we used FIL and QUICKI as indices of insulin sensitivity. Statistically significant increases in insulin levels were seen in patients with SCH and OH compared to euthyroid individuals. However, there was no statistically significant association between thyroid hormone levels and both these indices. Insulin sensitivity index (ISI) was found to be similar across all the groups, indicating ET subjects to be bordering on IR, too. Pisprasert et al.[13] advocated caution in using indices based on glucose and insulin levels as measures of peripheral insulin sensitivity when comparing mixed-gender and mixed-race populations.

In contrast, the study by Maratou et al. demonstrated a significant positive correlation between the Mastuda index and both free T3 and free T4 levels ($r = 0.41$, $p = 0.04$), suggesting IR in both SCH and OH groups when compared to the control group.[14] The study by Al Sayed et al.[15] could not deduce a statistically significant association of thyroid hormones with homeostatic model assessment (HOMA) IR in SCH. Gayoum et al.[16] found a significant positive correlation between TSH and TG ($r = 0.47$, $p = 0.002$) and HOMA-IR ($p = 0.001$, $r = 0.51$).

In the present study, TSH correlated to TG to a certain extent. Though there were subjects with varying TSH values, there was no significant correlation between TSH and HOMA-IR in the present study.

Table 1: Categorization based on thyroid profile and comparison of study parameters

Parameters	*ET*	*Hypothyroidism*	
		SCH	*OH*
Age (years)	41.11 ± 8.17	42.49 ± 11.54	46.0 ± 10.16¥
Height (M)	1.658 ± 0.1	1.638 ± 0.09	1.63 ± 0.109
Weight (kg)	69.64 ± 14.46	68.03 ± 11.65	68.44 ± 12.35
WC (cm)	85.52 ± 13.04	87.03 ± 10.25	89.74 ± 11.83
BMI (kg/m^2)	25.22 ± 4.05	25.46 ± 4.7	25.46 ± 3.33
T3 (µIU/mL)	1.204 ± 0.172	1.182 ± 0.204*	1.041 ± 0.246¥
T4 (µIU/ml)	7.303 ± 1.246	6.837 ± 1.551	5.15 ± 1.361¥
TSH (µIU/mL)[a]	2.3 (1.5–3.4)	5.7 (4.9–7.01)*	12.6 (11.23–15.94)¥
FPG (mg/dL)	96.8 ± 6.69	97.54 ± 6.77	98.48 ± 5.84
Insulin (µIU/mL)	16.88 (9.84–24)	19.35 (12.83–27.92)	19.6 (13.17–38.06)¥
HOMA-IR	3.6 (2.25–5.63)	4.28 (2.99–7.42)	4.94 (3.07–9.11)¥
ISI	0.317 ± 0.022	0.306 ± 0.026	0.304 ± 0.023¥
TG (mg/dL)[a]	127 (107–185)	123 (84–165)	140 (115–178)

Data are mean ± SD unless indicated; [a]median (interquartile range); *$p < 0.05$, comparison of ET with SCH; ¥$p < 0.05$, comparison of ET with OH

Table 2: Correlations of thyroid profile with anthropometric indices

Parameters	*OH*		*SCH*		*ET*	
	BMI (kg/m^2)	*WC (cm)*	*BMI (kg/m^2)*	*WC (cm)*	*BMI (kg/m^2)*	*WC (cm)*
T3 (ng/mL)	0.082	–0.179	0.089	–0.083	–0.276	–0.225
T4 (µg/mL)	0.011	0.047	–0.169	–0.325	0.66	0.172
TSH[a] (µIU/mL)	0.006	–0.047	0.015	–0.099	–0.189	–0.168

Data presented as Pearson's correlation unless otherwise indicated; [a]Spearman correlation

Conclusion

Though high insulin levels were observed in patients with SCH and OH, there was no statistically significant association between TSH levels and QUICKI. This could be attributed to the fact that the ISI of euthyroid subjects was decreased, too. Stringent categorization of subjects based on metabolic syndrome criteria and comparison with thyroid hormones may provide insight into the correlation.

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ORIGINAL ARTICLE

Study of Oral Hypoglycemic Agent-induced Hypoglycemia in Type 2 Diabetes Mellitus in a Tertiary Care Center

Milind Gaikwad[1*], Digvijay Chavan[2], Raghuvamsi M Pasupulati[3], Sayali Darunde[4], Sangeeta Pednekar[5], Charulata Londhe[6], Dharmendra Pandey[7]

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Abstract

Introduction: Diabetes prevalence is increasing rapidly; estimates from the International Diabetes Federation put the number at 381 million people have diabetes. Hypoglycemia is a commonly encountered complication in diabetic patients, which, in the short-term, can lead to mortality and, in the long-term, precludes maintenance of euglycemic control. Over 65.2 % of patients have reported at least one incidence of severe and nonsevere hypoglycemia when on oral hypoglycemic agents (OHA) at an annual crude incidence density of 35.1 events per year per person. Insulin more commonly causes hypoglycemia than OHA. However, this study was done with the aim of studying the hypoglycemia specifically caused by OHAs—clinical profile of patients, medications causing hypoglycemia, and the outcome.

Materials and methods: This prospective observational study was conducted in the Department of Medicine at a tertiary care hospital in Western Maharashtra. Data was collected over a period of 18 months from Indoor patients on admission having hypoglycemic symptoms with strip blood sugar levels of <70 and on OHAs. Patients on insulin were excluded from the study.

Results: There were 60 patients with hypoglycemia with a mean age of 53.65 years and a higher incidence of hypoglycemia in females, 35 (58.3%) compared to males. There was a statistically significant difference between outcome (i.e., discharged or death) and urine protein–creatinine ratio (UPCR), a deranged liver function, that is, serum albumin, serum glutamic oxaloacetic transaminase (SGOT)/aspartate transaminase, and serum glutamic pyruvic transaminase (SGPT)/alanine transaminase ($p < 0.05$). However, there was no statistically significant difference between outcome (discharged or death) and mean age, gender, mean duration of diabetes mellitus (DM), GCS scoring, and drug type of study subjects ($p > 0.05$).

Conclusion: The risk factors for hypoglycemia were middle-aged patients. Females are at higher risk of hypoglycemia than men. Hypoglycemia due to OHAs is known to have a recurrence of hypoglycemia due to the long half-life of the drug; however, patients who were hospitalized were well monitored and did not have any recurrence of hypoglycemia. Deranged liver function or raised UPCR have high mortality after OHA-induced hypoglycemia.

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Introduction

Globally, an estimated 422 million adults are living with diabetes mellitus (DM), according to the World Health Organization. Diabetes prevalence is increasing rapidly; the International Diabetes Federation puts the number at 381 million people having diabetes. The number is projected to almost double by 2030. Type 2 diabetes makes up about 85–90% of all cases. Increases in the overall diabetes prevalence rates largely reflect an increase in risk factors for type 2, notably greater longevity and being overweight or obese to treat type 2 diabetes.[1] In India, there are 77 million people with diabetes and 25 million per diabetics.

Definition of hypoglycemia, according to American Diabetes Association (ADA): hypoglycemia is defined by the presence of hypoglycemic symptoms with low sugar on a blood test, which improves with the administration of sugar.[2]

Hypoglycemia remains a major barrier to tight glycemic control and a common complication of diabetes treatment. For patients with type 1 diabetes and type 2 DM (T2DM), hypoglycemia remains one of the most enduring issues.[3]

Over 65.2 % of patients have reported at least one incidence of severe and nonsevere hypoglycemia when on oral hypoglycemic agents (OHAs) at an annual crude incidence density of 35.1 events per year per person.[4]

Hypoglycemia tops the list of hurdles in preventing tight glycemic control and is often observed in patients on insulin or insulin secretagogue (like sulfonylurea) therapies. Recent studies have demonstrated that though strict glycemic control results in reduced microvascular complications, it is associated with increased cardiovascular events and even mortality (ACCORD).[5]

Further recurrent episodes of hypoglycemia result in hypoglycemia unawareness.[6] Hypoglycemic episodes may result in significant psychosocial dysfunction and lower quality of life. In spite of the knowledge about the importance of hypoglycemia, it is still a relatively neglected complication in diabetes care in our setting.[7]

Given the significance of hypoglycemia in patients with T2DM and the limited knowledge of its frequency in patients on OHAs, this study was conducted with the aim to evaluate OHAs induced hypoglycemia in T2DM with respect to clinical profile, risk factors, and outcome of patients having OHA-induced hypoglycemia.

Materials and Methods

We conducted a prospective observational study at a tertiary care hospital in Mumbai, Maharashtra, India, between April 2019 and September 2020 after obtaining clearance from the local ethical committee. Around 60 type 2 diabetic patients on admission having hypoglycemic symptoms with strip blood sugar levels of <70 and OHAs were enrolled in the study. Hypoglycemia in nondiabetic and type one diabetic patients found to have other drugs which may cause hypoglycemia (like β-blocker, aspirin, and tricyclic antidepressants [TCA]), and patients on insulin therapy alone or along with OHA were excluded from the study as insulin is the most common cause of hypoglycemia.

Demographic details of the patients, like age, sex, occupation, and residence were noted. Disease history in detail of duration, a medication used in detail, and a previous episode of hypoglycemia, presenting complaints with duration, vitals were assessed. A detailed examination was done. Patients were classified into mild,

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moderate, and severe hypoglycemia based on ADA classification.

Routine investigations like complete blood count, renal function test (RFT), serum electrolytes, liver function test (LFT), blood sugar levels, urine routine microscopy, glycated hemoglobin (HbA1c), serum lipid profile, and urine protein–creatinine ratio (UPCR) were done.

The outcome was studied on the basis of recovery, morbidity, mortality, and change of treatment regimen.

Statistical Analysis

The collected data were entered into a Microsoft Office Excel spreadsheet and analyzed. Ratios and percentages were used for analysis. Excel functions like mean, standard deviation (SD), and *t*-test were used. Student's *t*-test and Chi-squared test were used to determine the statistical difference between variables. Results were considered significant if the *p*-value was <0.05.

Results

A total of 60 type 2 diabetic patients on admission having hypoglycemic symptoms with strip blood sugar levels <70 and on OHAs were recruited in the study. Out of 60 study subjects, 35 (58.3%) were female and 25 (41.7%) were male. The demographic and baseline characteristics of the study subjects are presented in Table 1. The mean ± SD age was 53.65 ± 10.52. ranging from 38- to 91-year-old subjects. The majority of study subjects, 27 (45%), had a duration of DM of ≤5 years, followed by 17 (28.3%) had 6–10 years, nine (15%) had 11–15 years, and seven (11.7%) had >15 years of duration of DM, respectively as shown in Figure 1.

The clinical profile of study subjects is presented in Table 2. The majority of study subjects, 50 (83.4%), had altered level of consciousness, six (10%) had giddiness, two (3.3%) patients had left-sided hemiparesis, and one patient (1.7%) had right-sided hemiparesis, one (1.7%) patient had only sweating palpitation. According to the grade of hypoglycemia, most of the study subjects, 50 (83.3%), had severe hypoglycemia, followed by nine (15%) had moderate hypoglycemia, and one (1.7%) had mild hypoglycemia. Mild hypoglycemia: 70–54 mg/dL blood sugar, moderate hypoglycemia: <54 mg/dL of the blood sugar level, and severe hypoglycemia: depressed mental status.[4] A total of 50 (83.3%) study subjects had neurogenic symptoms, and 59 (98.3%) had neuroglycopenic symptoms. Neurogenic symptoms like tremors, palpitation, sweating, anxiety, hunger, and parasthesia. While neuroglycopenic symptoms like confusion, cognitive symptoms, weakness, seizure, or coma. According to the Glasgow Coma Scale (GCS) classification, the majority of study subjects, 45 (75%), had a 3–8 score, 12 (20%) had a GCS of 13–15, and three (5%) had a 9–12 GCS scoring.

Table 3 shows the type of medication the patient was on. Most of the study subjects were on multiple pills: 30 (50%) followed by 24 (40%) were on fixed-drug combination (FDC) and six (10%) were on single pills. The most common class of drug which causes hypoglycemia are sulfonylureas or glinides. Metformin, thiazolidinediones, α-glucosidase inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, sodium-glucose cotransporter 2 (SGLT-2) inhibitors, and dipeptidyl peptidase IV (DPP-IV) inhibitors do not cause hypoglycemia.

Of 24 patients on FDC, 12 patients were on metformin 500 mg + glimepiride 1 mg, five patients were on metformin 500 mg + glimepiride 1 mg, four patients on metformin 1000 mg + glimepiride 2 mg, two patients on metformin 500 mg + glibenclamide 5 mg, and one patient on metformin 500 mg + glimepiride 1 mg + voglibose 0.2 mg. Daily doses were once or twice a day of these FDCs.

Of 30 patients on multiple OHA, 11 were on metformin 500 mg and glimepiride 1 mg, eight patients were on metformin 500 mg and glibenclamide 5 mg, four patients were on metformin 500 mg + gliclazide 30 mg, four were on metformin 500 mg + gliclazide 60 mg, and two patients on metformin 1000 mg + tablet glimepiride 2 mg. One patient was on metformin 500 mg + glibenclamide 5 mg + vildagliptin 50 mg. These medications were taken once or twice a day.

Of six patients on a single drug, two were on gliclazide 60 mg per day, two patients were on glimepiride 2 mg per day, one patient was on gliclazide 30 mg per day, and one patient was on metformin 1500 mg per day.

Total patients on sulfonylureas: 59.

Total patients on biguanides (metformin): 55.

Table 1: Baseline and demographic profile of study subjects

Baseline and demographic profile	*Number of study subjects*	*Percentage*
Age (mean ± SD)	53.65 ± 10.52	
Gender		
Male	25	41.7%
Female	35	58.3%
Duration of DM (years)		
≤5	27	45.0%
6–10	17	28.3%
11–15	9	15.0%
>15	7	11.7%

Table 2: Clinical profile of study subjects

Clinical profile	*Number of study subjects*	*Percentage*
Symptoms		
Altered consciousness	50	83.4%
Giddiness	6	10%
Left-sided hemiparesis	2	3.3%
Right-sided hemiparesis	1	1.7%
Only sweating and palpitation	1	1.7%
Hypoglycemia		
Mild hypoglycemia (blood sugar 70–54 mg/dL)	1	1.7%
Moderate hypoglycemia (blood sugar <54)	9	15%
Severe hypoglycemia (Altered sensorium)	50	83.3%
Neurogenic symptoms	50	83.3%
Neuroglycopenic symptoms	59	98.3%
GCS		
3–8	45	75%
9–12	3	5%
13–15	12	20%

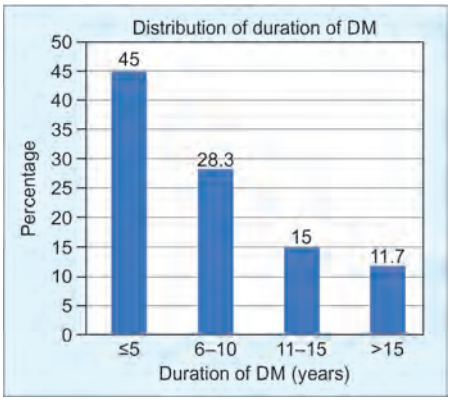

Fig. 1: Distribution of duration of DM

Table 3: Type of medication

Drug type		
FDC	24	40%
Multiple pills	30	50%
Single pill	6	10%

Total patients on dipeptidyl peptidase 4 inhibitors: One

Total patients on α-glucosidase inhibitors (voglibose): One

The various laboratory data are presented in Table 4. Blood glucose at admission was 37.28 mg/dL on average, which ranged from 15 to 68 mg/dL. After withdrawing OHAs, the patient had an increase in blood sugar on average to 170.74 mg/dL on day 2 and 200.34 mg/dL on day 4.

In RFTs, 26 patients had a raised creatinine (glomerular filtration rate below 60 mL/minute/1.73 m^2), and patients had an average creatinine of 1.5 mg/dL (glomerular filtration rate: 42 mL/minute/ 1.73 m^2), however, the range is wide from 0. to 3.9 mg/dL.

Both sodium and potassium were, on average, in the normal range; mean sodium was 133.65 mg/dL and potassium 3.98 mg/dL.

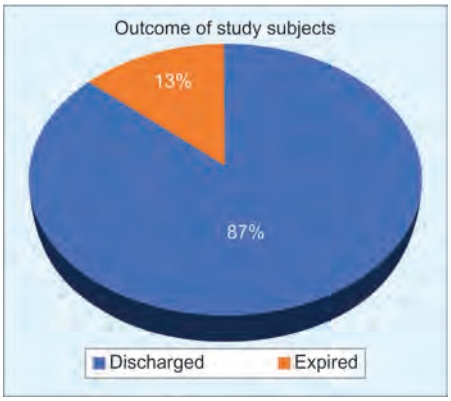

Fig. 2: Distribution of study subjects according to outcome

Table 4: Distribution of various laboratory data

Parameters	*Mean ± SD*
Blood glucose at admission	37.28 (13.35) mg/dL
Blood glucose day 2	170.74 (54.76) mg/dL
Blood glucose day 4	200.34 (75.72) mg/dL
BUN	21.07 (6.73) mg/dL
Creatinine	1.50 (0.71) mg/dL
Sodium	133.65 (5.75) mmol/L
Potassium	3.98 (0.50) mmol/L
Total bilirubin	1.01 (0.27) mg/dL
Total protein	7.20 (0.68) gm/dL
Serum albumin	3.59 (0.66) gm/dL
SGOT	57.17 (60.96) U/L
SGPT	69.43 (127.67) U/L
HbA1c	7.35 (1.52)%
UPCR	1.990 (1.655)
Total cholesterol	224.90 (74.95) mg/dL
Triglycerides	336.23 (135.78) mg/dL

In the LFT, most parameters were, on average, in the normal range. The mean total serum bilirubin was 1.01 mg/dL, the mean total serum protein was 7.20 gm/dL, and the mean serum albumin was 3.59 mg/dL; however, liver enzymes were mildly raised, mean serum glutamic-oxaloacetic transaminase (SGOT) or aspartate transaminase was 57.1 mg/dL and mean SGOT or alanine transaminase was 69.43 mg/dL.

Mean HbA1c was 7.35%, with a range from 5.7 to 14.3%.

The mean UPCR was 1.99 mg/dL.

The outcome of the study was assessed as discharged or expired (Fig. 2). Out of 60 patients, 52 were discharged, that is, 86.7%, and eight expired, that is, 13%.

Eight patients who expired were due to complications of hypoglycemia. Five subjects developed hypoglycemic encephalopathy (or hypoglycemic coma), and three patients died of aspiration pneumonia.

The association of outcome with baseline and demographic characteristics is given in Table 5. There was no statistically significant difference between outcome and mean age, gender, mean duration of DM, Glasgow Coma Scale (GCS) scoring, and drug type of study subjects ($p > 0.05$).

The association of outcome with clinical profile and lab parameters is given in Table 6. Among 60 patients who had hypoglycemia, their sugar at admission, on day 2 or 4, did not correlate with the outcome as discharged or expired ($p > 0.05$). RFT [i.e., blood urea nitrogen (BUN) and creatinine] and outcome did not show any significant difference ($p > 0.05$). There was a statistically significant difference with serum albumin, SGOT/aspartate transaminase, and SGPT/alanine transaminase between the discharged and the expired, with a *p*-value of <0.001, <0.003, and <0.001, respectively. Unpaired *t*-test showed a statistically significant difference (*p*-value of 0.021) seen between UPCR, with the mean UPCR of expired patients being 3.328 mg/dL and discharged patients being 1.80 mg/dL.

Table 5: Association of outcome with baseline and demographic characteristics

Baseline and demographic characteristics	*Discharged, N = 52*	*Expired; N = 8*	*p-value*
Mean age (years)	54 ± 10.93	51.38 ± 7.53	0.83
Female	28 (80%)	7 (20%)	0.07
Male	24 (96%)	1 (4%)	
The mean duration of DM (years)	8.41 ± 5.89	9 ± 5.75	0.68
GCS on admission			
3–8	39 (86.7%)	6 (13.3%)	0.52
9–12	2 (66.7%)	1 (33.3%)	
13–15	11 (91.7%)	1 (8.3%)	
Drug type			
FDC	20 (83.3%)	4 (16.7%)	0.56
Multiple pills	26 (86.7%)	4 (13.3%)	
Single pill	6 (100%)	0 (0%)	

Table 6: Association of outcome with clinical profile and lab parameters

Clinical profile and lab parameters	*Discharged; N = 52*	*Expired; N = 8*	*p-value*
Mean blood sugar (mg/dL)			
At admission	38.33 (13.47)	30.50 (10.98)	0.124
On day 2	173.98 (54.29)	142.67 (55.43)	0.187
On day 4	199.38 (77.76)	208.67 (59.84)	0.779
RFT			
Mean BUN (mg/dL)	21.00 (6.95)	21.50 (5.45)	0.847
Mean creatinine (mg/dL)	1.429 (0.665)	1.950 (0.914)	0.056
LFT			
Mean total bilirubin (mg/dL)	0.994 (0.212)	1.113 (0.559)	0.268
Mean total protein (gm/dL)	7.20 (0.71)	7.17 (0.49)	0.901
Mean albumin (gm/dL)	3.71 (0.55)	2.76 (0.78)	<0.001
Mean SGOT (IU)	48.13 (24.65)	115.88 (149.51)	0.003
Mean SGPT (IU)	46.67 (30.15)	217.38 (319.21)	<0.001
Mean UPCR (mg/mg)	1.802 (1.504)	3.328 (2.168)	0.021*

A total of 52 patients who survived had regained full sensorium at discharge. Eight patients who expired were due to complications of hypoglycemia. Five subjects developed hypoglycemic encephalopathy (or hypoglycemic coma), and three patients died of aspiration pneumonia.

Discussion

The present prospective observational study was done among 60 type 2 diabetic patients, on hospital admission having hypoglycemic symptoms with strip blood sugar levels <70 and on OHAs with the objective of finding predisposing factors and outcome of hypoglycemia due to OHAs in T2DM patients.

In this study, we found the mean age of study participants was 53.65 years, with a higher incidence of hypoglycemia in females 35 (58.3%). Similarly, Shorr et al.[8] and Samaya et al.[9] found more incidence of hypoglycemia in females, 82 and 73.3%, respectively.

The mean duration of diabetes in our study was 8.49 years, and Samya et al.[9] found 6.82 years.

We found the maximum number of patients (50) had come to the emergency in an altered sensorium (83.4%). The second most common symptom was giddiness, which affected six patients, accounting for 10%, that is, six patients. Three patients (5%) had hemiparesis (two left-sided and one right-sided). One patient had a fever. The study by Shorr et al.[8] studied symptoms of hypoglycemia. Alerted sensorium (49%), lethargy (34%), irrational behavior (6%), seizure (5%), and transient ischemic attack (10%).

We have tried to study if there is any difference between the outcome of having a FDC vs having separate tablets of OHAs. Out of the 60 patients, six patients were on only a single OHA, and 54 patients were on two or more hypoglycemic agents, either as a FDC or as different pills. The most common class of drugs that cause hypoglycemia are sulfonylureas or glinides, but in our study, 59 patients were on sulfonylureas, and no patient in our study was on glinides. Metformin, thiazolidinediones, α-glucosidase inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors, and DPP-IV inhibitors do not cause hypoglycemia. Among eight patients who died in the study, a FDC of multiple pills or a single pill did not make any difference in terms of outcome in our study ($p > 0.05$).

Among the 60 patients with hypoglycemia, the maximum had a Glasgow Coma Scale (GCS) of 3–8, that is, 45 patients or 75% of patients. Only three patients (5%) had a GCS between 9 and 12. A total of 12 patients (20%) had a good GCS between 13 and 15. There was no statistically significant difference between GCS at admission and outcome as expired (eight patients) vs discharged (52 patients) ($p > 0.05$).

Of the various laboratory data collected, the mean blood glucose at admission was 37.28 mg/dL, which ranged from 15 to 68 mg/dL. After withdrawing OHAs, the patient had an increase in blood sugar on average to 170.74 mg/dL on day 2 and 200.34 mg/dL on day 4. For patients who had hypoglycemia, their sugar at admission, on day 2 or on day 4, did not correlate with the outcome as discharged or expired ($p > 0.05$).

Shorr et al.[8] and Burg et al.[10] reported that the mean blood sugar level on admission was 33 and 40 mg/dL, respectively.

In the RFT, the mean serum creatinine was 1.5 of the 60 subjects, with a mean glomerular filtration rate (GFR) of 42 mL/minute/1.73 m^2. The number of subjects with creatinine >2 was 11 (18%) in our study and 16% in the Shorr et al. study. Deranged renal function did not correlate with the outcome of the patients as discharged or expired; however, 26 patients (43.3%) had an early renal involvement GFR below 60.

Subjects with creatinine ≥2 mg/dL (n = 11) were put on insulin. Of subjects with a creatinine of 1.1–1.9 mg/dL, 28% were put on insulin, 7% expired, and 18% were put off any anti-diabetics. This is because in diabetic patients with renal failure, the half-life of insulin increases, leading to more risk of hypoglycemia.

Liver function tests (LFT) showed that patients in the study had normal total bilirubin and total albumin. However, transaminases like SGOT and SGPT were elevated in a few of them, and the mean SGOT and SGPT were 57.17 and 69.43 IU/dL, respectively.

However, nine patients (15%) had SGOT and SGPT raised (above 45 U/L); in our study, raised transaminase is a risk factor for mortality in hypoglycemia due to OHAs.

Mean HbA1c was 7.35%, with a range from 5.7 to 14.3% in our study. HbA1c is not a risk factor for mortality in hypoglycemic patients; however, strict diabetic control is associated with the risk of hypoglycemia. Burge et al.[10] reported mean HbA1c was 8.6%.

The mean UCR is 1.99 mg/dL. UPCR with the mean UPCR of expired patients was 3.328 mg/dL and discharged patients being 1.80 mg/dL. This shows that proteinuria correlates with the outcome of the patients ($p < 0.05$).

Eight patients who expired were due to complications of hypoglycemia. Five subjects developed hypoglycemic encephalopathy (or hypoglycemic coma), and three patients died of aspiration pneumonia.

In conclusion, patients, mainly middle-aged patients and females, are at higher risk of hypoglycemia than men. Hypoglycemia due to OHAs is known to have a recurrence of hypoglycemia due to the long half-life of the drugs; however, patients who were hospitalized were well monitored and did not have any recurrence of hypoglycemia. Mortality correlation shows that the deranged LFT has a poor outcome. Proteinuria is a significant prediction for mortality in such patients.

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ORIGINAL ARTICLE

Androgen Deficiency in Aging Males (ADAM) Score as a Predictor of Total Testosterone Levels in Type 2 Diabetes Mellitus: A Prospective, Cross-sectional Study

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Abstract

Objective: Assessment of Androgen Deficiency in Aging Males (ADAM) questionnaire in predicting serum testosterone levels in type 2 diabetes mellitus (T2DM).

Materials and methods: A single centre, prospective, cross-sectional epidemiological study in 250 male individuals with T2DM. ADAM questionnaire and serum total testosterone (TT) levels were analyzed for correlation using a Chi-squared test. Jaccard analysis to evaluate the concordance and dissimilarity between ADAM score and TT levels, providing insights into ADAM's predictive ability for testosterone levels.

Results: The mean age of the study population was 49.1 ± 7.8 years. The mean duration of diabetes was 6.2 ± 5.1 years. 27.6% were diagnosed with hypogonadism, while 72.4% were eugonadal.

The mean age was 51.1 and 48.4 years in the hypogonadal and eugonadal cohorts, respectively ($p < 0.02$). The mean TT in the hypogonadal cohort was 220.6 ± 61.3 ng/dL, and in the eugonadal cohort was 475.4 ± 152.9 ng/dL ($p < 0.001$). The mean body mass index (BMI) in the hypogonadal cohort was 26.5 ± 4.0 kg/m^2, and in the eugonadal group was 25.2 ± 3.6 kg/m^2 ($p < 0.02$). Chi-square analysis established a strong positive correlation between the positive ADAM score and hypogonadism ($p < 0.011$). Of the 69 hypogonadal subjects, 84.05% had a positive ADAM score, yielding a sensitivity of 84.05% in detecting hypogonadism with a specificity of 32.04%.

Conclusion: The ADAM questionnaire is a practical and cost-effective initial screening tool for identifying symptoms suggestive of testosterone deficiency. It has high sensitivity in identifying men with hypogonadism, while caution must be in place as it has a very low specificity. In resource-poor settings, ADAM score could be a clinical marker of hypogonadism.

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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder linked to insulin resistance and impaired glucose regulation. Its prevalence in India is rising, with around 77 million cases in 2019. Alarmingly, about 57% of cases remain undiagnosed.[1] Besides known complications like cardiovascular disease, nephropathy, neuropathy, and retinopathy, emerging evidence suggests a strong connection between T2DM and male hypogonadism.[2–4]

Male hypogonadism is a condition characterized by low testosterone levels, resulting in various clinical manifestations, including reduced libido, erectile dysfunction, decreased muscle mass, fatigue, and depressive symptoms.[5] A large-scale study conducted on 1,849 subjects highlighted the high prevalence of low testosterone levels among men with T2DM.[6] Therefore, this condition has significant implications for the overall health and well-being of affected individuals, including sexual and reproductive dysfunction, decreased bone mineral density, reduced energy levels, increased visceral adiposity, impaired insulin sensitivity, and an elevated risk of cardiovascular disease.[3] Despite these consequences, hypogonadism in the context of diabetes receives minimal attention from both treating physicians and patients, largely due to sociocultural stigmas.

Although serum total testosterone (TT) levels are considered the gold standard for diagnosing hypogonadism, there are certain challenges associated with its routine use. The high cost and limited availability of laboratory testing for TT levels in peripheral healthcare settings pose significant barriers to widespread use in clinical practice.[7] This limitation highlights the need for alternative approaches to predict TT levels in a more accessible and cost-effective manner. Importantly, the assessment of symptoms related to androgen deficiency (AD) also plays a vital role in identifying individuals at risk.[8] One commonly used clinical screening tool is the Androgen Deficiency in Aging Males (ADAM) Questionnaire. This questionnaire comprises a series of questions that assess various symptoms associated with testosterone deficiency, such as diminished libido, erectile dysfunction, decreased energy, and changes in mood.[9,10] This questionnaire would/might offer a simple and practical method for initial screening, enabling healthcare practitioners to identify individuals who may be at risk of hypogonadism.

The aim of this study is to assess the ADAM score, derived from the ADAM questionnaire, as a reliable predictor of serum testosterone levels in males with T2DM. Through the ADAM questionnaire, individuals with high ADAM scores can be identified as potentially having testosterone deficiency. By identifying individuals at risk of testosterone deficiency through the ADAM score, healthcare practitioners can initiate appropriate management strategies promptly and provide a better quality of life. This approach will lead to improved recognition and management of hypogonadism in T2DM, ultimately enhancing the quality of life and overall health outcomes for affected individuals. By addressing this often neglected aspect of diabetes care, we would improve the overall well-being of male hypogonadism with T2DM.

Materials and Methods

Study Design

This was a single-center, a prospective, and cross-sectional epidemiological study conducted at Basaveshwar Teaching and General Hospital, affiliated to Mahadevappa Rampure (MR) Medical College, Kalaburagi,

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Karnataka, for a period of 18 months, from March 2021 to August 2022 to assess ADAM score as a potential predictor of TT levels in men with T2DM.

Sample Size and Recruitment

Prior to obtaining written informed consent from the patients in their own vernacular language for enrollment into the study, all patients were fully informed about the objective and procedures of the study. Those individuals who met the eligibility criteria and expressed their willingness to provide informed consent were enrolled in the study.

A total of 250 males aged between 18 and 60 years who were attending the outpatient department services during the specified study period and had a confirmed diagnosis of T2DM were included in the study using convenience sampling techniques. Specifically, the inclusion criteria targeted known diabetic males who were on either oral hypoglycemic drugs or a combination of oral hypoglycemic drugs and insulin. On the contrary, several exclusion criteria were implemented to maintain the homogeneity of the study population and avoid confounding factors. Individuals with T1DM or T3c DM, as well as those with newly diagnosed diabetes or prediabetes, were excluded from the study. Additionally, individuals with primary or secondary hypogonadism, panhypopituitarism, hyperthyroidism, chronic liver disease, chronic kidney disease, chronic infections such as human immunodeficiency virus or tuberculosis, known malignancies or undergoing chemotherapy or radiotherapy, long-term corticosteroid treatment, chronic alcoholism, or individuals with previous/current medications known to interfere with testosterone secretions such as opioids, antidepressants, hallucinogens, androgen or antiandrogen therapy were also excluded. Furthermore, individuals with a duration of diabetes of <1 year were excluded to focus on individuals with established T2DM.

With an interviewer-administered proforma, which included a prestructured questionnaire, relevant demographic and anthropometric information and medical history were obtained from the study subjects. Central obesity (abdominal obesity) was assessed by waist circumference (WC) measured at a point midway between the inferior border of the costal margin and the iliac crest in the midaxillary line to the nearest 0.5 cm. Two brachial blood pressure (BP) measurements were taken at least 10 minutes apart, and their mean was calculated. Subjects whose BP readings were ≥140/90 mm Hg or who were currently on antihypertensive medication were regarded hypertensive.

Laboratory Investigation

Fasting plasma glucose, postprandial plasma glucose, glycated hemoglobin (HbA1c), triglycerides, total cholesterol, low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) levels were measured. Morning (between 8:00 and 10:00 am) serum TT was measured in all the study subjects after an overnight fast of 10 hours, using an enzyme-linked fluorescent assay with a measurement range of 0.05–13.50 ng/mL using commercially available kits TOSOH. Low serum TT level was defined as serum TT <3 ng/mL (300 ng/dL). That study subjects with positive ADAM scores and serum TT <3 ng/mL were defined as having hypogonadism, while those who had serum TT >3 ng/mL (300 ng/dL) irrespective of symptoms were regarded eugonadal.

ADAM Questionnaire-based Clinical Assessment

The ADAM questionnaire was used for the clinical evaluation of AD symptoms and, therefore, probable hypogonadism. Briefly, it consists of 10 questions describing the most common symptoms suggestive of hypogonadism and covers three major dimensions mainly energy, mood and sexual disorders (Fig. 1). A positive ADAM test is considered if the participant answers "yes" to any of the sexual questions (such as decreases in libido or strength of erections) or any other three nonspecific questions including fatigability, decreases in muscle strength, mood changes, and loss of height (or if a patient gives an affirmative answer to either question 1 or 7 or any three other questions, he is considered to have a positive ADAM score).

Data Management

Using Medeva (https://medeva.io), analytics embedded Electronic Health Record platform, collected data from study pro forma and ADAM questionnaire was compiled and entered into a secure electronic database. Data entry was performed by trained personnel using a double-entry method to minimize errors. The database was regularly backed up and secured to maintain data integrity and confidentiality.

Ethical Consideration

The study protocol (HKES/MRMCK/IEC/210287) received ethical approval from the Institutional Ethics Committees (IEC), ensuring compliance with international guidelines, including the International Conference on Harmonisation Good Clinical Practice, the Declaration of Helsinki, and the ethical guidelines set forth by the Indian Council of Medical Research. The study was conducted in adherence to ethical standards and regulations to safeguard the rights, welfare, privacy and confidentiality of the study participants. Written informed consent was obtained from each individual, indicating their voluntary participation and understanding of the study requirements.

Statistical Analysis

The statistical analysis of the collected data was performed using Statistical Package for the Social Sciences software, version 20.0. Descriptive statistics such as frequencies and percentages were used to summarize

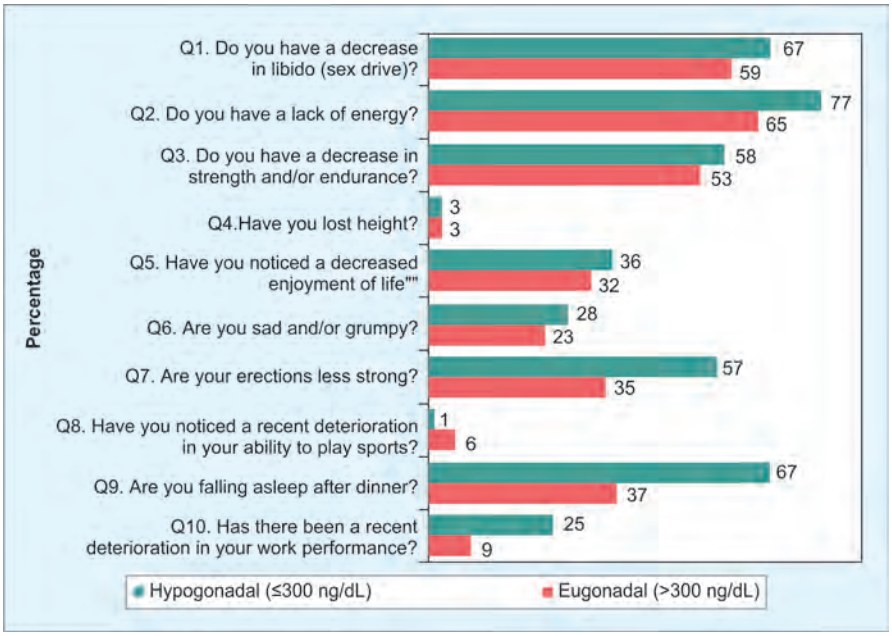


Fig. 1: Association of positive ADAM score and hypogonadism in T2DM patients

demographic and clinical characteristics (discrete variables) of the study population, while mean with standard deviation (SD) or medians or mean ranks were employed for continuous variables, as appropriate. To evaluate the relationship between TT and body mass index (BMI) or duration of diabetes, a nonparametric test of correlation, Spearman's test, was employed/used for nonnormally distributed data. For qualitative analysis, the Chi-squared test was employed to examine/assess associations between ADAM scores and testosterone levels. The significance level was set at $p < 0.05$, indicating statistical significance.

Results

Baseline Data and Anthropometric Characteristics

Among 250 study subjects, hypogonadism and eugonadism were evident in 27.6% (n = 69) and 72.4% (n = 181), respectively, considering serum TT level ≤300 ng/dL as a reference value for hypogonadism. The percentage of patients with hypogonadism progressively increased with age, from 1.4% in the age <35 years to 40.6% in the age ≥55 years. However, this phenomenon was not consistent in eugonadal subjects. The mean age was 51.1 and 48.4 years in the hypogonadal and eugonadal cohorts, respectively. Among them, >74% of the patients were older than 45 years of age. Notably, compared to eugonadal subjects, the average age of hypogonadal subjects was significantly higher ($p < 0.02$).

A similar significant difference was noted in the context of average BMI value. Among total study subjects, >43.0% were overweight in both cohorts, while in the context of obesity, the percentage of hypogonadal subjects was numerically higher (18.8%) than eugonadal subjects (8.3%). The detailed demographic data are given in Table 1. Table 2 depicts the clinical and biochemical parameters of the study cohorts. Surprisingly, the age of onset and average duration of T2DM did not affect the development of hypogonadism, although it has been considered an important causative factor for the development of AD. Moreover, no significant difference was observed between the two study cohorts in the context of biochemical characteristics.

Prevalence and Pattern of Hypogonadism in Various Comorbidities and Family History

Figure 2 and Table 3 depict variations in the prevalence of hypogonadism with comorbidities and family history of the study cohort. About 57 and 33% of the

Table 1: Baseline demographic and anthropometric characteristics of the study population (n = 250)

Variables	*Hypogonadal (≤300 ng/dL) (N = 69)*	*Eugonadal (>300 ng/dL) (N = 181)*	*p-value*
Age distribution/range in years, *n* (%)			
Mean age in year (SD)	51.1 (7.7)	48.4 (7.7)	0.02*
<35	1.4%	4.4%	
35–44	21.7%	21.5%	
45–54	36.2%	48.6%	
≥55 years	40.6%	25.4%	
BMI			
Average BMI (kg/m^2), mean (SD)	26.5 (4.0)	25.2 (3.6)	0.02*
BMI classification (category) (kg/m^2)			
Underweight—BMI < 19.0	–	4.4%	
Normal weight—BMI = 19.0–24.9 kg/m^2	34.8%	43.6%	
Overweight—BMI = 25.0–29.9 kg/m^2	46.4%	43.6%	
Obese—BMI ≥ 30.0 kg/m^2	18.8%	8.3%	
WC (cm), mean (SD)	98.8 (9.9)	94.9 (9.2)	0.02*

*Signifies that the *p*-value is <0.05, which is significant

Table 2: Clinical and biochemical characteristics of the study population (n = 250)

Variables	*Hypogonadal (≤300 ng/dL) (N = 69)*	*Eugonadal (>300 ng/dL) (N = 181)*	*p-value*
Diabetes			
Average age of onset of T2DM (years)	43.9	42.3	0.27
Duration of diabetes in years, *n* (%)			
1–5	50.7%	58.6%	–
6–10	30.4%	26.5%	–
11–15	7.2%	9.9%	–
> 15	11.6%	5.0%	–
Average duration of diabetes (year)	7.0	5.9	0.16
Biochemical characteristics			
FBS (mg/dL)	145.4 (50.4)	151.8 (62.7)	0.4
HbA1c (%)	8.8 (2.1)	8.7 (2.2)	0.74
Triglycerides (TG), mg/dL	184.0 (114.7)	170.8 (80.5)	0.38
eGFR (mL/ minute/1.73 m^2)	93.5 (22.5)	96.5 (21.8)	0.34
Total cholesterol, mg/dL	187.7 (44.9)	177.9 (41.7)	0.12
LDL	115.7 (43.1)	116.6 (34.9)	0.9
HDL	37.4 (10.5)	38.3 (22.6)	0.69

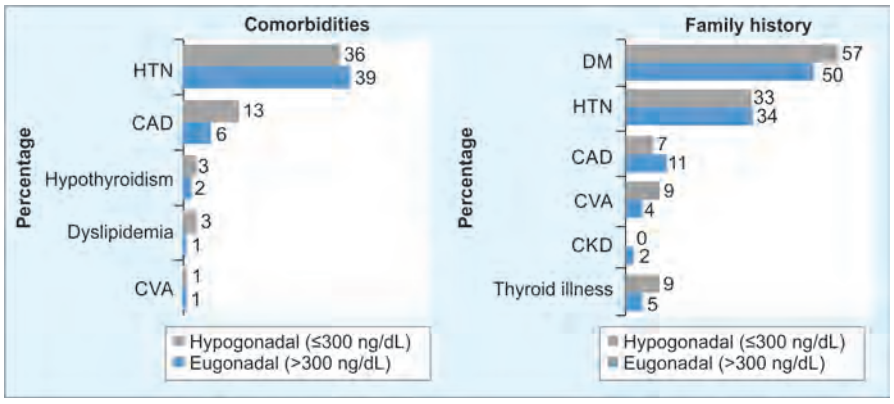


Fig. 2: Graphical representation of the prevalence of hypogonadism in comorbidities and family history

hypogonadal subjects had a family history of T2DM and hypertension, respectively. Further, hypertension and coronary artery diseases (CADs) were the most prevalent comorbidities observed in hypogonadal subjects. The majority of the subjects had diabetes lasting <5 years. Overall, no noticeable/remarkable difference was observed between the groups in terms of comorbidities and family history.

Association of Positive ADAM Score and Hypogonadism

The ADAM questionnaire is used for the clinical evaluation of androgen (testosterone) deficiency. We hypothesized that whether a positive or "yes" response to ADAM's questionnaire to question 1 (decreases in libido) or question 7 (strength of erections), or any three nonspecific questions, including fatigability, decreases in muscle strength, mood changes, and loss of height may predict testosterone levels. To test this hypothesis, all 250 study patients were subjected to the ADAM's questionnaire. Herein, the percentage of subjects with hypogonadism and eugonadism were compared according to the presence or absence of the symptoms of AD based on participant's "yes' or "no" answers to the ADAM questionnaire. As shown in Figure 1, except for question 8, the percentage of hypogonadal subjects was numerically higher than eugonadal subjects in all questionnaires, suggesting a positive ADAM score. Notably, >55% of participants answered "yes" to sexual questions, mainly questions 1 and 7, as well as other three questions, 2, 3, and 9, which satisfied the criteria of a positive ADAM test.[11]

Of the 69 subjects who had hypogonadism, 58 (84.05%) had a positive score on the ADAM questionnaire, with an average serum TT level of 218 ng/dL. The remaining 11 subjects, although they had a mean TT level of 236 ng/dL, exhibited a negative ADAM score. Therefore, the sensitivity of the ADAM questionnaire (defined as the ability of the model to correctly identify the patients with the disease) is 84.05%. Interestingly, of 181 eugonadal subjects, 58 subjects showed negative ADAM scores, suggesting that the specificity of this model (defined as the ability of the model to correctly identify the patients without the disease) was 32.04% (Flowchart 1).

The Chi-squared test (Fig. 3) allowed us to examine the relationship between the presence of a positive ADAM score and hypogonadism/eugonadism. The results demonstrated a significant association between a positive ADAM score and low serum TT levels, further validating the utility of the ADAM questionnaire as an effective

Table 3: Hypogonadism in various comorbid conditions

Variables	*Hypogonadal (≤300 ng/dL) (N = 69)*	*Eugonadal (>300 ng/dL) (N = 181)*
Comorbidities		
HTN	36.0%	39.0%
CAD	13%	6.0%
CVA	1.0%	1.0%
Hypothyroidism	3.0%	2.0%
Dyslipidemia	3.0%	1.0%
Alcohol habit, frequency (%)	9 (13.0)	32 (17.7)

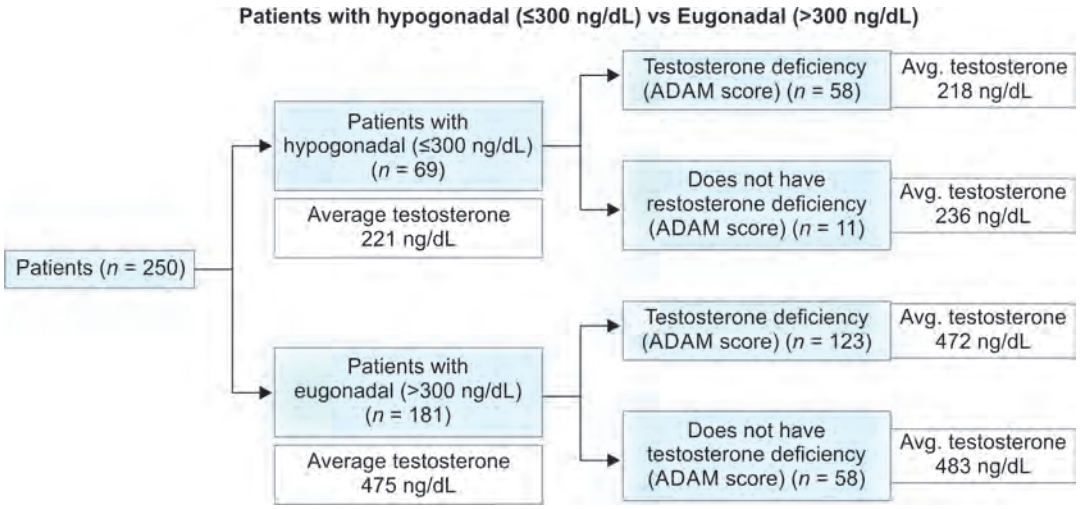
S.testosterone_grp_2		ADAM_Low Testesterone: No	Yes	Total
Eugonadal (>300)	Observed	58	123	181
	% within column	84.1%	68.0%	72.4%
Hypogonadal (≤300)	Observed	11	58	69
	% within column	15.9%	32.0%	27.6%
Total	Observed	68	181	250
	% within column	100.0%	100.0%	100.0%

χ^2 Tests

	Value	df	*P*
χ^2	6.48	1	0.011
N	250		

Fig. 3: Chi-square analysis to establish a correlation between the ADAM score and serum testosterone levels

Flowchart 1: Categorization/disposition of patients based on ADAM questionnaire in detecting hypogonadism in T2DM patients



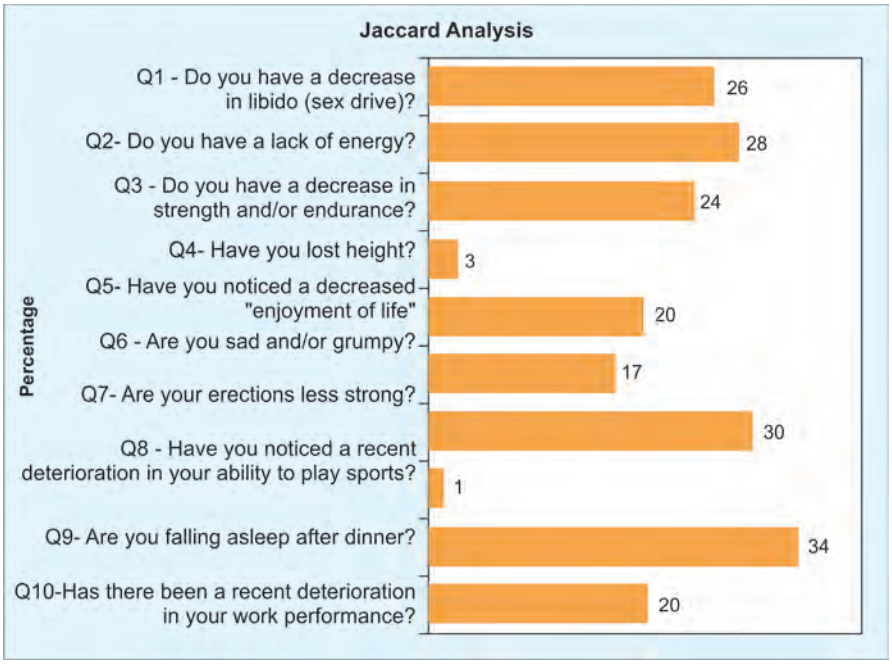


Fig. 4: Jaccard similarity coefficient

screening tool for identifying individuals with testosterone deficiency. The Chi-squared test provided strong evidence ($p = 0.011$) of the link between ADAM score positivity and hypogonadism, thereby highlighting the questionnaire's ability to correctly identify patients with the disease.

Jaccard Index or Jaccard Similarity Coefficient

Having observed a strong correlation between the ADAM score and testosterone levels, our next step was to assess the similarity and diversity among the sample groups using the Jaccard similarity coefficient (Fig. 4). Jaccard coefficient is a statistic used for comparing the similarity and diversity of sample groups. The data is first distiled in the format shown below in Table 4. Jaccard coefficient is then calculated as A/(A+B+C). It is used here to see if any of the questions from the ADAM score are driving the low testosterone [hypogonadal (≤300 ng/dL)] levels. A Jaccard value close to 1 means that it is a key positive differentiating attribute, and closer to "0" means that, at present, that attribute is not contributing much. Jaccard coefficients can also be seen as derived importance (drivers).

The chart analysis reveals that all the questions from the ADAM questionnaire demonstrate the importance of <0.4 (40%), including Q1 and Q7, which are generally considered key drivers for determining testosterone deficiency. This finding suggests that individual questions from the ADAM questionnaire might be significant indicators in isolation when it comes to predicting testosterone deficiency in our cohort of T2DM patients. Notably, the chart's results indicate that these questions hold a dominant influence on testosterone deficiency prediction when assessed individually.

Discussion

The bidirectional relationship between hypogonadism and T2DM is recognized and firmly established.[12–14] The interplay between these two conditions involves complex mechanisms that are still being investigated. Low serum testosterone levels contribute to insulin resistance by disrupting fatty acid metabolism, altering body composition, and impairing mitochondrial function in skeletal muscle, thereby increasing the risk of developing T2DM.[12,15] On the contrary, the mechanisms by which diabetes leads to hypogonadism are not yet fully elucidated. However, existing evidence suggests that chronic hyperglycemia and hypothalamic insulin resistance in diabetes may contribute to AD or hypogonadism through several mechanisms.[16,17] One such mechanism is prolonged exposure to high glucose levels, which may induce oxidative stress and inflammation, which can impair testicular function and reduce Leydig cell testosterone synthesis.[16,18] This could result in reduced circulating testosterone levels and contribute to the development of hypogonadism. Addressing hypogonadism in men with T2DM may have beneficial effects on insulin

Table 4: Distilled data of ADAM score with either testosterone deficiency or no deficiency

Variables	*Hypogonadal (≤300 ng/dL) (lab values)*	*Eugonadal (>300 ng/dL) (lab values)*
Testosterone deficiency (ADAM score)	A	B
Does not have a testosterone deficiency (ADAM score)	C	D

sensitivity, glucose regulation, and overall metabolic health. Similarly, managing T2DM effectively may help improve testosterone levels and alleviate symptoms associated with hypogonadism.[14] Hence, The Endocrine Society has recommended routine screening for AD in this patient group.[19]

In resource-limited settings, the routine measurement of testosterone levels in men with T2DM is impractical and challenging. The ADAM questionnaire is a potential candidate, widely utilized in Africa,[20] Iran,[21] Pakistan,[22] and Chile.[23] However, its reliability in accurately identifying AD or hypogonadism in diabetic males has not been definitively established. Therefore, to address this critical knowledge gap, we conducted this study to assess the reliability and effectiveness of the ADAM questionnaire as a diagnostic tool for predicting/detecting testosterone level/deficiency (hypogonadism) in T2DM males.

The baseline data and anthropometric characteristics of the studied cohorts revealed interesting patterns in the prevalence of hypogonadism among men with T2DM. Among the 250 study subjects, 27.6% were confirmed to have hypogonadism, while 72.4% were classified as eugonadal, using a serum TT level of ≤300 ng/dL as the reference value for hypogonadism.[24] The study demonstrated a progressive increase in the percentage (%) of patients with hypogonadism as age advanced, with a remarkably high percentage (40.6%) in the age-group ≥55 years. This finding supports the well-established concept of age-related decline in testosterone levels, particularly in men with T2DM.[14] However, this age-dependent phenomenon was not consistently observed in eugonadal subjects, indicating that factors other than age might be influencing the prevalence of hypogonadism in this population. Moreover, there was a notable difference in average BMI values between the two cohorts. The higher percentage of hypogonadal subjects being classified as obese (18.8%) compared to eugonadal subjects (8.3%) highlights the well-known association between obesity and testosterone deficiency in men.[25] Surprisingly,

no significant differences were observed between the two study cohorts in terms of biochemical characteristics, indicating that hormonal imbalances and metabolic parameters may not be the sole determinants of the development of hypogonadism in diabetic men. Other factors, such as genetic predisposition, insulin resistance, and individual hormonal responses, may play a more prominent role in the development of hypogonadism in this population.[3]

Of the hypogonadal subjects, approximately 57% had a family history of T2DM, and 33% had a family history of hypertension. This suggests a potential familial predisposition to both hypogonadism and existing comorbid conditions, which aligns with existing literature indicating a genetic component in the development of these conditions.[26] Moreover, hypertension and CADs were the most prevalent comorbidities observed in the hypogonadal subjects, implying a potential association between these conditions and AD.[27] However, when examining the duration of diabetes among the hypogonadal subjects, the majority had a diabetes duration of <5 years. This finding contrasts with previous evidence suggesting that longer diabetes duration might be associated with an increased risk of hypogonadism.[14] The discrepancy could be attributed to factors such as the heterogeneity of the study cohort, genetic variations, and lifestyle differences among the participants. Factors such as obesity, insulin resistance, and aging are well-known contributors to AD in diabetic males and may play a more dominant role in this context.[28]

The ADAM questionnaire offers a simple and practical method for the initial screening of testosterone deficiency or hypogonadism in men with T2DM, especially in resource-poor settings where routine testosterone assays using sophisticated instruments and kits may not be feasible. The ability to identify and manage AD in this population can lead to improved health outcomes and quality of life for affected individuals.[21] Among the 250 study participants, >55% of participants answered "yes" to sexual questions, particularly questions 1 and 7, as well as three other nonspecific questions. These responses satisfied the criteria for a positive ADAM test, indicating the presence of symptoms of AD. Notably, the percentage of subjects with hypogonadism was numerically higher than eugonadal subjects in all ADAM questionnaire items. This demonstrated the sensitivity of the ADAM questionnaire to correctly identify patients with hypogonadism and also suggested that while the ADAM questionnaire is effective at identifying those with hypogonadism, it may not always accurately distinguish eugonadal individuals. This correlation was further strengthened by analyzing data using a Chi-squared test, which provided robust evidence ($p = 0.011$) supporting the link between a positive ADAM score and low serum TT levels, further establishing the questionnaire's effectiveness as a screening tool for identifying individuals with testosterone deficiency/hypogonadism.

We believe that the findings of this study are novel for the Indian population and of immense clinical significance for healthcare practitioners. First, these unveil the potential of the ADAM questionnaire as an invaluable, accessible, and reliable tool for detecting AD/hypogonadism/testosterone deficits in males with T2DM, bridging critical diagnostic gaps and facilitating early detection of AD. Second, by offering a cost-effective and user-friendly alternative to expensive laboratory testing, the ADAM questionnaire provides a practical solution for resource-limited healthcare settings, allowing more patients to be screened for AD without straining financial resources. Third, the accurate detection of testosterone or AD or hypogonadism in diabetic men through the ADAM questionnaire enables timely and targeted interventions, leading to improved patient care and better management of hormonal imbalances. Overall, the findings of our study would contribute to a better understanding of the hormonal implications of T2DM in this specific population, guiding the development of targeted interventions and enhancing the overall management of T2DM among Indian males with hypogonadism. A similar study was performed by Anupam et al.,[29] which aimed to assess the predictive ability of TT and calculate FT (cFT) levels to classify ADAM status accurately. A positive predictive value of TT level < 300 ng/dL for assigning ADAM positive status was 89%, in concordance with our study. Similarly, a study done by Ugwu and Ikem[20] in black sub-Saharan African men with T2DM found that the sensitivity of the ADAM questionnaire was 88.1%, closely correlating with our findings.

Limitations

The main limitation of our study is that the ADAM questionnaire does not allow for the quantification of responses. Secondly, our study design being cross-sectional limits the ability to track changes in AD or hypogonadism overtime. Longitudinal data would provide a more comprehensive understanding of the dynamic nature of AD or hypogonadism in T2DM males. In addition, the present study was conducted in specific centers and geographical regions, potentially limiting the generalizability of findings to broader populations or diverse healthcare settings. And finally, we did not measure free testosterone levels owing to financial constraints. Larger sample-sized studies across the country can yield a better outlook on the current data.

Conclusion

The ADAM questionnaire is a practical and cost-effective initial screening tool for identifying symptoms of testosterone deficiency. It has high sensitivity in identifying men with hypogonadism, while caution must be in place as it has a very low specificity. In resource-poor settings, the ADAM score can be a good clinical marker of hypogonadism.

It also suggests that a holistic approach, considering the combination of symptoms and responses from the entire ADAM questionnaire, may provide a more reliable indication of testosterone deficiency in this particular population. Additionally, large-scale studies are needed to confirm these findings and validate the utility of the ADAM questionnaire in diverse populations.

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ORIGINAL ARTICLE

Impact of Oral Nutritional Supplementation in Chronic Kidney Disease Patients on Maintenance Hemodialysis: An Open-label, Single-arm Study among Indian Patients

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Abstract

Background: Protein-energy wasting (PEW) affects about 50–75% of patients with chronic kidney disease (CKD), particularly those who are on maintenance hemodialysis (MHD). This study evaluated the efficacy and tolerability of an oral nutritional supplement in Indian patients receiving MHD.

Materials and methods: This was a 3-month, prospective, open-label, and single-centered study. Eligible participants supplemented their regular diet with one sachet (40 gm) of oral nutritional supplement powder twice daily for 90 days. The study efficacy endpoints were mean change in acute phase proteins (albumin and prealbumin), anthropometric measurements [weight, body mass index (BMI), and triceps skin fold thickness], handgrip strength, hemoglobin, total iron binding capacity (TIBC), potassium, and phosphorus levels, malnutrition score (MS)—modified subjective global assessment (modified SGA), malnutrition inflammation score (MIS), and nutritional status.

Results: The study population comprised 36 (42.9%) men and 48 (57.1%) women with a mean age of 54.85 ± 15.50 years. A paired sample *t*-test was used to compare the baseline with end-of-study values for continuous variables. Serum albumin, prealbumin, hemoglobin, and phosphorus levels remained stable throughout the study period. The mean change in weight, BMI, triceps skin fold thickness, handgrip strength, and TIBC for the overall study population was 1.11 kg (1.82%, $p < 0.0001$), 0.46 kg/m^2 (1.98%, $p < 0.0001$), 3.47 mm (30.78%, $p < 0.0001$), 6.05 kg (44.98%, $p < 0.0001$) and 11.80 µg/dL (6.06%, $p < 0.0001$), respectively. At the end of the study period, there was a significant ($p < 0.0001$) improvement in the SGA and MIS scores. Further, there was a significant improvement in nutritional status as demonstrated by the overall intake of calories ($p < 0.001$), proteins ($p < 0.0001$), carbohydrates ($p = 0.003$, and fats ($p < 0.0001$).

Conclusion: Protein–energy malnutrition is a strong predictor of morbidity, mortality, and poor outcomes in CKD patients. A scientifically designed formula in accordance with KDOQI standards was able to improve the nutritional status, overall body composition, sarcopenia, and quality of life in CKD patients on MHD.

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Introduction

Chronic kidney disease (CKD) is a state of progressive kidney damage with an estimated glomerular filtration rate (eGFR) of <60 mL/minute/1.73 m^2 for a period of 3 months or longer.[1] However, CKD is asymptomatic in the early-moderate stage, and nearly 50% of patients are diagnosed when their eGFR is <15 mL/minute/1.73 m^2.[2] The survival of patients with CKD is drastically reduced unless kidney replacement therapy (KRT) is initiated through dialysis or transplantation. Nearly 89% of all dialysis and 69% of all KRT are performed using hemodialysis,[3] and maintenance hemodialysis (MHD) continues to be the primary treatment for end-stage renal disease (ESRD). ESRD has a worse prognosis than most malignancies since >20% of patients who begin dialysis die within the 1st year, and >70% of diabetic patients who begin dialysis die within 5 years.[4] Short-term patient care is essential since mortality is highest during the first 3 months of initiation of hemodialysis.[3]

In addition to being expensive, MHD alters the nutritional state of 20–70% of patients, resulting in cachexia and malnutrition.[5] Severe and mild malnutrition is seen in 6–8% and 30–65% of MHD patients, respectively.[6] Protein-energy wasting (PEW), also known as uremic malnutrition, is linked to low protein intake, inflammation, catabolic state, oxidative stress, decreased albumin and prealbumin levels, sarcopenia, weight loss, and comorbidities in these individuals. As a result, PEW is by far the best predictive indicator for poor outcomes and mortality in CKD patients.[7] As little as a 1 gm/L change in serum albumin concentration over the course of a few months might result in an increase or decrease in survival.[7,8] The serum prealbumin is also gaining attention as a reliable marker of PEW status.[9] Consequently, the clinical practice guidelines of KDOQI recommend serum albumin and prealbumin levels along with adjusted potassium–phosphorus levels and handgrip strength as nutritional indicators to predict the survival of MHD patients. Furthermore, the guidelines also support the use of a nutritional screening tool, a subjective global assessment-dialysis malnutrition score (MS), that determines the nutritional status of MHD patients.

Studies have shown the importance of nutritional supplements in avoiding PEW and reducing treatment expenses in individuals who are severely malnourished.[10] As opposed to conventional interventions like angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers that do not induce remission and sodium/glucose cotransporter 2 inhibitors that are contraindicated in advanced renal patients, the risk of short-term mortality in MHD patients can be decreased by preventing PEW through an improvement in nutritional intake.[4] Even while the number of CKD-related mortality in India is still greater than in low-income nations, there is a paucity of data on Indian patients receiving MHD.[11] Given this information, the current study's objective was to assess the effects of an oral nutritional supplement in Indian CKD patients receiving MHD.

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Materials and Methods

Study Design and Eligibility Criteria

This was a 3-month, prospective, single-center, open-label, and single-arm study. Male and female patients on MHD who were diagnosed as malnourished (serum albumin concentration <4 gm/dL with or without a loss of ≥ 5% dry weight over the past 3 months), older than 18 years, with a record of body weight for the previous 6 months, and who were willing to take the oral nutritional supplement met the eligibility requirements. Exclusion criteria were any of the following: unable or unwilling to provide informed consent and comply with the protocol procedures, had a history of dialysis noncompliance, malabsorption syndromes, chronic inflammatory diseases of unknown origin, malignancy, nephrotic syndrome, or chronic liver disease, the presence of recurrent acute illnesses, body weight <40 kg, or if they were pregnant or lactating females. Patients were also disqualified if they had recently undergone surgery or were using any other dietary supplements. The study was carried out in accordance with the ethical principles outlined in the latest version of the Declaration of Helsinki and the applicable guidelines for good clinical practice. Ethics committee approval was obtained for this study, and the study was registered at the Clinical Trials Registry of India.

Study Intervention

Patients who met the eligibility criteria were included in the study and underwent baseline assessments, anthropometric measurements, and laboratory testing both before and after the study. Patients received an oral nutritional supplement in addition to their regular diet during the study period. The oral nutritional supplement was scientifically designed with high protein (whey protein isolate as a primary source), low glycemic index, and energy-dense formula with added medium chain triglycerides and low potassium and phosphorous levels. Patients were instructed to consume one sachet (40 gm) of oral nutritional supplement powder twice a day for 90 days. One serving (40 gm) was reconstituted in 180 mL of plain water.

Efficacy Endpoints

The study efficacy endpoints were mean change in acute phase proteins (albumin and prealbumin), anthropometric measurements [weight, body mass index (BMI), triceps skin fold thickness], handgrip strength, hemoglobin, total iron binding capacity (TIBC), potassium, and phosphorus levels, MS [modified subjective global assessment (modified SGA)], malnutrition inflammation score (MIS), and nutritional status (proteins, carbohydrates, and fats) at the end of the study period. The primary endpoint was a mean change in acute phase proteins used to assess the effectiveness of PEW prevention at the end of the study period. The other endpoint was to evaluate the impact of the study intervention on sarcopenia, nutritional status, and quality of life among CKD patients. BMI was computed using the height and weight calculation and classified according to World Health Organization guidelines. The triceps skinfold was measured at the back of the left arm, midway between the acromial process of the scapula and the olecranon process of the ulna, with a Harpenden caliper. The Durnin and Womesley equation was used to calculate the percentage of body fat. Handgrip strength was measured using a handgrip dynamometer. The measurements were taken three times at 5-second intervals before and after the dialysis session, with the highest value chosen for analysis. The photometric approach was used to test hemoglobin in the DXH 800 equipment. Serum albumin was measured using the albumin bromocresol green technique, whereas serum prealbumin was measured using immunoturbidimetry. TIBC was estimated as the sum of serum iron and serum unsaturated iron-binding capacity. The indirect ion-selective electrodes technique was used to assess potassium, whereas the molybdate ultraviolet method was used to assess phosphorus. A 24-hour dietary recall was used to collect thorough information on all the foods and beverages taken by the patients in the previous 24 hours, and a mean of macronutrients was determined based on the previous 3 days' dietary intake during site visits. Modified SGA was used as a reliable and valid tool for the nutritional assessment of hemodialyzed patients.[12,13] It has two components—patient-related medical history on five items (weight change, dietary intake, gastrointestinal symptoms, functional capacity, and comorbidity) and physical examination on two items (decreased fat stores or loss of subcutaneous fat and signs of muscle wasting). Each component has a score between 1 and 5, a total ranging between 7 (normal) and 35 (very severe). Thus, an MS between 7 and 10 represents a well-nourished individual, whereas an MS score between 11 and 22 represents mild to moderate malnutrition. MIS was used to examine PEW (malnutrition) and inflammation.[14] The MIS has 10 components across four sections, namely the patient's medical history (change in end dialysis dry weight, dietary intake, gastrointestinal symptoms, functional capacity, and comorbidity), physical examination (decreased fat stores or loss of subcutaneous fat and signs of muscle wasting), BMI, and laboratory parameters (serum albumin and serum TIBC). Each component has four levels of severity, ranging from 0 (normal) to 3 (severely abnormal). The sum of all 10 components ranges between 0 (normal) and 30 (severe degree of malnutrition and inflammation). The patient's diary entries were used to monitor their compliance with the study intervention.

Statistical Analysis

Continuous data was tested for normal distribution using the Shapiro–Wilk test, and a *p*-value of <0.05 indicated that the normal distribution had failed. Continuous data are summarized as arithmetic means with standard deviation (SD). Changes from baseline to day 90 were computed for all continuous variables and presented as mean change with 95% confidence intervals (CI). Since all continuous data were normally distributed, a paired sample *t*-test was used to compare the baseline with day 90 (end of study) values for continuous variables. Categorical and nominal data are presented as numbers with percentages. All testing was done using two-sided tests at α 0.05 (95% confidence level). Statistical analysis was performed using Stata IC 13.1 (StataCorp LLC, Texas, United States of America).

Results

Baseline Characteristics of Participants

A total of 100 eligible patients were included in the study, and 84 completed it. Therefore, the results were analyzed for these 84 patients. There were 48 (57.1%) women and 36 (42.9%) men with a mean age of 54.85 ± 15.50 years. The demography and vital parameters of the study participants at baseline are presented in Table 1.

Table 1: Demography and vital parameters at baseline

Parameter	*N = 84*
Age, mean ± SD, year	54.85 ± 15.50
Gender, *n* (%)	
Male	36 (42.9)
Female	48 (57.1)
SBP, mean ± SD, mm Hg	137.50 ± 18.16
DBP, mean ± SD, mm Hg	81.10 ± 8.99
SpO_2, *n* (%)	98.29 ± 0.89
Weight, mean ± SD, kg	60.74 ± 14.25
BMI, mean ± SD, kg/m^2	23.20 ± 4.12

Change in Acute Phase Proteins, Handgrip Strength, PEW, MS, MIS, and Laboratory Parameters

Compared to baseline levels, there was no significant drop in albumin (mean difference −0.01 gm/dL, 95% CI, −0.09–0.12; $p = 0.822$), and prealbumin (mean difference −0.02 gm/L 95% CI, −0.03–0.001; $p = 0.068$) levels and the same were kept close to the baseline values at the end of the study period (Table 2 and Fig. 1). However, a significant improvement was observed in handgrip strength ($p < 0.0001$), PEW ($p < 0.0001$), MS ($p < 0.0001$), MIS ($p < 0.0001$), and TIBC ($p = 0.027$) levels (Table 2 and Figs 1 and 2).

Change in Nutritional Status

There was a significant improvement in nutritional status demonstrated by the overall intake of calories (798.12 ± 188.7 vs 1071.09 ± 196.72 kcal, mean difference = 272.96, $p < 0.001$), proteins (34.14 ± 10.86 vs 68.18 ± 7.18 gm, mean difference = 34.04, $p < 0.0001$), carbohydrates (127.97 ± 35.71 vs 139.92 ± 28.04 gm, mean difference =11.95, $p = 0.003$) and fats (17.16 ± 9.59 vs 27.96 ± 4.52 gm, mean difference =10.80, $p < 0.0001$) at the end of the study period (Table 3 and Fig. 3).

Discussion

Chronic kidney disease (CKD) is a global healthcare burden with mortality higher than many cancers.[4] Nearly a third of the 697.5 million cases of CKD reported in 2017 originated in China (132.3 million) and India (115.1 million).[15] Despite years of progress in the clinical results of hemodialysis, MHD patients continue to have a poor quality of life due to comorbidities, recurring infections, frequent hospitalization, financial burden, and unacceptably high mortality. In 2014, a 2-year prospective study at an Indian tertiary care hospital observed 63.12% deaths within the first 6 months of hemodialysis initiation.[16] Therefore, measures to improve the longevity of MHD patients should focus especially on the first few months of the treatment. A consensus statement suggests oral, enteral, or parenteral nutritional supplements to fulfil the protein and energy demands when oral dietary intake from regular meals is insufficient.[17] Considering this, we gave MHD patients an oral nutritional supplement for 3 months to address their dietary issues and test the effectiveness and tolerance of our product.

The nutritional status and outcomes of CKD may be reliably predicted by serum albumin and prealbumin levels.[9] A systematic review and meta-analysis revealed that oral nutritional supplements can increase

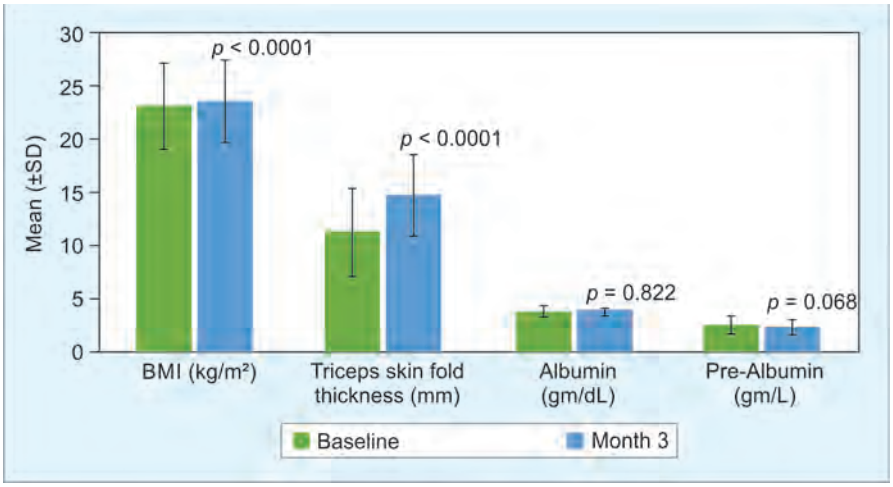

Fig. 1: Change in BMI, triceps skin fold thickness, and acute phase proteins ($n = 84$)

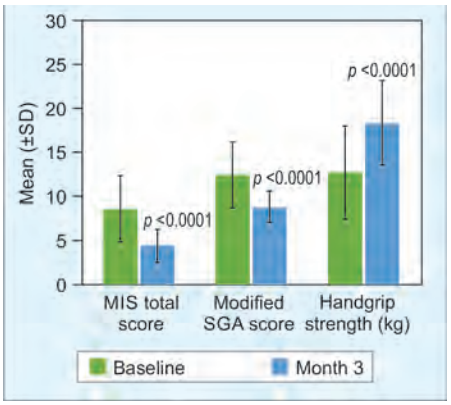

Fig. 2: Change in MIS, MS (modified SGA), and handgrip strength ($n = 84$)

Table 2: Change in acute phase proteins, handgrip strength, PEW, MS, MIS, and laboratory parameters ($N = 84$)

Parameters	*Baseline*	*Day 90*	*Change*	*t-test*
	Mean ± SD	*Mean ± SD*	*Mean (95% CI)*	*p*
Serum albumin levels, gm/dL	3.85 ± 0.52	3.84 ± 0.36	−0.01 (−0.09–0.12)	0.822
Serum prealbumin levels, gm/L	0.26 ± 0.08	0.24 ± 0.07	−0.02 (−0.03–0.001)	0.068
Handgrip strength by handgrip dynamometer, (kg)				
Before	13.45 ± 5.72	19.50 ± 5.03	6.05 (4.87–7.23)	<0.0001*
After	13.45 ± 5.72	19.08 ± 5.29	5.88 (4.61–7.16)	<0.0001*
PEW				
Body weight, kg	60.74 ± 14.25	61.85 ± 13.45	1.11 (0.53–1.70)	<0.0001*
BMI, kg/m^2	23.20 ± 4.12	23.66 ± 3.87	0.46 (0.24–0.68)	<0.0001*
Triceps skin fold thickness, mm	11.27 ± 4.16	14.74 ± 3.81	3.47 (2.95–3.99)	<0.0001*
MS (modified SGA)	13.25 ± 3.99	9.37 ± 1.86	−3.88 (−4.60 to −3.16)	<0.0001*
MIS	9.13 ± 3.96	4.73 ± 2.00	−4.39 (−5.16 to −3.64)	<0.0001*
Hemoglobin (gm/dL)	10.33 ± 2.18	10.08 ± 2.03	−0.24 (−0.70–0.22)	0.305
TIBC, µg/dL	194.66 ± 36.97	206.46 ± 48.98	11.80 (1.40–22.19)	0.027*
Potassium, mmol/L	5.20 ± 0.69	5.62 ± 0.78	0.43 (0.23–0.62)	<0.0001*
Phosphorous, mmol/mL	4.71 ± 1.51	4.91 ± 1.91	−0.20 (−0.22–0.62)	0.344

*, significant

Table 3: Change in nutritional status (*N* = 84)

Parameters	*Baseline*	*Day 90*	*Change*	*t-test*
	Mean ± SD	*Mean ± SD*	*Mean (95% CI)*	*p*
Total calories consumed (kcal)	798.12 ± 188.7	1071.09 ± 196.72	272.96 (228.44–317.49)	<0.001*
Proteins (gm)	34.14 ± 10.86	68.18 ± 7.18	34.04 (31.62–36.46)	<0.0001*
Carbohydrate (gm)	127.97 ± 35.71	139.92 ± 28.04	11.95 (19.78–4.12)	0.003*
Fats (gm)	17.16 ± 9.59	27.96 ± 4.52	10.80 (12.97–8.62)	<0.0001*

*, significant

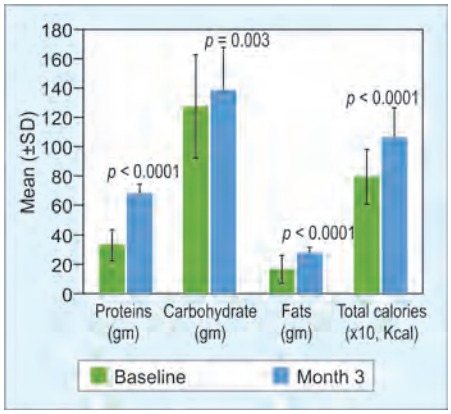

Fig. 3: Change in nutritional intake (*n* = 84)

albumin levels by 2.17 gm/L (95% CI, 0.89–3.45, $p < 0.001$; $I^2 = 90\%$) in MHD patients.[18] After receiving short-term enteral nutritional supplementation for 1 month, serum albumin levels were found to be higher in MHD patients (3.4 ± 0.4 vs 3.9 ± 0.3, $p = 0.000$) in another study.[19] Similar outcomes were observed by other authors, where serum albumin levels increased from 3.01 ± 0.44 to 3.85 ± 0.32 ($p < 0.0001$) and from 3.0 ± 0.05 to 3.5 ± 0.06 ($p < 0.001$) following 3 months of predialytic and intradialytic oral nutritional supplements, respectively.[20,21] Oral nutrition supplements are useful for maintaining albumin and prealbumin levels and preventing further decline in these levels. As a result, they have helped CKD patients on MHD improve their nutritional status and quality of life. The findings of our study also revealed that serum albumin levels could be maintained from baseline to 3 months of intervention without any further depletion (3.85 ± 0.52 vs 3.84 ± 0.36, $p = 0.822$). In keeping with our findings, Fouque et al. found no differences in serum albumin levels across groups with energy-dense, renal-specific oral supplements between groups after 3 months.[22] Patients undergoing hemodialysis have a 2.47 times increased risk of complications when their serum albumin level is below 3.8 gm/dL (hazard ratio higher in females). As a result of our intervention, the serum albumin levels were effectively kept above this limit. Similarly, for each 1 mg/dL increase in the serum prealbumin, a 9% decrease in the risk of death is seen.[9] Studies have shown both significant and nonsignificant rises in serum prealbumin levels after oral supplementation.[21,22] In contrast, our result showed a nonsignificant decline in serum prealbumin levels (0.26 ± 0.08 vs 0.24 ± 0.07, $p = 0.068$).

Generally, with each dialysis cycle, 6–12 gm amino acids and 7–8 gm protein are lost along with loss of water-soluble vitamins and trace elements such as zinc, carnitine, folate, calcium, and dietary fiber leading to PEW, a complex syndrome of muscle wasting, malnutrition, and inflammation.[6] We used a range of indicators to accurately assess distinct nutritional status/PEW in the MHD population. Our study found a significant improvement in weight (60.74 ± 14.25 vs 61.85 ± 13.45 kg, $p < 0.0001$) and BMI (23.20 ± 4.12 vs 23.66 ± 3.87 kg/m^2, $p < 0.0001$) at the end of the study period. In line with our results, two previous studies have shown a similar increase in weight (58.78 ± 11.20 vs 59.41 ± 10.60 kg, $p < 0.0001$) and (59.9 ± 1.55 vs 60.4 ± 1.49 kg, $p = 0.022$) following 3 months of nutritional supplementation.[20,21] Also, a similar result was observed for the BMI (21.1 ± 0.50 vs 21.3 ± 0.47 kg/m^2, $p = 0.019$) in one of these studies.[21] Furthermore, two systemic reviews and meta-analyses have also shown an increase in BMI by 0.40 kg/m^2 (95% CI, 0.10–0.71, p = 0.01; $I^2 = 49\%$) and 0.30 kg/m^2 (95% CI, 0.09–0.52, $p = 0.005$; $I^2 = 41.4\%$), respectively with oral nutritional supplements.[18,23] Additionally, there are reports of stable BMI with nutritional intervention and a decline in BMI in the control group during the study period of 3 and 6 months, respectively.[24,25]

Our study showed a significant increase in the triceps skin fold thickness at the end of the study period (11.27 ± 4.16 vs 14.74 ± 3.81 mm, $p < 0.0001$). A similar result was observed in a previous study where triceps skin fold thickness increased (10.5 ± 5.0–11.9 ± 5.0 cm, $p < 0.001$) after 6 months of oral nutrition supplementation and decreased (12.6 ± 5.4–11.3 ± 5.5 cm, $p < 0.001$) in the control group.[25] Another study[26] found that using oral fat-based high-energy supplements daily for 80 days did not significantly enhance the thickness of the triceps skin folds (20.40 ± 6.17 vs 21.55 ± 5.37 mm, $p = 0.538$). Furthermore, our study demonstrated a significant improvement in the handgrip strength (13.45 ± 5.72 vs 19.50 ± 5.03 kg, $p < 0.0001$). In a prior study, a similar increase in handgrip strength was seen after 3 months (17.79 ± 7.9 vs 20.9 ± 6.4 kg) and 6 months (17.79 ± 7.9 vs 23.7 ± 6.5 kg, $p < 0.05$) of oral nutritional supplementation.[27] Our findings were also in agreement with a systematic review and meta-analysis of 22 randomized controlled trials that showed a significant improvement in handgrip strength following oral nutritional supplementation [0.96 kg (95% CI, 0.07–1.84, $p = 0.034$; $I^2 = 41.4\%$)] when compared to placebo or routine care.[23]

In two previous studies, three months of supplementation resulted in significant increases (9.23 ± 1.88 vs 10.16 ± 1.82, $p = 0.0001$ and 9.3 ± 0.28 vs 9.8 ± 0.16, $p = 0.048$) in the hemoglobin levels.[20,21] We did note a nonsignificant decrease in the hemoglobin levels, though. Our findings were consistent with a previous study that found no changes in hemoglobin concentration.[27] Although there were no differences between the control and supplement groups in another trial, the control group required considerably more erythropoietin doses to maintain constant hemoglobin levels ($p = 0.012$) than the supplement group.[25] Our study had more females than males, which may have contributed to the nonsignificant reduction in hemoglobin levels.

Increased mortality is linked to a significant change in the levels of serum potassium and phosphorus. The serum phosphorus levels at 3 months in our study did not differ significantly from two prior studies (6.65 ± 1.86 vs 6.66 ± 1.25 mg/dL and 6.05 ± 0.26 vs 6.09 ± 0.25 mg/dl, $p = 0.895$).[20,21] Another research that supports our findings[19] found an increase in serum potassium levels (3.8 ± 0.8 vs 4.8 ± 0.7 mEq/L, $p = 0.02$). Likewise, few studies have reported no significant changes in serum potassium levels after 3 months.[20,21] The oral nutritional supplement used in the study was designed to provide low potassium and phosphorus levels according to KDOQI guidelines. Renin–angiotensin–aldosterone system inhibitors, which are known to increase the risk of hyperkalemia in individuals with impaired kidney function, may be the cause of the rise in serum potassium levels.[28]

Our SGA and MIS scores correlate favorably with the positive findings. At the end of the study period, the nutritional status of our patients had improved, going from mild-moderate malnutrition (score 11–22)

to well-nourished (score 7–10), as shown by the modified SGA score. No patient had significant malnutrition, either. Our results corroborated with another study in which the supplement group showed improved SGA scores ($p < 0.05$) and quality of life, whereas the control group continued to have a mild-to-moderate risk of malnutrition at 3 months.[22] Intradialytic amino acid supplementation was also shown to improve the SGA score at 3 months (16 vs 12, $p = 0.01$) and at 6 months (16 vs 11, $p = 0.01$).[29] Patients with PEW had considerably higher MIS scores, with scores greater than 5 indicating malnourishment. After the patients received the oral nutritional supplement, our intervention successfully reduced their MIS scores to below 5, showing that they were well-nourished. The whey protein and vitamin E in our supplement may have contributed to this impact, as shown in a previous randomized control trial.[30] Additionally, one research found that while MIS scores in the intervention group remained stable (8.3 ± 2.8 vs 8.2 ± 3.0), the same significantly increased ($p = 0.006$) in the control group after 6 months.[25] Serum TIBC in MIS scoring is an indirect measurement of serum transferrin concentration. It is a helpful indicator of inflammation and nutritional status. It is known that a decrease in TIBC > 20 mg/dL during the first 6 months increases the risk of mortality to 57% when compared to those with stable TIBC levels.[31] In agreement with a previous study,[21] our investigation found considerably higher levels of TIBC (194.66 ± 36.97 vs 206.46 ± 48.98, $p = 0.027$).

Lastly, there was a significant improvement in the nutritional status of our study population in terms of daily intake of proteins, carbohydrates, fats, and total calories. The nutritional status of hemodialysis patients can be improved by oral nutritional supplements that can supply an additional 7–10 kcal/kg per day of energy and 0.3–0.4 gm/kg per day of protein to fulfil daily energy and protein consumption.[7] In a previous study, an increasing trend ($p = 0.08$) in relative protein intake was observed in the supplement group after 6 months.[32] Another study found that supplement groups consumed more total calories (approximately 250 kcal mean), energy, fat, protein (12 mg on average), and fiber at 3 and 6 months.[27] Therefore, in our investigation, improved dietary intake was associated with an overall improvement in the nutritional status of MHD patients, as shown by SGA and MIS scores (indicating a well-nourished condition). Additionally, our oral supplement showed improved body composition following supplementation, probably converting the catabolic effect of the dialysis therapy to an anabolic condition. Beyond protein and calories, our supplement included a range of micronutrients (vitamins, trace elements, and fiber) that MHD patients ordinarily insufficiently consume/absorb, which may be the reason we saw the desired benefits in our study population. None of the patients reported any adverse effects related to our nutritional supplement, and it was very well tolerated.

Conclusion

Malnutrition is a key contributor to the risk of complications in MHD patients; hence, its prevention is essential for extending life. Giving nutritional supplements for at least three months (as advised by KDOQI standards) may make it simple and affordable to reverse PEW and, consequently, the risk of short-term death. The positive findings of our study support the ardent recommendation of oral nutritional supplements for CKD patients undergoing MHD.

Practical Application

Although hemodialysis successfully delays otherwise impending death, the morbidity and mortality risk in MHD patients remains unacceptably high. The prevention of malnutrition is critical since it contributes significantly to the high rates of hospitalization, infection, comorbidities, and poor quality of life experienced by MHD patients. Our study's positive findings support the use of oral nutritional supplements for CKD patients undergoing MHD.

Limitations of the Study

It was a short-duration study. A study on the impact of long-term oral nutrition supplementation (6–12 months) in CKD patients who are on MHD suffering from PEW can be explored further to improve malnutrition and PEW status.

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Consent for Publication

The author consents to Editorial Board to publish the paper. The author(s) accept responsibility for publishing this material in his own name, if any.

Availability of Data and Materials

The data analyzed is available from the corresponding author and could be available at a reasonable request.

Ethics Approval and Consent to Participate

Ethics approval for the study was obtained from the Institutional Ethics Committees of BAN Hospital, Mumbai, Maharashtra, India.

Authors' Contributions

All the authors were responsible for the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting of the article, and final approval of the version to be published. Dr Rachana M Bhoite and Praneeth Immadisetti helped conceptualize and design the study. Dr Arun Shah and Dr Rachana M Bhoite supervised and approved the final draft of the study. Praneeth Immadisetti monitored and supervised the study. Dr Wasi Shaikh and Dr Ruta Deshmukh helped with data collection during the study. Dr Rahul Rathod and Dr Vinita Satyavrat provided input and scientific support during the study period. All authors critically reviewed all manuscript drafts and provided comments. All authors gave their approval for the final version to be published. Dr Rachana M Bhoite is the guarantor of this work and, as such, takes full responsibility for the integrity and accuracy of the data analysis.

CTRI Registration Number

CTRI/2022/04/041763.

Conflicts of Interest

The study investigators received a research grant from Dr Reddy's Laboratory, India, and as such, they report no conflict of interest for the study product used. Dr Rachana Bhoite, Praneeth Immadisetti, Dr Rahul Rathod, and Dr Vinita Satyavrat are all Dr Reddy's Laboratory, India employees.

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ORIGINAL ARTICLE

Assessment of Epidemiology and Clinical Profile of Psoriatic Arthritis Patients in India

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Abstract

Background: Psoriasis is an inflammatory skin disease associated with significant comorbidity. However, the characteristics of patients with psoriasis are not well documented in India, and a more detailed understanding is needed to delineate the epidemiologic profile at the regional level for better management of psoriasis. Herein, we reported the clinical profile and demographic pattern of psoriasis to further understand its burden in the Indian setting.

Methods: We conducted a retrospective observational study of patients diagnosed with psoriasis who fulfilled the classification criteria for psoriatic arthritis (CASPAR) criteria. Patients were included from the rheumatology outpatient department of Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute in Mumbai, India. The outcomes included demographic and clinical profiles, patterns of joint involvement, and comorbidities associated with psoriasis. A *p*-value of <0.05 was considered significant.

Results: We enrolled 60 patients, with a mean age of 50.87 years and a higher proportion of females (62%). The majority of patients with less than five joints had associated comorbidities (40 out of 60). Psoriatic arthritis (PsA) occurred in 41 patients [mean ± standard deviation (SD) age of onset—38.88 ± 13.24 years], with the highest occurrence in the 30–50 years (53.3%). The majority of patients with PsA developed it within 2 to ≥5 years of psoriasis occurrence. We did not find any significant correlation between the occurrence of PsA and comorbidities, as well as the duration of PsA and the number of joints ($p = 0.152$). Pitting and enthesitis were the most common morphological changes noted in almost half of the patients.

Conclusion: Our study provides an overview of the epidemiologic and clinical characteristics of psoriasis patients in India. These findings could be useful for early diagnosis of PsA and help clinicians in assessing the progression of psoriasis into PsA.

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Introduction

Psoriasis is an inflammatory skin disease that is associated with significant morbidity and a negative impact on the patient's well-being.[1] It has a complex and multifactorial etiopathogenesis that affects nearly 2–3% of the population worldwide. In India, it accounts for 2.3% of total dermatology outpatients.[2,3] The common clinical type of psoriasis is plaque psoriasis, which is associated with a range of comorbidities, including psoriatic arthritis (PsA), cardiometabolic diseases, and depression.[4]

Psoriatic arthritis (PsA) is a potentially severe joint disease affecting both the appendicular and the axial skeleton and is strongly associated with psoriasis.[5] Notably, ~30% of patients with psoriasis may develop PsA during their lifetime.[3] In the majority of cases, psoriasis usually precedes joint disease within 7–10 years, but the two can also appear simultaneously.[6] In about 15% of cases, PsA may develop long before the skin is affected.[7] In addition, in some cases, the skin lesions are evident, but a diagnosis may not be achieved. Many patients with PsA also have comorbidities such as obesity, metabolic syndrome, and depression.[8]

Psoriatic arthritis (PsA) has diverse clinical manifestations, and in about 5% of cases, PsA can present with arthritis mutilans, a severe, destructive, deforming manifestation. Moreover, enthesitis and dactylitis are two important clinical features that may be considered a hallmark of PsA.[9] Enthesitis is an inflammation of the junction where the tendon, ligament, or joint capsule inserts into the bone and may be the primary pathological process underlying spondyloarthritis (SpA)—associated skeletal inflammation.[10] Although enthesitis affects 35–50% of patients with PsA, it can be challenging for the clinician to identify enthesitis in patients with PsA. On the contrary, dactylitis is characterized by diffuse swelling of a finger and toe and is an important feature for the diagnosis of PsA.[11]

Although significant progress has been made in various fields of psoriasis research, understanding epidemiologic profiles of the disease is still important. A more elaborated understanding to delineate the epidemiologic profile at the regional level is essential to refine the management of psoriasis. Unlike many developed countries, where data from many large-scale epidemiologic studies are available, the characteristics of patients with psoriasis are not well documented in India.[12–16] Furthermore, clinically, there are no diagnostic markers for PsA, and clinical diagnosis of PsA is largely based on recognizing patterns of inflammatory joint involvement.[17] It is therefore important to understand the clinical profile and demographic pattern of psoriasis patients to further understand the disease burden as it could potentially impact the psoriasis treatment. In this study, we aimed to evaluate the patient characteristics and clinical profile of psoriasis patients studied over 5 years in a tertiary care setting in India.

Methods

Study Design and Population

The present single-center retrospective observational study collected data between January 2016 and December 2021 at Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Mumbai, India. The study included male and female adults (≥18 years of age) attending the rheumatology outpatient department who were previously diagnosed with PsA and fulfilling the classification criteria for psoriatic arthritis (CASPAR) criteria. Patients who were >18 years of age and admitted patients were excluded from this study. Psoriasis was diagnosed clinically based on the presence of characteristic skin lesions.

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Table 1: Baseline characteristics of patients

Variables	*N = 60*
Age (years), mean ± SD (minimum, maximum)	50.87 ± 14.02 (19, 83)
Age distribution, *n* (%)	
<30 years	4 (6.7)
30–50 years	26 (43.3)
>50 years	30 (50.0)
Male, *n* (%)	23 (38)
Female, *n* (%)	37 (62)
Number of joints involved, mean ± SD (minimum, maximum)	9.43 ± 5.94 (2, 22)
Distribution of number of joints, *n* (%)	
≤5 joints	21 (42)
6–10 joints	16 (32)
>10 joints	23 (46)
Family history of psoriasis, *n* (%)	
Present	9 (15)
Absent	21 (85)
Comorbidities, *n* (%)	
Diabetes	8 (13.3)
Hypertension	11 (18.3)
Ischemic heart disease	4 (6.67)
Dyslipidemia	17 (28.3)

The study was approved by the Institutional Ethics Committee (IEC) and conducted in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use- Guideline for Good Clinical Practice (ICH-GCP) guideline and Declaration of Helsinki. Since this was a retrospective observational study with no intention to disclose any confidential data of the participants, the IEC gave a waiver for an informed consent form. Patient identification was kept confidential through anonymization, and data confidentiality was maintained throughout the study.

Data Collection

The data were collected from patients' medical records. Demographic and disease characteristics data, including the age of onset, comorbidity, family history of psoriasis, duration of skin lesions, morphological types of psoriasis, family history of psoriasis, and presence of nail psoriasis were recorded in a predesigned case report form.

Outcomes

In this study, demographic and clinical profiles, patterns of joint involvement, and comorbidities associated with PsA patients were analyzed. The pattern and number of tender or swollen joints, as well as the pattern of arthritis, were recorded according to Moll and Wright's classification criteria. These criteria included distal interphalangeal arthritis, asymmetric oligoarthritis (≤4 joints), symmetric polyarthritis (≥5 joints), arthritis mutilans, and arthritis of the spine (spondylitis). To diagnose spondylitis, at least tenderness on the spine or sacroiliac joint, sacroiliitis on pelvis X-ray (anteroposterior view), or spinal syndesmophytes on spine X-ray should be present in PsA patients along with inflammatory back pain, with or without the peripheral joint disease.

The presence of enthesitis and dactylitis was diagnosed clinically and recorded. Enthesitis was diagnosed on clinical examination at common extensor insertion at the lateral epicondyle of the humerus, medial femoral epicondyle, and Achilles tendon insertion at the calcaneus. Dactylitis was diagnosed by spontaneous fusiform swelling or redness in either fingers or toes extending beyond the joint line associated with tenderness.

Statistical Analysis

The prevalence of PsA in India ranges from 0.44 to 8.7% in patients with psoriasis.[18] In this study, we considered an average prevalence of 5% for sample size calculation. To achieve 95% confidence limits at a 90% confidence level and a design effect of 1, a sample size of 51 was calculated. An additional 15% of patients were recruited on account of incomplete data. Therefore, we collected data from 60 patients in our study.

Statistical analyzes were performed using Statistical Package for the Social Sciences/ Excel. Categorical variables were summarized using percentages, mean, standard deviation (SD), and frequency (interquartile range). The difference in categorical variables was analyzed using the Chi-squared or Fisher exact test. The p-value < 0.05 was considered statistically significant.

Results

A total of 60 patients were enrolled in this study. The mean age of patients was 50.87 years, and a higher proportion were females (62%). Half of the patients (50%) were in the age-group of >50 years. The joint abnormalities showed involvement of a mean of 9.43 joints, with the majority of patients having less than five joints involved. The family history was positive for 15% of patients. A number of associated diseases were present concomitantly in 40 out of 60 patients (Table 1).

Clinical Characteristics of Psoriasis

The mean ± SD age at the onset of psoriasis was 38.88 ± 13.24 years. The largest group was the age-group of 30–50 years (53.3%). Duration of psoriasis ranged between 1 and 45 years (mean ± SD—11.32 ± 11.16 years), with most study patients (43.3%) having psoriasis from <5 years followed >11 years (40.0%) (Table 2).

According to the clinical types, psoriasis patients were classified into four clinical types, namely plaque, guttate, pustular, and erythrodermic. Plaque psoriasis was the most common type, while the proportion of patients with other types (guttate, pustular, and erythrodermic) was very low. All patients in the study reported joint pain. Symmetrical oligoarthritis (43.34%) was the most common pattern of joint involvement, followed by spondyloarthropathy with polyarthritis and asymmetrical oligoarthritis, which were observed in ~15% of patients (Table 2).

Psoriatic arthritis (PsA) occurred in 41 patients, and in the majority of them, it developed within 2 to ≥5 years of the onset of psoriasis. In a small proportion of patients (10%), PsA appeared almost simultaneously or after the onset of psoriasis (Table 2).

Associations of Comorbidities and Number of Joints

During the evaluation of the association between comorbidities and involvement of ≥10 joints in patients, our study did not find any significant correlation with any of the comorbidities (Fig.1). Of the patients with associated comorbidities, 25.0, 45.4, and 41.7% with diabetes, hypertension, and dyslipidemia, respectively, had ≥10 joints involved. No patients with associated ischemic heart disease (IHD) had ≥10 joints involved. The number of patients without diabetes and IHD was higher for the involvement of ≥10 joints compared to those with the disease.

However, the number of patients without hypertension and dyslipidemia was lower than that of their disease counterparts for the involvement of ≥10 joints (Fig. 1).

When the duration of PsA and the number of joints were assessed, it yielded no correlation with the coefficient ($r = 0.199$, $p = 0.152$) (Fig. 2).

Table 2: Clinical characteristics of patients

Variables	*N = 60*
Age (years) of onset of psoriasis, mean ± SD (minimum, maximum)	38.88 ± 13.24 (14, 74)
Age (years) distribution, *n* (%)	
<30 years	16 (26.7)
30–50 years	32 (53.3)
>50 years	12 (20.0)
Duration of psoriasis (years) mean ± SD (minimum, maximum)	11.32 ± 11.16 (1, 45)
Duration of psoriasis distribution (years), *n* (%)	
≤5 years	26 (43.3)
6–10 years	10 (16.7)
>11 years	24 (40.0)
Types of psoriasis, *n* (%)	
Plaque	52 (86.67)
Guttate	4 (6.66)
Pustular	2 (3.34)
Erythroderma	2 (3.34)
Pattern of involvement of joints, *n* (%)	
Symmetrical	26 (43.34)
Spondyloarthropathy with polyarthritis	10 (16.67)
Asymmetrical oligoarthritis	9 (15)
Distal Interphalangeal arthritis	6 (10)
Spondyloarthropathy with oligoarthritis	5 (8.34)
Spondyloarthropathy alone	3 (5)
Arthritis mutilans	1 (1.67)
Relationship between psoriasis onset and PsA onset	
PsA appeared first and psoriasis appeared later	6 (10)
PsA and psoriasis appeared almost together	6 (10)
PsA appeared within 2 years of psoriasis appearance	13 (21.67)
PsA appeared between 2–5 years of psoriasis appearance	16 (26.67)
PsA appeared 5 years after psoriasis appearance	19 (31.67)

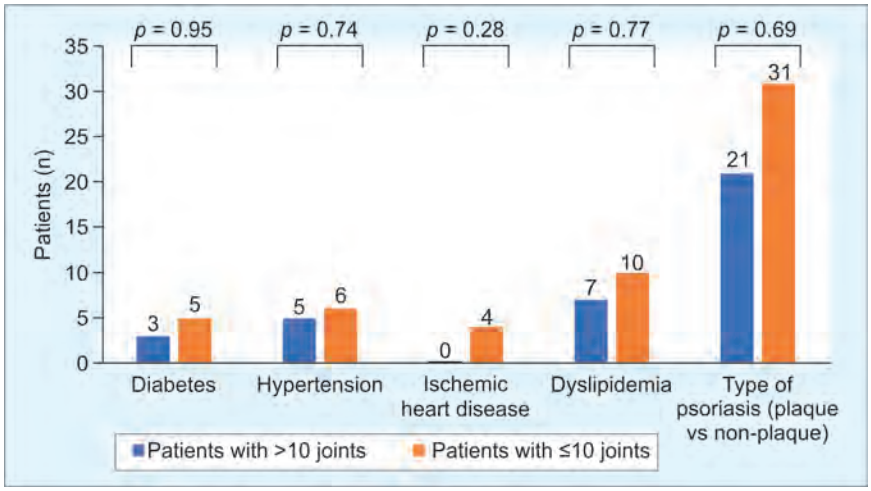

Fig. 1: Association of comorbidities with number of joints involved

Morphological Changes on Psoriasis Patients

Pitting and enthesitis were the most common morphological changes noted in almost half of the patients. The less common changes were dactylitis and onycholysis. While mixed changes were observed in 15% of patients, hyperkeratosis was very rare (Fig. 3).

Discussion

We aimed to analyze the characteristics of patients with psoriasis and their comorbidities with PsA over 5 years in order to delineate the clinical profile of patients in India. Given the diversity and multifactorial pathophysiology of PsA, its diagnosis is often difficult in clinical practice, especially in a primary care setting. An understanding of the clinical profile of patients suffering from psoriasis could potentially help clinicians predict an early diagnosis of PsA.

The mean age of the patients included in our study was 50.86 years, which was similar to the findings from other studies wherein the mean age of patients was noted to be 50.1–51.7 years.[19,20] However, Vastarella et al. described a much younger population in their study, with a mean age of 39.8 years, and

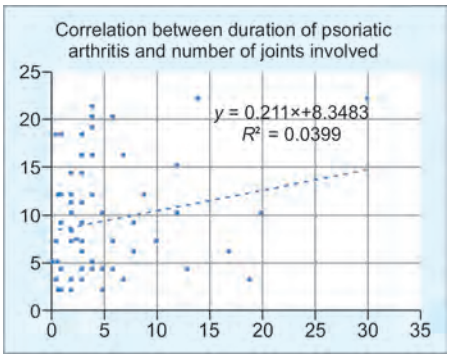

Fig. 2: Correlation between duration of PsA and number of joints involved

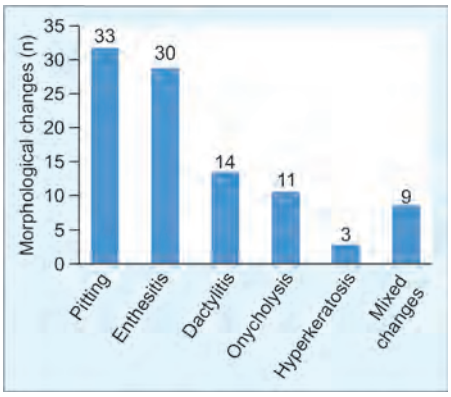

Fig. 3: Distribution of morphological changes observed in patients

Jatwani et al. noted a much older population, with a mean age of 63.1 years.[21,22] A review by Ogdie and Weiss suggests that the usual age that gets affected by PsA is 40–50 years of age, which constitute 25% of our study population.[23]

Our study demonstrated that the age for the onset of psoriasis is 38.88 years, which is consistent with other published studies in the Asian subcontinent, such as India (36.9 years), China (41.8 years), and Malaysia (38.8 years).[24–26] On the contrary, studies from other regions of the world, such as Japan (45.5 years) and Taiwan (46.4 years), have shown a higher age of onset for psoriasis.[27,28] These differences may be attributed to patients' clinical and genetic variations as they play a key role in the development of psoriasis.[29] Our study also revealed a dual peak of psoriasis onset, located in the late 20s and 40s, which declined as the age progressed. Similar observations were reported in other Asian studies where peaks were identified in the 20s and 40s.[25–27] A ratio of early onset (<40 years) versus late onset (≥40 years) at diagnosis was 1.6. A similar observation was reported in a Korean study, where >50% of patients were diagnosed with psoriasis before 40 years of age.[30]

The age of onset appears to have an impact on the clinical characteristics of PsA. In our study, PsA appeared 5 years after the appearance of psoriasis in nearly one-third of patients (31.67%). In only 10% of patients, PsA appeared first, or both appeared together. These results agreed with Nigam et al., where skin lesions usually preceded arthritis in 50% of the subjects. The onset of symptoms was synchronous in 41.7% of the patients.[31] In another study by Rather et al., cutaneous involvement occurred prior to joint involvement in more than three-fourths of patients (75.33%). They further observed that cutaneous involvement occurred simultaneously with joint involvement in 20% of cases, while joint involvement preceded skin involvement in <5% of cases.[32]

We did not find any impact of age on the number of joints involved. However, this study was not focused on the impact of gender, and the sample size was not adequate for this analysis. Elderly onset patients appear to have worse outcomes compared to those with younger age onset patients. The early onset group appears to have a higher proportion of scalp psoriasis at onset and a higher proportion of extremity lesions. Overall, there seem to be significant differences between the clinical features of those with early-onset and late-onset psoriasis, and there is likely a different genetic background as well.

Psoriasis prevalence has been reported to be equal between men and women in Western studies.[33,34] However, in Asian studies, male predominance has been reported in multiple studies (Jatwani et al., 62% and Nigam et al., 66.0%).[22,35] Gazitt et al. showed an almost equal distribution of males (53%) and females (47%).[20] Our study revealed the predominance of this disease in females. Although this phenomenon may be unique to the study population, it could potentially be due to the smaller sample size of our study.

It is well known that comorbidities are closely related to psoriasis, and metabolic syndromes have emerged as a comorbidity in many recent clinical studies.[4] In our study, we did not find an association between psoriasis and diabetes, as only eight patients presented with joint involvement and had diabetes (8/60, 13.3%). These findings were not in agreement with other studies, as a significant association between PsA and diabetes was shown previously.[36,37] We further found 18% hypertensive patients in our cohort, which is in sync with the findings from Jafri et al., wherein the proportion of patients with hypertension was 22.4%.[38] Quite a few studies have shown a much higher prevalence of hypertension (34%); however, not many of them have reported the association, and hence, comparison with the Indian context appears difficult.[39] In our study, the prevalence of ischemic heart disease and dyslipidemia were 6.6 and 28%, respectively. In a study by Egeberg et al., the hazard ratio of developing coronary artery disease in psoriasis patients was 1.74, which was not sustained when patients were stratified by age.[40] The proportion of dyslipidemia patients in our study was comparable to the results from a systematic review, which estimated a 34.0% pooled prevalence of dyslipidemia among PsA patients.[39] Overall, we did not find any significant correlation with any of the comorbidities and number of joints affected. These results could be misleading owing to its smaller sample size, and the relationship between PsA and comorbidities needs further clarification.

In our study, we found that patients had 86.6% plaque-type psoriasis, which was the predominant clinical type in India and consistent with observations in other Asian populations. Pitting and enthesitis were the most common morphological changes noted in almost half of the patients, indicating that attention toward pitting and enthesitis is also crucial to understanding the progression of psoriasis.

The diagnosis of PsA can generally be made in a patient who has both psoriasis and inflammatory arthritis in a pattern typical of PsA. This can generally be done based on the pattern of joint involvement, laboratory testing, imaging, and synovial fluid analysis. Laboratory findings in PsA are nonspecific and reveal varying degrees of acute phase response and the degree and chronicity of inflammation. Given this backdrop, we suggest that dermatologists should be alert to the presence of relevant characteristics experienced by their patients, which could potentially help them in evaluating the risk and predicting psoriasis progression at an early stage in clinical practice.

The patients recruited in our study were from a single center, and hence, results cannot be generalized for a larger population. Due to the smaller sample size in our study, we were not able to analyze the association of the severity of psoriasis with individual clinical parameters in detail. Being a retrospective study design, it was not possible to ascertain the "current" situation of the patients. Objective grading of the severity of the disease was also not possible.

Conclusion

Our study provides an overview of the clinical and demographic profile of psoriasis patients. These features could be indicative of psoriasis diagnosis also help dermatologists in assessing the progression of psoriasis into PsA. Clinical diagnoses, in conjunction with patient characteristics and medical profiles, could be indicative of an assertive treatment. The pattern of clinical features is not consistent across various studies, and nationwide epidemiologic profiling is necessary for further research and better policy-making for patients with psoriasis in India.

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REVIEW ARTICLE

Cilnidipine, a Dual L/N-type Ca^{2+} Channel Blocker in Hypertension Management: A Review

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Abstract

Calcium channel blockers (CCBs) are widely used antihypertensive agents due to their effectiveness in reducing blood pressure (BP), along with their good tolerability and evidence of reducing hypertension (HTN)—related cardiovascular and renal diseases. Cilnidipine, a unique dihydropyridine calcium antagonist, exhibits potent inhibitory action on both N-type and L-type voltage-dependent calcium channels. With excellent oral absorption and a prolonged duration of action, it demonstrates a significant antihypertensive effect. It effectively reduces BP both systolic and diastolic while providing renal, neurological, and cardiovascular protection. Unlike L-type CCBs, cilnidipine does not increase pulse rates (PRs) and is associated with reduced occurrence of pedal edema. Cilnidipine is an effective treatment choice for individuals with mild to moderate essential HTN, whether it is administered alone or in conjunction with other treatment modalities.

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Overview

Hypertension (HTN) increases the risk of developing major cardiovascular, cerebrovascular, and renal complications significantly. The risk of developing complications can be significantly reduced and the cardiovascular prognosis can be improved through the effective treatment of HTN.

Within the drug class used to treat HTN, calcium channel blockers (CCBs) exhibit distinct variations in their pharmacokinetic and pharmacodynamic properties, selectivity, and duration of pharmacological action. However, it is noteworthy that their interaction with L-type voltage-dependent transmembrane calcium channels remains consistent. These differences have an influence on the clinical and therapeutic efficacy, tolerability, and safety characteristics in various clinical environments.[1]

Cilnidipine, a fourth-generation CCB, stands out as a distinctive medication due to its inhibitory effects on both the sympathetic N-type and L-type calcium channels. This unique characteristic is attributed to its actions on sympathetic neurotransmitter release. Through its distinct mechanism of action on sympathetic N-type Ca^{2+} channels, it decreases the release of norepinephrine, resulting in vasodilation, a reduction in heart rate, and an elevation in renal blood flow. Its antihypertensive and cardio/kidney/neuroprotective effects have been reported in preclinical and clinical trials.[2]

As per the JNC 8 recommendations, CCB is recommended as initial therapy in patients with HTN, including those with diabetes.[3] The management of HTN in patients with diabetes mellitus, as per the Research Society for the Study of Diabetes in India (RSSDI) guidelines, suggests the use of cilnidipine. This novel molecule is considered to be more effective and safer than conventional CCBs for Indian diabetic hypertensive patients. Cilnidipine is the recommended choice among other CCBs for individuals with diabetes and HTN due to its kidney and heart-protective effects and improved safety and tolerability profile, specifically in relation to pedal edema.[4]

Advantages of Two-pronged Approach with Cilnidipine

Cilnidipine, a combined L- and N-type calcium channel blocker (dual L/N-type Ca^{2+} channel-blocking action) with its two-pronged approach has been proven to be more effective and safer in managing HTN.[5,6] The inhibition of N-type Ca^{2+} channels efficiently hinders the neurohumoral control in the cardiovascular system, encompassing the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS).[6,7] Blocking the L-type Ca^{2+} channel results in the dilation of peripheral resistance vessels, while inhibiting the N-type Ca^{2+} channels in neurons disrupts the sympathetic nervous outflow. This disruption leads to a decrease in plasma catecholamine levels, which in turn causes additional vasodilation. The vasodilation of pre- and postcapillary resistance vessels leads to a decrease in capillary HTN resulting in excessive filtration of fluid into the interstitium.[8]

Cilnidipine is anticipated to be beneficial for a range of complications linked to HTN.[6,7] The remarkable antihypertensive efficacy and low incidence of ankle edema can be attributed to its dual mechanisms of action (Fig. 1).[9,10]

Cilnidipine is a first-line CCB that can effectively manage HTN either as a standalone treatment or as part of a combined therapy.[11]

- Is a newer dihydropyridine CCB, an L/N-type dual CCB, proven to have a long-lasting antihypertensive effect that has been in clinical use since 1995.
- Demonstrates a prolonged duration of effectiveness in lowering blood pressure (BP) despite a shorter half-life (7.5 hours) and a high protein binding (98%).
- Effectively lowers both systolic blood pressure (SBP) and diastolic blood pressure (DBP) without causing any elevation in pulse rates (PR) or plasma catecholamines.
- Demonstrates consistent antihypertensive efficacy with minimized negative consequences.
- Equal in effectiveness to L-type CCB in reducing BP with lower incidence of pedal edema in people with HTN.
- Extensively researched in controlling high BP and has demonstrated efficacy in providing renal protection, neuroprotection, and cardioprotection.

Cilnidipine: an Effective Antihypertensive

Cilnidipine is a potent antihypertensive medication used to treat mild-to-moderate essential HTN. It exhibits similar antihypertensive properties as other first-line antihypertensive drugs.[12] Patients with HTN can have a significant and sustained decrease

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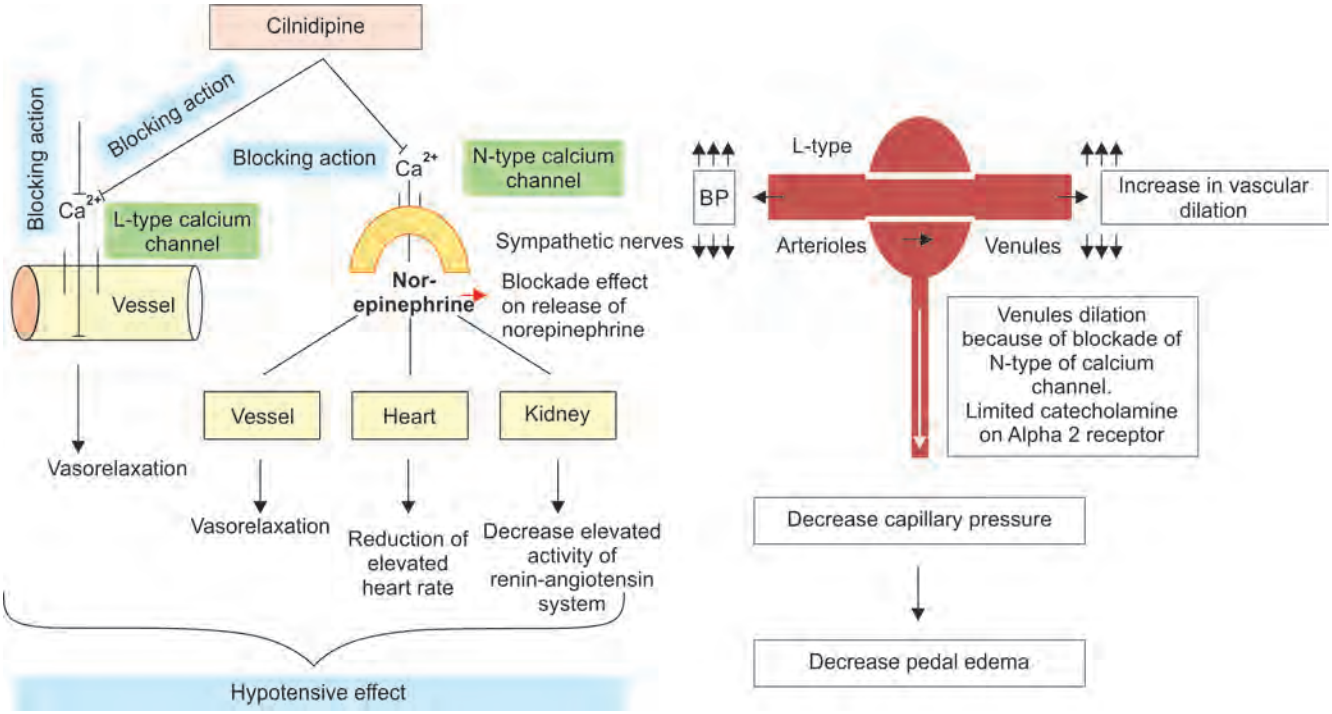
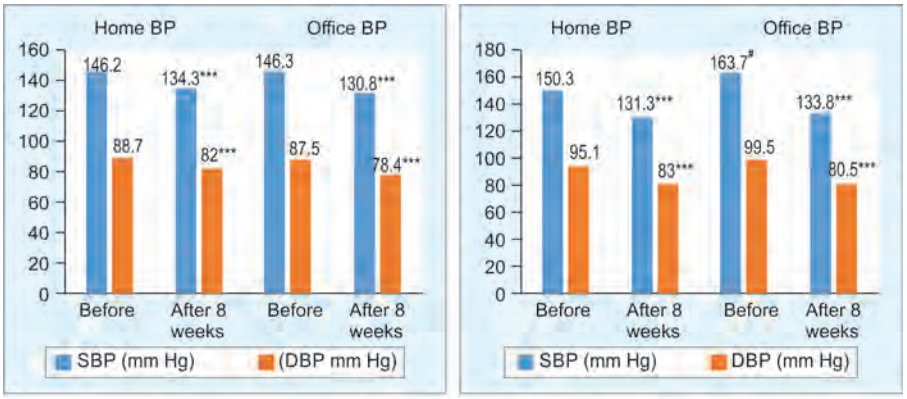


Fig. 1: Dual mechanisms of action of cilnidipine[9,10]



	Home		Office	
Pulse rate	Before	After 8 weeks	Before	After 8 weeks
A	71.5 ± 11.8	74.7 ± 14.6	68.0 ± 9.0**	72.6 ± 11.1
B	69.7± 8.7	81.0 ± 16.0#	66.2 ± 9.4	72.4 ± 16.0**

Figs 2A and B: Morning BP at home and office BP and PR before and after cilnidipine administration in (A) currently treated patients; (B) newly diagnosed patients; DBP, diastolic blood pressure; SBP, systolic blood pressure; values are expressed as the mean ± SD. **, $p < 0.01$; ***, $p < 0.001$ vs. before administration, and #, $p < 0.05$ vs. home blood pressure or home PR in the morning[18]

in BP without any elevation in the heart rate when they are prescribed a once-daily dosage[13,14] that leads to satisfactory clinical control of BP with negligible side effects and lesser pedal edema.[15] It does not induce reflex tachycardia and sympathetic over-activation, instead, it functions to counteract vasodilation[16] and has a substantial impact on decreasing clinic and round-the-clock SBP and DBP that is statistically significant ($p < 0.005$).[16,17]

Efficient for Treating Morning Hypertension and Whitecoat Hypertension

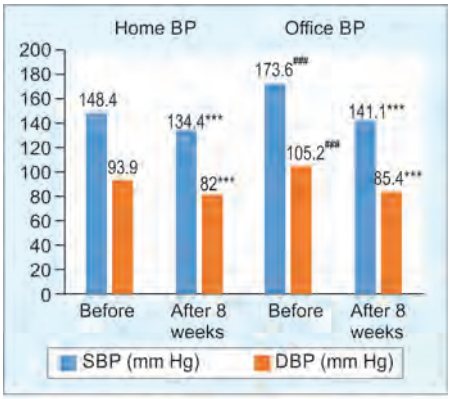
Cilnidipine demonstrates efficacy in patients with HTN who experience morning HTN as a result of possible overactivity of the sympathetic nerves. It is known to greatly reduce BP during sleep when there is an excessive activation of the sympathetic nerve.[11]

Cilnidipine proves to be a valuable medication for managing morning HTN and morning surge, while also effectively reducing the whitecoat effect in individuals with essential HTN.

The morning BP measured at home and the BP measured at the office, which was not well controlled initially (146 ± 11/89 ± 7 mm Hg and 146 ± 17/88 ± 11 mm Hg, respectively) (Figs 2A and B), showed a significant reduction (both $p < 0.001$). In 8 weeks, the morning SBP values of currently treated patients were successfully lowered to the desired level of < 135 mm Hg in 58% of cases. Additionally, 80% of new patients achieved the target level with the once-daily administration of cilnidipine, resulting in a decrease in PR. Furthermore, the administration of cilnidipine also significantly reduced the whitecoat effect (Fig. 3).[18]

Cilnidipine effectively mitigates the whitecoat effect in patients with HTN by inhibiting the N-type voltage-dependent calcium channel. Moreover, it proves to be advantageous for the long-term management of HTN.[19]

In a comprehensive evaluation and meta-analysis of randomized controlled trials (RCTs) conducted among Chinese patients (total of 11 RCTs, $n = 790$) by Xu et al., cilnidipine was reported to have the same antihypertensive effects compared to first-line antihypertensive in managing patients with mild to moderate essential HTN. Cilnidipine has the ability to decrease arterial BP and total peripheral resistance while having no impact on heart rate, cardiac index, or cardiovascular structure.[12]



	Home		Office	
Pulse rate	Before	After 8 weeks	Before	After 8 weeks
	71.6 ± 10.9	82.5 ± 15.1#	67.0 ± 9.6**	73.6 ± 13.9***

Fig. 3: BP and PR in patients with whitecoat effect before and after cilnidipine therapy;18 DBP, diastolic blood pressure; PR, pulse rate; SBP, systolic blood pressure. Values are expressed as the mean ± SD. **, $p < 0.01$; ***, $p < 0.001$ vs. before administration, and #, $p < 0.05$; ###, $p < 0.001$ vs. home blood pressure or home PR in the morning

The clinical utility of cilnidipine lies in its ability to exert sympathoinhibitory effects and achieve balanced vasodilation of both arteries and veins. This makes it an effective treatment option for hypertensive patients.[20] The ACHIEVE-ONE trial conducted in Japan was a comprehensive clinical study on BP and PR using cilnidipine in real-world settings. The results of this large-scale study revealed that cilnidipine effectively reduced both morning systolic blood pressure (MSBP) and morning pulse rate (MPR). Notably, the reduction was more significant in patients with higher MSBP at the beginning of the trial. Similarly, patients with higher MPR at baseline experienced a more pronounced decrease in both MPR and MSBP when treated with Cilnidipine. Conventional L-type CCBs do not exhibit these effects observed with cilnidipine. Cilnidipine effectively decreased mean systolic blood pressure (mean SBP) and mean pulse rate (mean PR) in patients, regardless of their prior administration of β-blockers or renin–angiotensin system (RAS) inhibitors such as angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors. The observed reduction in BP and PR caused by cilnidipine can be attributed to its ability to block both L-type and N-type calcium channels. This mechanism of action is distinct from the blocking of β-adrenergic receptors and inhibition of the RAAS.[21]

Pleiotropic Effects of Cilnidipine

The contrasting nature of cilnidipine's antisympathetic effects sets it apart from other Ca^{2+} channel blockers.[7] Besides the N-type Ca^{2+} channel-blocking action, it has pleiotropic effects. It is found to have renoprotective, cardioprotective and neuroprotective in preclinical and clinical studies.[6]

Renoprotective Effects

L/N-type CCBs exhibit sympatholytic properties and offer renal protection by dilating both afferent and efferent arterioles of the renal glomerulus. This mechanism provides a stronger shield against organ damage caused by HTN when compared to L-type CCBs.[22,23] Cilnidipine has been found to exhibit superior effects in reducing proteinuria progression among hypertensive patients when compared to L-type CCBs.[11] The activation of the ACE2/Ang(1–7) pathway and the suppression of the ACE-Ang II–angiotensin II type 1 receptor pathway are responsible for the renoprotective effect of cilnidipine.[24]

The greater renoprotective effect of cilnidipine is probably due to its antioxidative properties.[11,23] Cilnidipine is known to induce a more pronounced inhibition of proteinuria escalation and a greater decrease in glomerular filtration rate (GFR). Additionally, it demonstrates similar effects to renin–angiotensin inhibitors.[25] It has comparable effects on serum creatinine and eGFR in hypertensive patients while being more efficient in reducing proteinuria or preventing its progression compared to L-type CCBs.[26]

Cilnidipine has been found to possess antihypertensive effects comparable to L-type CCBs in individuals diagnosed with chronic kidney disease (CKD). By transitioning from an L-type CCB to cilnidipine, renal functions can be improved and proteinuria reduced. However, the reverse switch is not found to yield the same results.[27–29]

Cilnidipine is recognized as a distinctive CCB capable of halting the advancement of diabetic nephropathy in individuals with type 2 diabetes and HTN.[30] It may prove to be a valuable additional therapy in cases where only the administration of RAS inhibitors proves inadequate in lowering BP or reducing proteinuria.[31]

Cilnidipine exhibits great potential for treating HTN and hyperuricemia in patients with CKD. It effectively lowers the production of uric acid without any negative impact on the serum uric acid level. Following a switch to cilnidipine, patients with increased urinary uric acid excretion (urinary uric acid/creatinine of ≥0.50 g/g) showed a noticeable reduction of approximately 0.1 g/g in the urinary uric acid/creatinine ratio.[32]

Cilnidipine has been proven to be a safe and effective treatment for Indian patients with mild-to-moderate HTN and type 2 diabetes mellitus. It has shown significant results in reducing both SBP and DBP, as well as microalbuminuria. After 6 months of treatment, the mean SBP decreased from 150.07 ± 5.44 to 123.03 ± 5.23 mm Hg, the mean DBP decreased from 95.5 ± 8.15 to 80.8 ± 2.42 mm Hg, and microalbuminuria decreased from 66.62 ± 8.39 to 38.8 ± 6.45 mg/L. The overall mean reduction in microalbuminuria was 27.56 ± 10.25 mg/L.[33]

Cardioprotective Effects

A prolonged risk of cardiovascular mortality is linked to an elevated heart rate, regardless of other factors that contribute to heart disease. The conventional dihydropyridine calcium antagonists commonly cause adverse effects such as increased PR, increased sympathetic activity, and reflex tachycardia due to a decrease in BP.[17]

Cilnidipine effectively reduces cardiac sympathetic overactivity in patients with essential HTN, without inducing coronary sympathetic hypertonia in response to BP reduction, which sets it apart from L-type CCBs.[34] Additionally, cilnidipine's N-type calcium channel blockade does not lead to reflex tachycardia, making it a beneficial alternative.[17] Cilnidipine has also shown efficacy in improving arterial stiffness in individuals with essential HTN.[22]

Cilnidipine effectively reduces vascular endothelial dysfunction and is beneficial in the long-term treatment of cardiovascular disorders.[11] Cilnidipine has been recognized for its ability to inhibit excessive cardiac sympathetic activity through the blockade of N-type calcium channels. Additionally, it has been shown to enhance left ventricular (LV) diastolic function in individuals with hypertensive heart disease (HHD).[7,35]

Patients with HHD witness significant improvements in their LV diastolic function and cardiac sympathetic activity after 6 months of treatment, with no alterations in the LV mass.[35]

Cilnidipine has been recognized for its ability to enhance LV systolic function in patients with HTN, regardless of any BP alterations.[36] The response to cilnidipine treatment in patients with essential HTN shows a biphasic pattern in LV diastolic performance. Initially, there is an increase in early diastolic transmitral flow velocity, followed by a later increase in early diastolic LV wall motion velocity, resulting in improved LV relaxation. This finding is suggestive of cilnidipine's positive impact on LV diastolic function in patients with essential HTN.[37]

Neuroprotective Effects

Cilnidipine, which inhibits the N-type calcium channels, exhibits a lower variability in BP and proves to be a more advantageous option for managing BP in patients with cerebrovascular disease when compared to other CCBs. In a study conducted by Nishioka et al., the 24-hour BP variability was assessed in 309 patients who had a previous cerebrovascular disease and were undergoing treatment with either an ACE inhibitor, ARB, β-blocker, or CCB. Among the different CCBs examined, Cilnidipine was observed to have a higher occurrence of reducing BP variability. This finding suggests that cilnidipine may be more effective in stabilizing BP levels.[38]

Aoki et al. conducted a large-scale prospective postmarketing, real-world study in Japan to evaluate the effectiveness of cilnidipine in treating uncontrolled BP in poststroke hypertensive patients. The study included 2,667 patients (60.4% male; mean age 69.0 ± 10.9 years). The results showed that cilnidipine was effective in reducing BP and was well tolerated. The proportion of patients who achieved well-controlled BP (<140/90 mm Hg) increased from 21.5 to 65.3% with cilnidipine treatment. The efficacy of cilnidipine was consistent across different clinical subtypes of stroke. This study highlights the potential of cilnidipine as a treatment option for poststroke HTN.[39]

Cilnidipine in Combination Therapy

Use of a combination of a CCB and an ARB is widely recognized as the standard approach for treating HTN.[40] Cilnidipine is a potent antihypertensive medication that effectively inhibits the progression of CKD and reduces the risk of cardiovascular complications when used in combination with RAS inhibitors.[41] The combination of cilnidipine and ARB can lead to improved renoprotective effects in hypertensive patients. This is achieved through a reduction in urinary albumin excretion and an increase in the ratio of Ang(1–7) to Ang II in plasma.[24]

Safety and Tolerability of Cilnidipine

Ankle edema, a frequently occurring side effect of L-type CCBs caused by dilatation of precapillary vessels, is aesthetically unappealing and may lead to reduced adherence to medication and discontinuation of treatment. Cilnidipine, by blocking both N- and L-type channels, induces dilation in both pre- and postcapillary vessels, which limits fluid filtration and consequently reduces pedal edema. Moreover, cilnidipine does not elevate heart rate as it inhibits sympathetic activity *via* the N-type calcium channel.[5,34] Cilnidipine proves to be a reliable and safe option for managing essential HTN (Table 1), with improved patient adherence and reduced rates of treatment discontinuation.

Table 1: Cilnidipine use in HTN management

Novel and unique CCB	Inhibits sympathetic N-type Ca^{2+} channels in addition to vascular L-type Ca^{2+} channels[7,42] Advantageous over other L-type CCBs—less influence on HR and autonomic nervous system causing less tachycardia[14,41] Favorable for various types of complications of HTN[6] Better safety and tolerability vs L-type CCBs with reduced proteinuria and pedal edema[5,43]
A lesser degree of RAAS activation	Superior organ protection in addition to anti-albuminuric effect[44] A promising option for the treatment of HTN in patients with CKD already on RAAS inhibitors[44]
Greater antiproteinuria effect	Superior to L-type CCBs in preventing the progression of proteinuria in HTN patients when coupled with an RAS inhibitor[45]
Efficient antihypertensive with convenience of dosing	Administered once daily is an efficient antihypertensive regardless of the time of dosing; without reflex tachycardia; and no increase in sympathetic nervous activity compared to other CCBs[13,16,42]

Conclusion

Cilnidipine is distinguished from other L-type CCBs and other antihypertensive agents in that it suppresses sympathetic N-type Ca^{2+} channels alongside vascular L-type Ca^{2+} channels, leading to harmonious vasodilation of both arteries and veins. This attribute proves to be beneficial in the treatment of patients with HTN. At therapeutic dosages, it offers good BP regulation and its antihypertensive effects are comparable to other primary antihypertensive medications. The usual recommended dosage is 5–10 mg/day, which can be increased to a maximum of 20 mg/day. It causes a gradual and prolonged reduction in BP without triggering an increase in heart rate. It serves as a superior option for individuals experiencing heightened sympathetic activity, proteinuria, or pedal edema. The inhibition of N-type Ca^{2+} channels effectively hinders the neurohumoral regulation within the cardiovascular system, encompassing the sympathetic nervous system and the RAAS. This blockade proves advantageous in managing diverse complications associated with HTN.

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REVIEW ARTICLE

Exploring the Labyrinth: Imaging in Systemic Vasculitis

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Abstract

Systemic vasculitis is an immune-mediated group of disorders broadly classified based on the involved vessel type. It has myriad clinical presentations, adding to the challenge of timely diagnosis and management. Thus, imaging has taken center stage in the diagnosis of these disorders as there is a lack of definitive clinical diagnostic markers. Various available imaging modalities can be used for diagnosis and follow-up on these patients.

The coronavirus disease 2019 (COVID-19) has added a new dimension to the already existing problem of vasculitis. The virus has shown great affinity for the vascular endothelium, leading to multisystem organ vasculitis. There has been a spike in vasculitis cases in the COVID-19 pandemic era, thus necessitating more research and studies in this field for a better understanding of the disease.

In this review, we wish to summarize the various imaging spectrums of classical systemic vasculitis along with the new addition of COVID-19-related vasculitis to the already long list.

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Introduction

Vasculitis is a multisystem disorder that causes immune-mediated inflammation of the blood vessel walls. In 1994, the Chapel Hill Consensus Conference (CHCC) gave a classification system based on the size of the predominantly involved vessel (Fig. 1).[1] The International CHCC in 2012 proposed nomenclature for previously poorly defined systemic vasculitis classification adopted since 1994. It has been classified into three broad categories based on the affected vessel size, namely large vessel vasculitis (LVV), medium vessel vasculitis (MVV), and small vessel vasculitis (SVV).[2] The basic concept states that any type of vasculitis can affect a vessel of any size; only the predominantly involved vessel has been included in the definition.

Role of Imaging

A suspected case of vasculitis needs a comprehensive clinical and radiological evaluation for confirmation of the diagnosis as well as for following up on the disease. Ultrasonography (USG) and contrast-enhanced ultrasound (CEUS) help in both structural and functional evaluation of the disease. Computed tomography (CT), computed tomography angiography (CTA), magnetic resonance imaging (MRI), and magnetic resonance angiography (MRA) help better demonstrate the vessel wall pathology, *viz* circumferential mural thickening, areas of stenoses, occlusions, and aneurysmal dilatations. Positron emission tomography (PET) CT and CEUS can tell us about disease activity and, hence, can play an important role in patient follow-up.[2] Digital subtraction angiography (DSA) has been the best investigation for diagnosis with the added advantage of its role in intervention. However, it is invasive, with an additional risk of radiation exposure.

Thus, these imaging techniques play a great role in assessing the distribution patterns as well as the extent of the disease with numerous advantages as well as limitations as described in (Table 1).[3]

Large Vessel Vasculitis

Large vessel vasculitis (LVV) usually involves the aorta and its main branches, excluding the most peripheral branches. It is the most common primary vasculitis, and it includes giant cell arteritis (GCA) and Takayasu arteritis (TKA). There is considerable overlap between the distribution patterns and histopathology of both GCA and TKA with atypical involvement of small- and medium-sized arteries as well as the coronary arteries in TKA (Table 2).[4]

Giant Cell Arteritis

Giant cell arteritis (GCA) is commonly seen in North European people who are >50 years of age.[5] It involves the aorta with an affinity for the carotid artery and its extracranial branches, typically sparing the intracranial branches. Cranial GCA presents with headache, jaw claudication, visual disturbances, and tenderness of temporal arteries. It includes the involvement of the superficial temporal artery, occipital, and facial artery.[6]

Giant cell arteritis (GCA) is considered a rare entity in the Indian subcontinent population, but the involved population shows a higher rate of ophthalmic complications resulting from ischemia, such as permanent vision loss.[7]

Temporal artery biopsy was considered the gold standard for the diagnosis of GCA, but it is still important for the diagnosis of cranial GCA. With the advancement in imaging, temporal artery biopsy has largely been replaced by imaging. However, European League against Rheumatism (EULAR) has recommended biopsy in cases of GCA that have not been confirmed in clinical, laboratory, and imaging studies.[6]

Imaging

On USG, hypoechoic circumferential wall thickening is seen, known as the "halo sign." On Doppler, vessel stenosis and occlusions with consecutive alterations in flow velocities are seen.

Magnetic resonance imaging (MRI) of the cranial arteries shows mural thickening, contrast enhancement, stenosis, occlusion, and aneurysmal dilatations.[8] The EULAR recommends USG of the temporal artery along with the axillary artery to look for noncompressibility and halo sign. MRI is advised in cases where USG is not feasible in cranial arteries to look for mural inflammation. CT and PET are not currently recommended for assessment. For extracranial GCA, USG, CT, PET, and MRI are advised. USG, however, has a lesser role among all these modalities due to the limited accessibility of the thoracic aorta.[6]

On CEUS, grading between vascularization and carotid intima–medial thickness (IMT) can be performed. No current role of DSA has been described in the diagnosis of LVV.[9]

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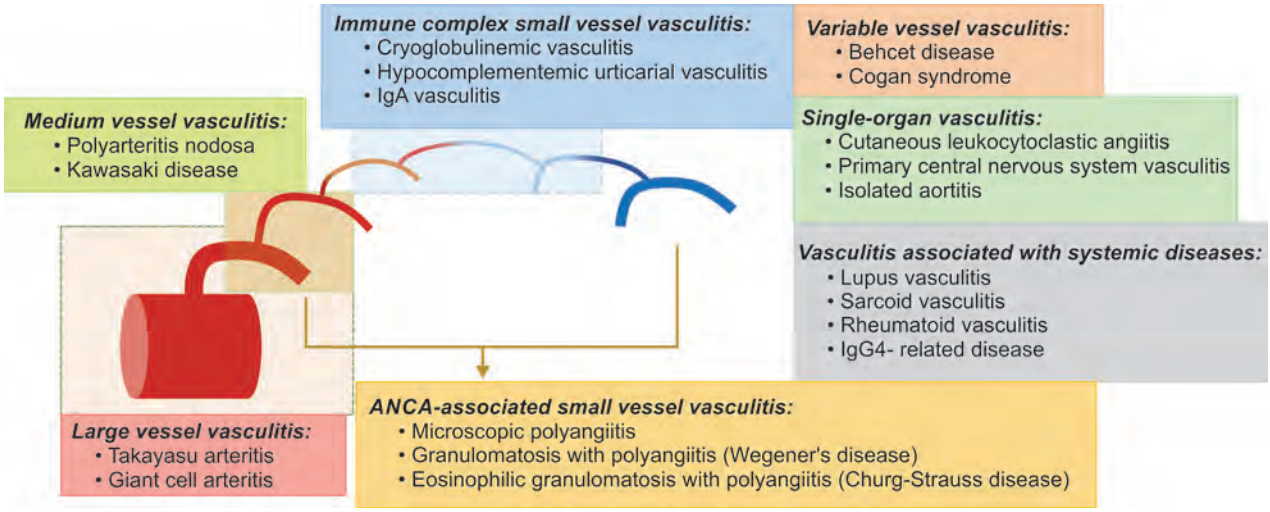


Fig. 1: Revised Chapel Hill Consensus criteria (2012) for vasculitis[2]; ANCA, antineutrophilic cytoplasmic antibody; Ig, immunoglobulin

Table 1: Role of current imaging modalities

Modality	*Imaging findings*	*Benefits*	*Limitations*
USG	Mural thickening; noncompressible halo	Lower cost, no ionizing radiation	Operator dependent; aorta disease undetected
CEUS	Contrast enhancement of the wall	It can be used for monitoring disease activity without using a nephrotoxic agent	Ultrasound contrast is not easily available, and every USG machine may not be compatible with CEUS
CT/CTA	Vessel wall thickening; late contrast enhancement; areas of occlusions and aneurysmal dilatations	Operator independent	Ionizing radiation; renal injury risk from Iodinated contrast
MRI/MRA	Vessel wall thickening; contrast enhancement; areas of occlusions and aneurysmal dilatations	Assesses disease load, complications, no radiation	Time-consuming; expensive, renal injury risk from gadolinium-based contrast
PET	Increased tracer uptake	Assesses disease load and activity; hybrid CT/MRI	Radiation exposure; lack of specific tracers
DSA	Stenosis/occlusion/aneurysmal dilatation	Diagnostic as well as therapeutic	Ionizing radiation; invasive, renal injury risk from Iodinated contrast

CEUS, contrast-enhanced ultrasound; CT, computed tomography; CTA, computed tomography angiography; DSA, digital subtraction angiography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PET, positron emission tomography; USG, ultrasonography

Takayasu Arteritis

Takayasu arteritis (TKA) affects the younger age group, which is fewer than 40 years of age, with a female preponderance. It is more common among Asian and African people than among Europeans, and it was first described in Japan.[4] Most of the clinical manifestations that are similar to GPA include asymmetricity of pulses, pulselessness, or difference in blood pressure in both limbs.[10]

Imaging

Aorta, common iliac arteries, and external iliac arteries may show changes in stenosis with collateral formation. The coronary and pulmonary arteries are frequently involved as compared to GCA.[4] EULAR recommends MRI as the initial investigation for evaluation of TKA changes. Alternatively, USG, CT, or PET may also be used. USG has a limited role in the assessment of the thoracic aorta.[3]

Digital subtraction angiography (DSA) plays both diagnostic and therapeutic roles. It is not very useful in early diagnosis as it can't detect the early vasculitis changes of the vessel wall. Due to other disadvantages such as exposure to ionizing radiation, invasive nature, and use of iodinated contrast, it is mainly being used for endovascular treatment rather than in diagnosis.[11] Based on angiographic appearance, Hata et al. divided TKA into five types. Type I includes the involvement of major arch branches, IIA is the involvement of the ascending aorta, arch, and its branches, and IIB is IIA includes the descending thoracic aorta as well. Type III is the involvement of the descending thoracic aorta, including the abdominal aorta as well, with or without the involvement of the renal vessels. Type IV includes the involvement of the abdominal aorta with or without the involvement of the renal arteries. Type V is the entire thoracic and abdominal aorta with or without the involvement of the renal arteries.[12,13]

Contrast-enhanced ultrasound (CEUS) is a noninvasive modality without the risk of nephrotoxicity, which can improve the visualization and quantification of vessel wall vascularization (Figs 2A and B). Vessel wall enhancement can be seen in the circumferential, hypoechoic, homogenous wall thickening of the carotid vessels. The grade of vasa vasorum neovascularization can be compared to the vessel wall thickness, that is, IMT.[14]

Computed tomography (CT) angiography helps find out the extent of the disease. The presence of mural

thickening and wall enhancement, luminal stenosis, and aneurysmal dilatations can be easily delineated (Figs 3A to F). Concentric mural thickening of the arteries with a lower attenuating inner wall and higher attenuating outer wall, as seen in the venous phase, gives rise to the "double ring" sign.[15] Involvement of abdominal arteries is common, mainly involving renal arteries, superior mesenteric artery, coeliac artery, and inferior mesenteric artery.[16] Ionizing radiation and iodinated contrast hinder its use in young patients as well as for repeated follow-up imaging.[2]

Table 2: Difference between TKA and GCA

Finding	*TKA*	*GCA*
Age	20s–30s	After 50s
Incidence	2/million	20/100,000
Vessels involved	Large elastic arteries; spare temporal artery	A predilection for carotid artery branches in neck and temporal arteries; typically spares intracranial vessels
Large vessel involvement	Long narrowed segments; mural thickening; dilatation and thrombosis are more frequent	Long stenotic segments; mural thickening; dilatation and thrombosis
Cardiac involvement	More	Less

Magnetic resonance imaging/angiography (MRI/MRA) is the recommended investigation in the younger age group as it provides better soft tissue resolution and is free of ionizing radiation. The use of fat suppression and black blood sequences further improves the visualization of contrast enhancement and helps in the assessment of disease activity and burden.[17] MRA helps in recognizing the disease extent and vessel status. MRI T2 weighted images show hyperintensity in the vessel wall, suggesting mural edema, which, if it shows contrast enhancement, suggests active inflammation. Diffusion-weighted imaging (DWI) helps differentiate chronic disease from active disease (Figs 4A to F). This is due to the impaired diffusion in the aortic wall in the acute phase of the TKA.[18]

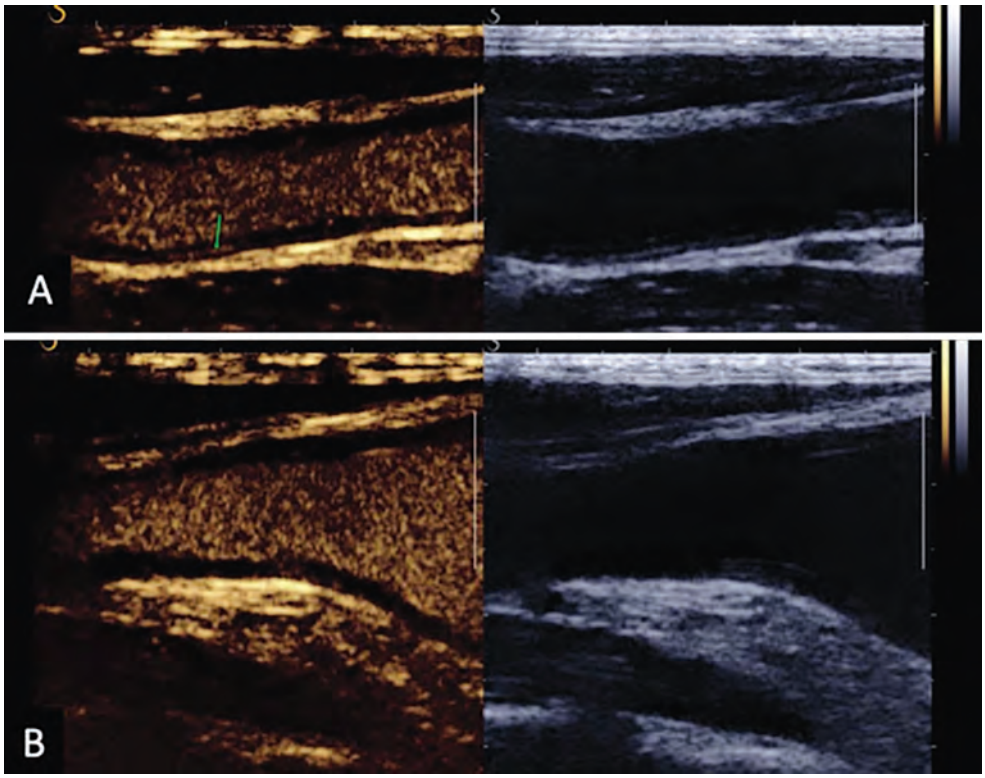
Positron emission tomography (PET) CT is highly sensitive for measuring disease activity. All vessels with a diameter of more than 4 mm can be virtually seen on PET, but smaller arteries, like temporal or renal arteries, cannot be visualized. In active disease, the inflamed vascular wall shows increased tracer uptake in a linear fashion (Figs 5A to D).[19] For semiquantitative estimation of tracer uptake, a scale known as the Meller scale has been devised, in which vessel uptake is compared to the uptake in the liver.[20] PET/CT usage has a concern for radiation exposure for patients with TKA, who are predominantly young women.[18]

Medium Vessel Vasculitis

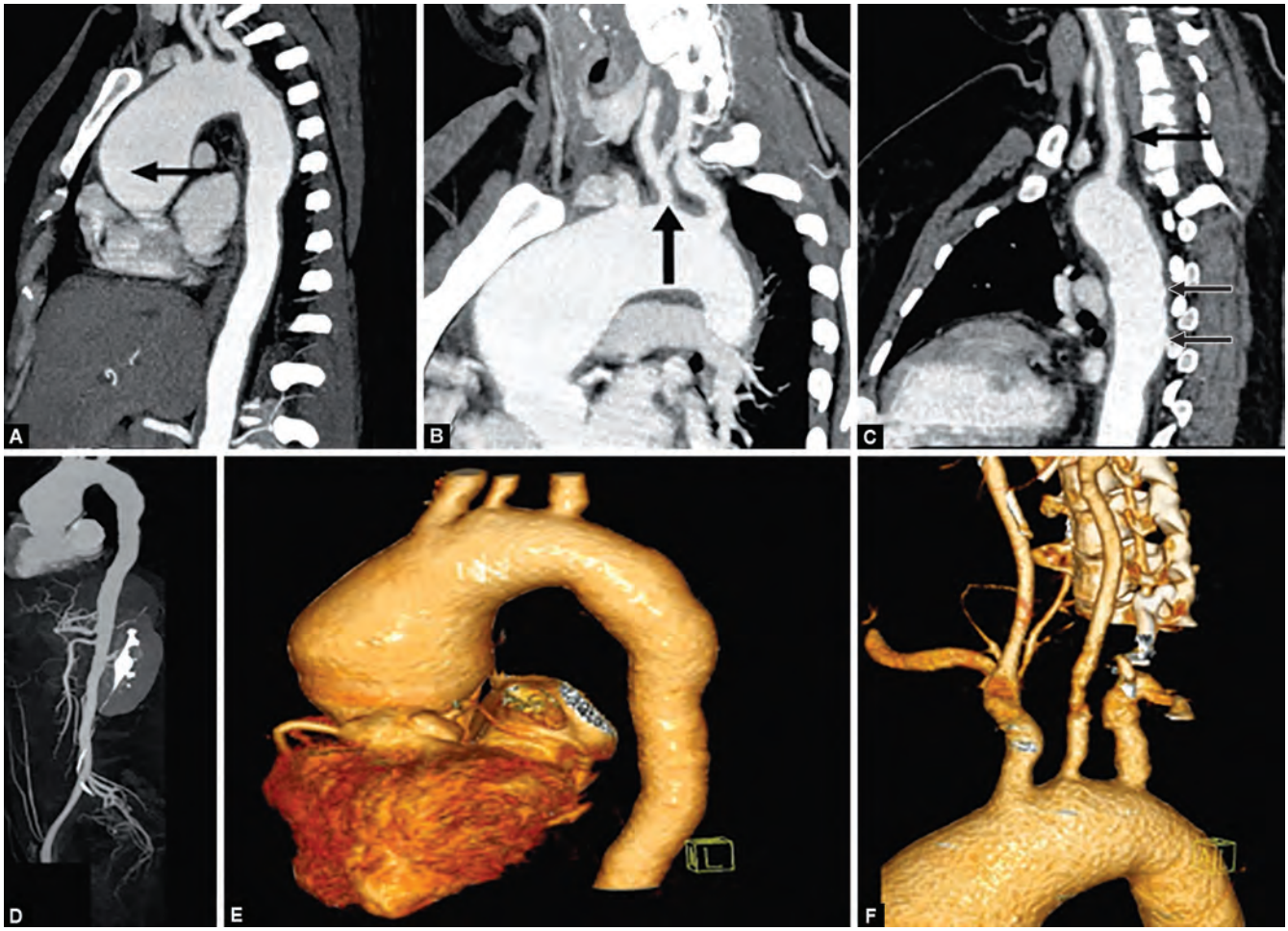
Medium vessel vasculitis (MVV) mainly consists of two entities, namely polyarteritis nodosa (PAN) and Kawasaki disease (KD).

Polyarteritis Nodosa

It necrotizes arteritis in medium and small vessels. In CHCC's 1994 classification, ANCA was thought to be associated with PAN; however, in the 2012 update, ANCA-associated vasculitis and PAN were declared separate entities, though they can appear clinically and pathologically similar. It is seen commonly in men in their 50s–70s with male preponderance. An association between HIV, hepatitis B virus, and PAN has been proposed, but the exact etiology is not known.[21]



Figs 2A and B: Takayasu arteritis: (A) CEUS with corresponding grayscale images of a carotid artery demonstrating minimal intimal contrast enhancement in an active disease (arrow) (B) As compared to a posttreatment inactive disease showing no obvious uptake in the hypoechoic intima layer; CEUS, contrast-enhanced ultrasound



Figs 3A to F: Takayasu arteritis—sagittal reformatted; (A, B, C) CT angiography images show a case of a 25-year-old staff nurse who presented with easy fatigability and general weakness on imaging showed aneurysmal dilatation as well as diffuse, circumferential wall thickening of the root of the aorta (arrow in A), aortic arch branches (arrow in B), and descending thoracic aorta showing long segment diffuse intimal thickening (arrows in C); (D) MIP reformatted and (E, F) volume rendered; follow-up images after 1 year of steroid therapy show residual dilatation of the aortic root, arch, and branches; CT, computed tomography; MIP, maximum intensity projection

Imaging

Computed tomography angiography (CTA) and MRA may show larger aneurysms, diffuse wall thickening, occlusions, and ischemic areas in the involved organs.[22] Multiple complications can occur in PAN following rupture of aneurysms leading to hemobilia (Figs 6A to H), peritoneal, and retroperitoneal hemorrhage, depending upon the site.[23]

Digital subtraction angiography (DSA) is mainly performed for renal and mesenteric vessels. The angiography findings include multiple microaneurysms, segmental narrowing, and narrowing of the peripheral vascular tree (Figs 6A to H). A total of >10 aneurysms of 2–5 mm in size are seen in any of the visceral circulatory systems. The main area of involvement is the point where arterial branching occurs.[23] Endovascular embolization may be performed to manage complications like hemobilia (Figs 6A to H).

Kawasaki Disease

Kawasaki disease (KD) is a vasculitis involving the medium and small vessels, often affecting the coronary arteries. The highest incidence has been noted in Japanese and Korean children <5 years of age with a predilection towards the male.[24]

Imaging

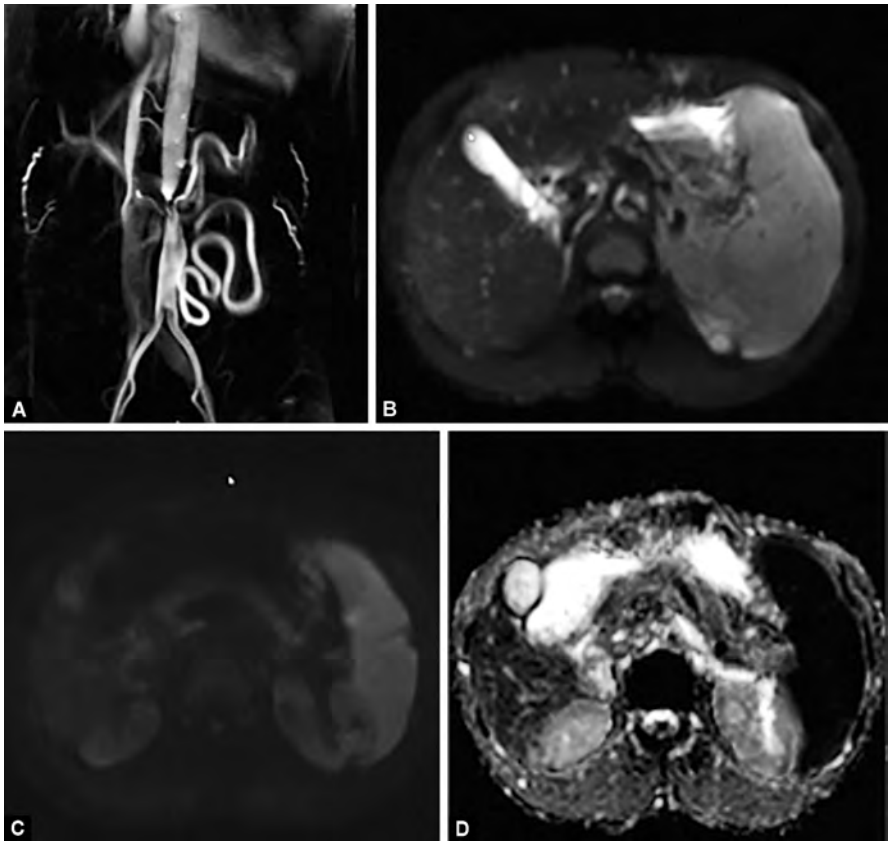
Ultrasonography (USG) can be used for the evaluation of cervical lymphadenopathy in children. Gall bladder wall edema is seen in the acute phase due to perivascular inflammatory infiltration.[25]

Computed-enhanced CT of the neck has been used to differentiate between KD and non-KD-related cervical lymphadenopathy. KD patients have characteristic findings of edema in the nasopharynx, retropharyngeal space, and lateral cervical region. Level IIA lymph nodes are the most common group of involved lymph nodes, along with the absence of involvement of the VB nodes.[24]

Computed tomography angiography (CTA) and MRA help in the noninvasive delineation of coronary artery aneurysms (Figs 7A and B) along with the classification of the aneurysms based on their size, which helps in prognosis. Small aneurysms have a diameter of <5 mm, medium-sized aneurysms are 5–8 mm in size, and large-sized aneurysms have a size of >8 mm. Smaller aneurysms may eventually regress; however, larger aneurysms are more prone to thrombosis.[26] Cardiac MR may help in better assessment of myocardial perfusion and function.[25]

Small Vessel Vasculitis

Small vessel vasculitis (SVV) is a necrotizing inflammation affecting intraparenchymal small arteries along with arterioles, capillaries,



Figs 4A to D: Takayasu arteritis; (A) Coronal MRI MIP angiography; (B) T2 axial image shows the presence of show luminal narrowing and wall thickening of the aorta at the level of renal arteries; (C) Diffusion-weighted and (D) ADC images shows the absence of diffusion restriction in the aortic wall thickening, suggestive of inactive disease; MRI, magnetic resonance imaging; MIP, maximal intensity projection.

and venules in skin, lungs, intestines, peripheral nerves, and skeletal muscles.[27] It is subdivided based on the paucity or prominence of immunoglobulins in the vessel walls. Vasculitis with few or no immune complexes in the vessel wall is called antineutrophilic cytoplasmic amtibody (ANCA) associated vasculitis, and the other type is called immune complex-associated vasculitis. ANCA-associated vasculitis shows the presence of autoantibodies against neutrophilic cytoplasmic granular proteins proteinase-3 and myeloperoxidase.[2] Variable vessel vasculitis and vasculitis associated with systemic diseases have also been included in this category.[28] It occurs in the peak age of 50s–60s without any obvious sex predilection.[2]

Imaging

Chest radiographs are done for the initial workup; USG can help diagnose pleural and renal pathologies, whereas disease extent can be better evaluated on CT. CT further helps in looking at the abnormalities of the heart, sinonasal cavities, and lungs. Intracranial, orbital, and sinonasal involvement is better appreciated on MRI.[29]

Antineutrophilic Cytoplasmic Antibody-associated Small Vessel Vasculitis

It has three subtypes *viz* granulomatosis with polyangiitis (GPA), microscopic polyangiitis, and eosinophilic GPA (EGPA)

Granulomatosis with polyangiitis: Granulomatosis with polyangiitis (GPA), earlier known as Wegener's granulomatosis, is characterized by upper respiratory involvement (100%), lower respiratory involvement (90%), and glomerulonephritis (80%).[30]

Sinonasal involvement in CT scans is seen in the form of mucosal thickening, erosions, and new bone formation. The most common site for erosions is the anterior ethmoidal region. Punctate areas of bony erosions may be seen in the midline septum, with turbinates extending into the adjacent antra and other sinuses. The concurrent bony destruction and new bone formation are characteristic of GPA. Disease from the sinonasal and orbital location can extend into the skull base, resulting in cranial neuropathy; however, intracranial involvement is rare. Serous otitis media can result from temporal bone involvement.[30]

Common CT findings in most patients with pulmonary involvement are nodules and masses. The characteristic finding is the waxing and waning of nodules, which are randomly distributed. Larger nodules are more prone to cavitation and are seen in up to 50% of the cases. Surrounding hemorrhage can result in the formation of ground glass opacities (GGOs). Adjacent organizing pneumonia can give rise to the "reverse halo sign." Pleural effusions are the most common pleural abnormality. Other rare forms of involvement may be thickening, nodularity, and pneumothorax[31] (Figs 8A and B).

Computed tomography (CT) is also an excellent modality to document the larynx and tracheal involvement. The most commonly involved location is subglottic. Involvement may be a short segment or multifocal, smooth, or nodular. Differentials include relapsing polychondritis, tracheobronchopathia osteochondroplastica, and amyloidosis.[32]

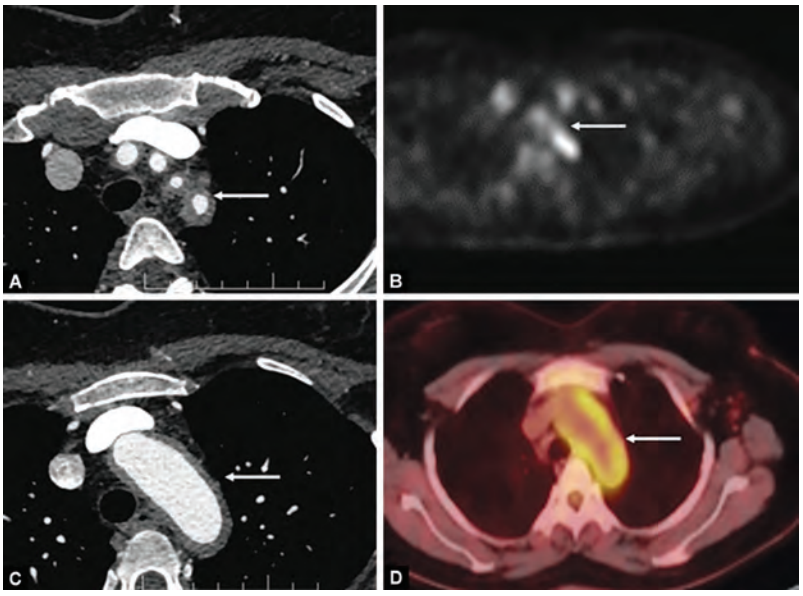
The most common orbital manifestation of the GPA is the orbital pseudotumor. Unilateral and extraconal diffuse inflammatory infiltrate is seen. Enopthalmos can result from diffuse fibrotic tissue, leading to orbital contracture.

Eosinophilic granulomatosis with polyangiitis: Eosinophilic GPA (EGPA) is also known as Churg-Strauss syndrome. Lungs are most commonly affected, resulting in CT appearance of GGOs, consolidations, nodules, interstitial thickening, and bronchial wall thickening. The predominant pattern of involvement is subpleural and lobular distribution, which most commonly involves the lungs. (Figs 9A to D). Cardiovascular complications include myocarditis, coronary arteritis, pericarditis, and pericardial effusion, for which MRI may be warranted.[33]

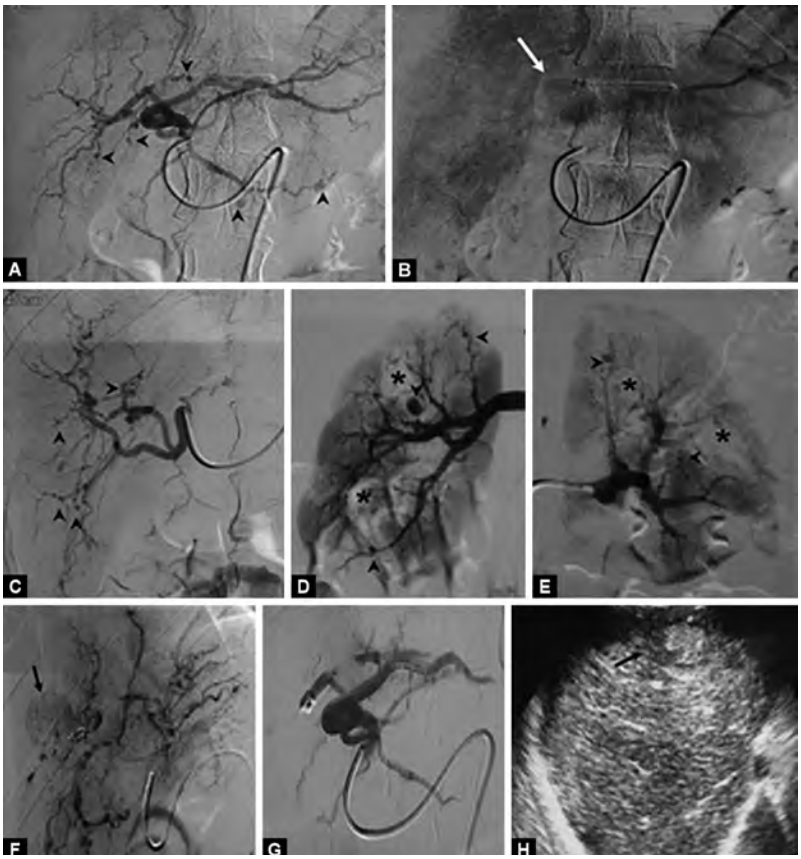
Microscopic polyangiitis: Microscopic polyangiitis commonly involves the kidneys, lungs, skin, and gastrointestinal system. Kidney involvement is in the form of necrotizing glomerulonephritis. GGOs, consolidations, and diffuse alveolar hemorrhage are noted in pulmonary involvement.[34] It cannot be differentiated from EGPA on imaging.

Immune Complex Small Vessel Vasculitis

Immunoglobulin A (IgA) vasculitis (Henoch–Schoenlein purpura) is the prototype of immune complex SVV. It presents with purpuric skin rash, gastrointestinal bleeding, abdominal pain, and glomerulonephritis. Ultrasound helps diagnose epididymal orchitis, hydrocele, and funiculitis. CT may



Figs 5A to D: Role of PET-CT in Takayasu arteritis—case of a 33-year-old lady with occasional pain and numbness in left hand and giddiness on and off for the last 3 years following pregnancy; axial CT angiography images show circumferential mural thickening of the aortic arch (arrow in C) and branches (arrow in A); (B) Tracer uptake in PET images; PET-CT (D) showing uptake in the circumferential mural thickening of the aortic arch and its branches, confirming active nature of the disease; PET, positron emission tomography; CT, computed tomography



Figs 6A to H: Polyarteritis nodosa (PAN) with hemobilia; DSA images show multiple small aneurysms arising from the branches of the hepatic arteries (arrowheads A and C); multiple small aneurysms from the segmental renal artery branches; (D, E) Postcoiling hepatic artery DSA run shows the disappearance of the aneurysms; (F, G) Ultrasound image shows (H) hypoechoic area in the liver, suggesting infarct following embolization

help in case of gastrointestinal bleeding and ischemia.[35]

Variable Vessel Vasculitis

Behçet's disease is the prototype of variable vessel vasculitis with multiorgan involvement. It presents with recurrent aphthous oral ulcers, uveitis, and genital ulcers, along with other multisystem involvement. The most common form of vascular involvement is venous stenosis, followed by arterial stenosis and aneurysm. Sudden death can occur due to rupture of large aortic or arterial aneurysms.[36]

Vasculitis Associated with Systemic Diseases

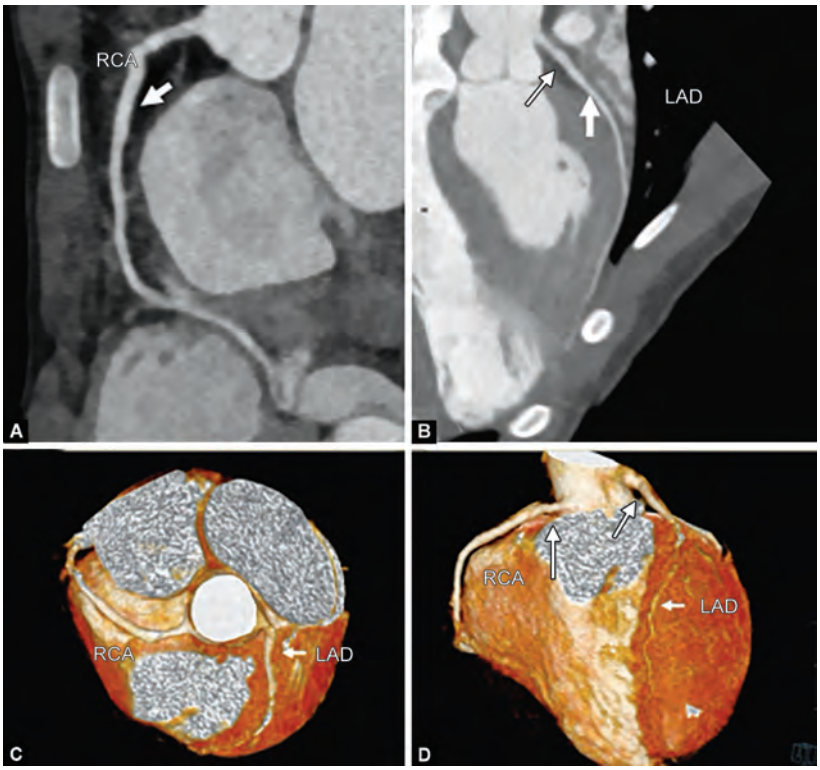
Vasculitis associated with systemic diseases is systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) related vasculitis.

Systemic lupus erythematosus (SLE) is an autoimmune disease with a peak age in the 20s–40s, in which there is complex immune deposition and inflammation involving multiple systems.[37] The respiratory system is relatively commonly involved, leading to symptoms of dyspnoea and poor physical activity tolerance in 40–57% of the patients, either secondary to infection or pulmonary edema from renal failure.[38] CT may show pleural effusion due to serositis, lymphadenopathy, and areas of ground glass opacity (Figs 10A and B). Recurrent infections lead to bronchiectasis and respiratory dysfunction.[39]

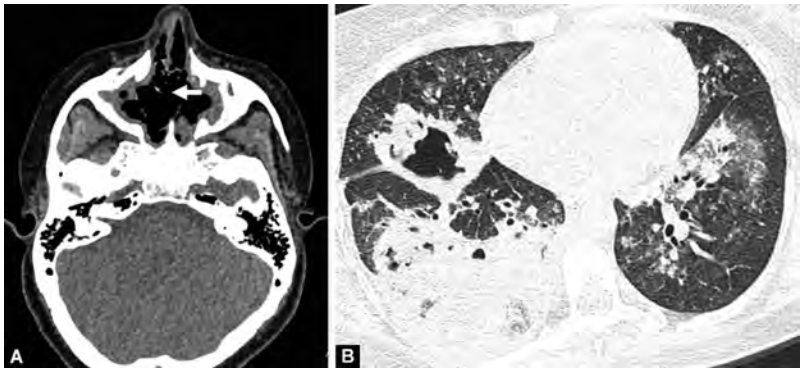
Rheumatoid arthritis (RA) is a multisystem disease that commonly can involve the lungs and is the cause of significant morbidity.[40] Pulmonary vasculitis occurs in severe forms of RA.[41] Another rare presentation is diffuse alveolar hemorrhage, which occurs in association with capillaritis or vasculitis[42] (Figs 11A and B).

Coronavirus Disease 2019-related Vasculitis

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to spread across the countries since its first report in December 2019 from China. During this pandemic, there has been an emergence of COVID-19-associated multisystem inflammatory vascular disease. It leads to endothelial cell inflammation, dysfunction, and apoptosis. Younger age groups, including children, have shown multisystem inflammatory syndrome (MIS-C), which mimics KD. Cytokine-related inflammatory disorder is commonly seen within 2 weeks of infection in adults; however, in children, MIS-C is seen after 2 weeks.[43]



Figs 7A to D: Kawasaki disease (KD); coronary angiographic sagittal reformatted images; (A, B) 4-year-old male child diagnosed with KD shows a mildly dilated pRCA (arrow in A) and pLAD (arrow in B); coronary angiographic volume reformatted images (C, D); pRCA, proximal right coronary artery; pLAD, posterior left anterior descending artery



Figs 8A and B: Granulomatosis with polyangiitis (GPA); NCCT (A) Axial image showing destroyed nasal septum (white arrow) with mucosal thickening in bilateral maxillary sinuses; CT image (B) Lung window shows multifocal areas of consolidation and GGO in both lungs and cavity formation in the right middle lobe; there are small random nodules in the left lower lobe

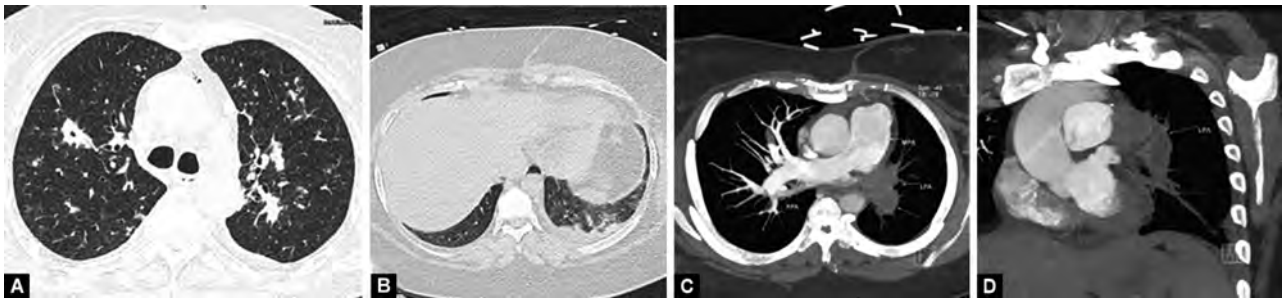
Coronary artery abnormalities in the form of dilatation and small aneurysms have been found in 9–24% of the patients (Figs 12A to D).[44] Some association between COVID-19 and other IgA-related diseases has also been found, which could be the cause of coronary involvement.[45]

Pulmonary vasculitis presents as vessel dilatation with mosaic perfusion patterns. Perfusion abnormalities may also be demonstrated on dual-energy CT. Hanafi et al. reported neurologic complications of COVID-19, which include cerebral vasculitis leading to extensive cerebral small-vessel ischemic lesions, hemorrhage, and punctate postcontrast enhancement pattern.[46]

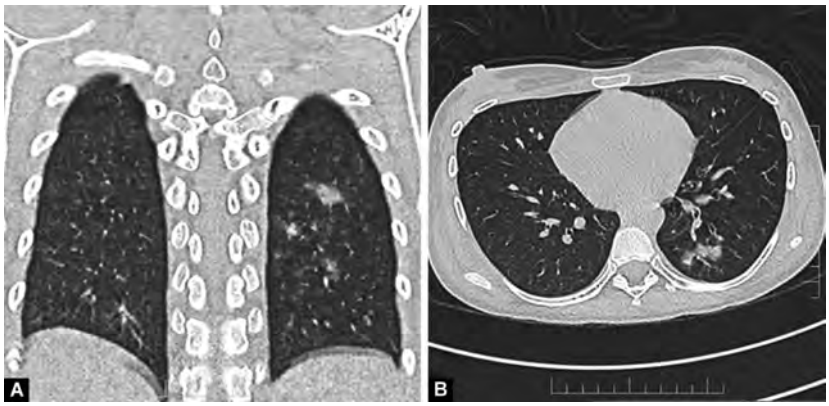
Another key aspect of imaging in COVID-19 is to decrease the exposure to the technicians and medical personnel, so imaging should be done in a controlled environment and with proper precautions. Ultrasound can be avoided in the initial diagnosis to avoid direct exposure, so CTA and MRA may be more useful in such patients.

Conclusion

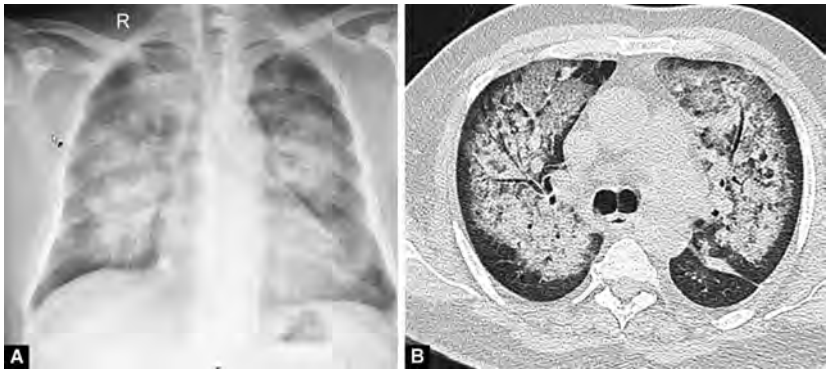
Due to advancements in imaging techniques, radiology has taken center stage in the diagnosis, follow-up, and treatment of systemic vasculitis. These modalities, combined with clinical pictures, help assess the disease status, thus helping the patient manage the disease in the long term. Imaging and management should be performed by well-trained specialists and multidisciplinary teams. Further refinement is needed in the currently followed protocols of imaging in vasculitis patients to better elucidate the role of imaging in disease monitoring, precise management, and individualized tailoring of treatment protocols. The COVID-19 pandemic has added a new dimension to the already existing problem of vasculitis, and radiologists must be aware of this new emerging clinical entity.



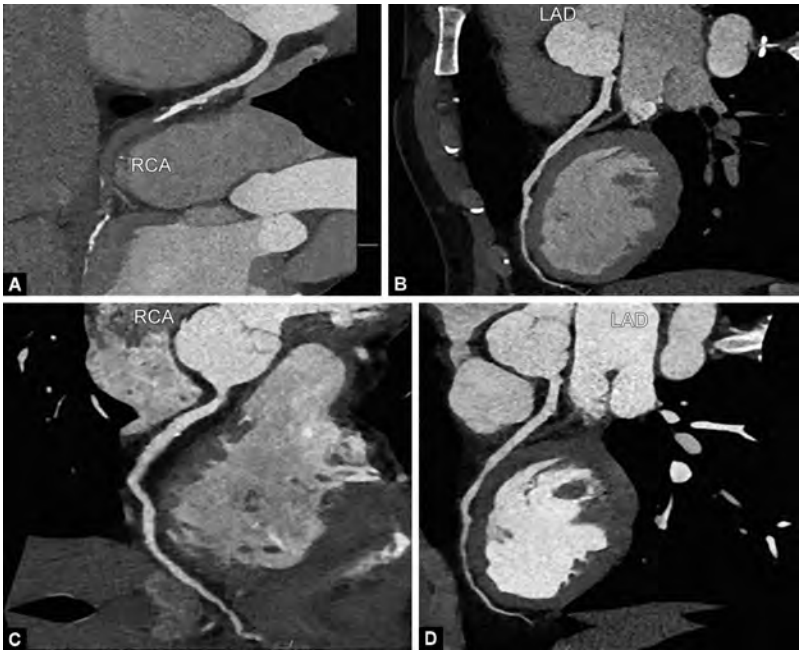
Figs 9A to D: Cytoplasmic antineutrophilic antibody (c-ANCA) and U1–RNP positive mixed connective tissue disorder; (A, B) Axial CT chest lung window shows bilateral perihilar patchy fibrotic opacities with surrounding centrilobular nodules and left pleural effusion; (C, D) CT pulmonary angiographic coronal reformatted images show nonopacification of the left branch of the pulmonary artery s/o thrombus; c-ANCA, cytoplasmic antineutrophilic antibody; U1-RNP, uridine rich smaller nuclear RNA; CT, computed tomography



Figs 10A and B: Systemic lupus erythematosus (SLE) vasculitis; a 22-year-old female diagnosed with SLE; (A) Coronal and (B) Axial reformatted lung CT window shows the presence of patchy consolidations in the left upper lobe; CT, computed tomography



Figs 11A and B: Rheumatoid arthritis (RA) with vasculitis; (A) Chest radiograph shows diffuse bilateral lung opacities predominantly in the central mid zones with mild peripheral sparing; (B) Axial HRCT lung window shows bilateral diffuse consolidations with GGO in the same area; features suggest diffuse alveolar hemorrhage (DAH)



Figs 12A to D: Coronavirus disease 2019 (COVID-19) vasculitis; (A, B) Coronary angiography MIP reformatted images and (C) Volume rendered images show acute thrombotic occlusion of the mid, distal RCA and bifurcation involving 7 cm long segment (arrow in A); (B) Diffuse segmental ectasia of the proximal and mid LAD; (C, D) Follow-up of the same patient shows resolution of thrombotic occlusion of the RCA and narrowing of the LAD; MIP, maximal intensity projection; CA, right coronary artery; LAD, left anterior descending

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POSITION STATEMENT

Indian Perspective on De-escalation from Dual Antiplatelet Therapy to Single Antiplatelet Therapy Study: A Knowledge, Attitude, and Practice Study among Indian Interventional Cardiologists

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Abstract

Background: Coronary artery disease (CAD) management is one of the most significant facets of interventional cardiology. Evidence from several clinical trials has redefined the drug management of CAD, including optimizing the duration of antiplatelet treatment regimens in the management of CAD, which is an intricate clinical issue. The available evidence indicates that East Asians have a higher bleeding risk. However, the Indian phenotype differs from that of East Asians, making this data confounding when applied to clinical decision-making among Indian patients. There is a need for a close understanding of Indian interventional cardiologists' perceptions of complex decision-making pertaining to antiplatelet agents among Indian CAD patients in real-world clinical settings.

Aim: This Indian Perspective on De-escalation from Dual Antiplatelet Therapy to Single Antiplatelet Therapy (INDEPTH) study aims to assess the perspective of Indian interventional cardiologists regarding de-escalating from dual antiplatelet therapy (DAPT) to single antiplatelet therapy (SAPT), approach to decision-making, barriers, and related challenges in CAD management.

Methods: A cross-sectional knowledge, attitude, and practice (KAP) study survey was carried out among Indian interventional cardiologists practicing across different regions of India. A total of 209 responses were received. Descriptive statistics was used to summarize all the parameters. IBM Statistical Package for the Social Sciences (SPSS) statistics was used for biostatistical analysis.

Results: The study indicated that >90% of CAD patients received DAPT therapy immediately after percutaneous coronary intervention (PCI) (86.1%, $p < 0.001$). About 115 (55%) of the respondents reported using calculator-based scoring for evaluating bleeding risk in patients on DAPT therapy for the management of acute coronary syndrome (ACS) with post-PCI ($p = 0.167$).

Regarding the usual duration of DAPT therapy post-ACS, nearly half of the respondents, 94 (45%), said that 6–12 months is the usual duration for DAPT therapy in post-ACS patients, followed by > 12 months 94 (45%) of the respondents; 17 (8.1%) of the respondents reported it is 3–6 months, and lastly up to 3 months as per four (1.9%) of the respondents ($p < 0.001$). A total of 128 (61%) of the respondents strongly believe that balancing bleeding with ischemic risk influenced the choice of antiplatelet agent when treating established CAD.

As per interventional cardiologists surveyed, the perfect de-escalation time frame for Indian CAD patients with high bleeding risk (HBR) is up to 3 months (35.9%, $p < 0.001$), 6–12 months for medium bleeding risk (48.8%, $p < 0.001$), and >12 months for low bleeding risk (65.6%, $p < 0.001$).

Regarding SAPT therapy, almost one-third of the respondents, 65 (31.1%), reported that they prescribed antiplatelet therapy other than aspirin in 20–40% of their SAPT-eligible patients. Furthermore, 69 (33%) of the respondents said that they preferred to prescribe clopidogrel in 50–75% of SAPT-eligible patients. While 64 (30.5%) prescribed in 25–50%, 53 (25.4%) prescribed in <25% and 23 (11%) of the respondents prescribed the drug in >75% of the SAPT-eligible patients. ($p < 0.001$). "Atorvastatin + clopidogrel" is the most preferred combination of SAPT primarily for the management of CAD among the majority of interventional cardiologists [33%, 95% confidence interval (CI): 1.97–2.24, $p < 0.001$]. The study respondents also indicated a need for Indian-specific guidelines on de-escalating from DAPT to SAPT in CAD management.

Conclusion: The INDEPTH study indicated that the majority of CAD patients received DAPT immediately after PCI. The perfect de-escalation time frame for Indian CAD patients with "high-bleeding" risk is up to 3 and 6–12 months for "medium-bleeding" risk and >12 months for "low-bleeding" risk. One-third of respondents used clopidogrel as an antiplatelet agent in 50–75% of SAPT-eligible patients. Atorvastatin + clopidogrel is predominantly the most preferred combination of statin + SAPT for the management of CAD. Although the current international guidelines cover the Indian perspective to some extent, there is a need for Indian-specific guidelines on de-escalating from DAPT to SAPT.

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Introduction

Coronary Artery Disease in India: Overview and Management

Coronary artery disease (CAD), sometimes referred to as coronary heart disease (CHD), results from decreased myocardial perfusion that causes angina, myocardial infarction (MI), and/or heart failure (HF). It accounts for one-third to one-half of the cases of cardiovascular diseases (CVD).[1,2] An increasing burden of CAD in India is a major cause of concern.[3] The prevalence of CAD in urban populations in India has been estimated between 5 and 10% and 3.3–7.4% in rural India.[4–8] Hospitalizations due to CAD were reported in 10% of urban and 4% of rural populations, with an average hospitalization burden of 6.0%.[9] Many studies have reported that Indians are more susceptible to CAD and have a higher case-fatality rate than the Western populations.[10,11] The mortality associated with CAD among Asian Indians is 20–50% higher than any other population.[12,13]

Various international organizations have formulated recommendations and guidelines for the management of CAD. Studies have shown that evidence-based medicine, with

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treatment according to the clinical practice guidelines (CPG), improves patient care outcomes.[14,15] Multiple approaches, including medical therapies and interventional procedures, may be useful and form key pillars of intervention for optimizing treatment outcomes in CAD management.[11] These include different classes of pharmacological agents such as antiplatelet agents, antianginal, antihypertensive, HF therapies, and lipid-lowering agents.[16]

Antiplatelet Therapy in Coronary Artery Disease Management

Acute coronary syndrome (ACS) is principally driven by platelet aggregation. Dual antiplatelet therapy (DAPT) has demonstrated a reduction in recurrent ischemic events.[17] Antiplatelet therapy is an essential component of the medical regimen in ACS as well as for secondary prevention. Multiple randomized trials have conclusively indicated that DAPT that includes aspirin and P2Y12 inhibitors should be taken for at least 12 months following ACS.[11] Approximately, 8–10% of patients undergoing percutaneous coronary intervention (PCI) have atrial fibrillation and other indications for an oral anticoagulant.[11,18] DAPT has become the cornerstone of the management of CAD. The two major guidelines by the American College of Cardiology (ACC)/American Heart Association (AHA-2016) and the European Society of Cardiology (ESC-2017) have stated class IA recommendation to initiate DAPT for a minimum duration of 12 months, post-ACS.[19,20] The latest recommendations from the ACC/AHA Guidelines 2023 for the management of chronic coronary disease reemphasized the significant benefits of aspirin use in secondary prevention. The guideline suggests using DAPT in those with high thrombotic risk and low bleeding risk. The guideline recommended DAPT, which consisted of clopidogrel and aspirin for 6 months post-PCI, followed by single antiplatelet therapy (SAPT) to reduce major adverse cardiovascular event (MACE) and bleeding events (class of recommendation: 1, level of evidence: A).[21]

Challenges in Applying Antiplatelet Therapy in CAD: More than Meets the Eye

Among antiplatelet agents, aspirin and clopidogrel (P2Y12 receptor antagonists) are widely prescribed medications in CAD.[22] Recent guidelines have proposed a personalization of therapy according to the patient's bleeding and ischemic risks, with dedicated scores designed to predict such risks.[23]

Factors associated with an increased risk of ischemic events include recent ACS, prior MI, diabetes, complex coronary lesions, and procedural aspects, while a history of bleeding is the principal risk factor for bleeding events. The tools to support decision-making are the DAPT score and the predicting bleeding complications in patients undergoing stent implantation and subsequent DAPT (PRECISE-DAPT) score. A high DAPT score of >2 in patients who have received a 12-month course of DAPT without experiencing ischemic or bleeding events favors prolongation to 30 months. Conversely, a high PRECISE-DAPT score of >25 at the index event signifies a high risk of bleeding and a potential benefit from shortened DAPT duration.[24]

Moreover, compared with Caucasian patients, East Asian patients are considered to have a different ischemia/bleeding propensity in response to antiplatelet and antithrombotic therapy, known as the "East Asian Paradox" (i.e., more bleeding events but fewer thromboembolic events).[25] This is consistent with the available epidemiological data collated from cerebrovascular events, especially those incorporating hospital-based registries in Asia. The striking clinical features of stroke in Asia include a relatively high prevalence of intracerebral hemorrhage, lacunar infarction, intracranial atherosclerosis, and stroke in young patients. Studies indicate that intracerebral hemorrhage is reported in 22% of the Asian population, as opposed to 9.8% of the Caucasian population.[26] One of the plausible mechanisms explaining the East Asian paradox is the low body weight phenotype of this population.[25]

However, it is noteworthy that the Indian phenotype differs from East Asians in that they have a relatively higher body weight and body mass index than some of the East Asian regional populations.[27] The consistency of patterns of bleeding tendencies and events between East Asian and Indian populations have not been elaborately studied. Hence, applying this scientific evidence may pose a dilemma in clinical decision-making pertaining to the modulation of antiplatelet therapeutic strategies among CAD patients.

Moreover, in real-world settings, prolonged and potent therapy is often difficult to maintain due to the patient's clinical characteristics and comorbidities, and the use of scores is limited by several practical challenges, such as the large overlap between factors associated with increased ischemic and bleeding events.[28] Both ischemic and bleeding events may occur in post-PCI; applying medication choices and defining specific treatment duration are areas in need of more certainty with regard to their impact on individual risks in real-world settings.[29] A better understanding of ischemic and bleeding risk profile, as well as individual responsiveness to antiplatelet agents, has been instrumental in defining the optimal regimen for the individual patient. In particular, the intensity and duration of aspirin and P2Y12 inhibiting therapy need to be adjusted to reduce the risk of ischemic complications while minimizing the risk of bleeding.[30]

Strategies developed to mitigate the risk of bleeding include shortening DAPT duration, P2Y12 inhibitor monotherapy, and de-escalation.[30] De-escalation of DAPT duration appears to be a favorable intervention, with a reduction in risk of bleeding, mostly without an increase in ischemic events, despite an increase in ischemic events reported in some studies using abbreviated DAPT.[31] A great deal of uncertainty persists among clinicians and healthcare providers regarding the default time of de-escalating strategy for most patients with ACS.[32] Switching between P2Y12 receptor antagonists is frequently seen in clinical practice as prasugrel and ticagrelor used early on after a PCI are de-escalated to clopidogrel maintenance to decrease the risk of bleeding and reduce treatment costs. Certain pieces of evidence show that CYP2C19 genotyping to guide this de-escalation is effective in optimizing the clinical outcomes in patients undergoing PCI.[33] The interpretation and application of the evidence in the rapidly progressing field of antiplatelet therapy can be challenging.[17]

Background

The clinical decision-making regarding de-escalation and switching of antiplatelet therapy in real-world settings is challenging, and it is based on cardiologists' clinical acumen combined with the judicious application of scientific evidence. While the scientific evidence is available, many trials may not represent the entire diversity of patients presenting to a cardiologist due to their stringent inclusion/exclusion criteria and insufficient representation of the patient population encountered in real-world settings. The available evidence indicates that East Asians have a higher bleeding risk. This corroborates with the Asian epidemiological data pertaining to hemorrhagic cerebrovascular events. However, the Indian phenotype differs from that of East Asians, and hence, this data may be confounding when applied to clinical decision-making among Indian patients.

The Indian interventional cardiologists' perception of de-escalation and switching to antiplatelet therapy is limited. Hence, there is

a need for a knowledge, attitude, and practice (KAP) study to assimilate practical insights regarding the applicability of antiplatelet therapies among Indian CAD patients.

Aim of the Study

This Indian Perspective on De-escalation from Dual Antiplatelet Therapy to Single Antiplatelet Therapy (INDEPTH) study aims to assess the perspective of Indian interventional cardiologists regarding de-escalating from DAPT to SAPT, approach to clinical decision-making, barriers, and related challenges in CAD management. The study is conducted to understand and seek practical insights regarding the use of antiplatelet agents in the Indian CAD patient population.

Methods of the Study

The INDEPTH study is a nationwide, cross-sectional, voluntary, questionnaire-based KAP survey conducted among practicing interventional cardiologists in India. The survey questionnaire consisted of 32 questions prepared in English under the guidance of an eminent, academically authoritative group of five interventional cardiologists in the country. As the study did not involve the collection or analysis of human data, ethics committee approval was not deemed necessary. Digital tools, such as Google Forms, were used to capture, record, and collate the study data. Statistical package software was used to analyze the data for biostatistical analysis [Statistical Package for the Social Sciences (SPSS), IBM Corp; Windows version 29].

A total of 209 responses were received, and all responses were included in the final analysis. The data were presented using frequencies and percentages for categorical variables and as means through descriptive statistics. The Chi-squared test was used to compare categorical data. A *p*-value of <0.05 was considered significant. A confidence interval (CI) of 95% was applied to represent the statistical significance of the results.

Results

Geographical Distribution of Responses

Upon analyzing the geographical distribution of survey responses, it was noted responses to the survey were received more from the Southern region 81 (38.7%), followed by Central 49 (23.44%), Eastern 37 (17.7%), Northern 26 (12.4%), Western 10 (4.7%), and six (2.8%) from Northeastern regions, respectively. The survey responses covered the opinions of interventional cardiologists from heterogeneous geographical locations across the country.

Bleeding Risk Evaluation in CAD

More than half of the respondents, 115 (55%), reported using calculator-based scoring for evaluating bleeding risk in patients who are on DAPT therapy for the management of ACS with post-PCI. Another 94 (45%) reported that they used their own clinical judgment ($p = 0.167$) (Table 1).

DAPT Therapy

The majority of the respondents, 180 (86.1%), reported that >90% of the patients received DAPT therapy immediately after PCI. However, 27 (12.9%) respondents said that around 50–90% of the patients received the same treatment after PCI ($p < 0.001$).

Regarding the preference for the combination of DAPT, most respondents indicated 142 (67.9%), "ticagrelor + aspirin" as the most preferred combination (CI 95%: 1.38–1.61, $p < 0.001$), while other respondents, 112 (53.6%), indicated "clopidogrel + aspirin" as the second preference (CI 95%: 1.93–2.12, $p < 0.001$), and some respondents 120 (57.4%) indicated "prasugrel + aspirin" as the third preference (CI 95%: 2.75–2.95, $p < 0.001$).

Duration of DAPT Therapy

Regarding the usual duration of DAPT therapy post-ACS, nearly half of the respondents, 94 (45%), said that 6–12 months is the usual duration for DAPT therapy in post-ACS patients, followed by >12 months according to 94 (45%) of the respondents, 17 (8.1%) of the respondents reported it is 3–6 months, and lastly up to 3 months as per four (1.9%) of the respondents ($p < 0.001$) (Table 2).

Impact of Bleeding Risk in Modulating DAPT Therapy

About 89 (42.6%) of the respondents rated bleeding as a risk "in few patients," followed by "sometimes" by 72 (34.4%); other 33 (15.3%) of the respondents said that it is "always" a risk concern and lastly 16 (7.7%) of the respondents opined bleeding as a "rarely" a concern while prescribing DAPT for secondary prevention ($p < 0.001$).

Furthermore, 86 (41.1%) of the interventional cardiologists indicated that they considered shortening the duration of DAPT due to bleeding concerns "in few patients." A total of 80 (38.3%) of the respondents considered shortening the therapy "sometimes," while 31 (14.8%) of the respondents "frequently" considered shortening the DAPT therapy due to bleeding, and lastly, 12 (5.7%) said that they "rarely" considered it ($p < 0.001$).

The survey response also indicated that nearly half of the respondents, 99 (47.4%),

Table 1: Evaluation of bleeding risk

Parameters	*Total (N = 209) N (%)*	*p-value*
Bleeding risk evaluation		$p = 0.167$
Calculated based on scoring	115 (55%)	
Self-clinical judgment	94 (45%)	

Table 2: Patterns of antiplatelet therapy strategy

Parameters	*Total (N = 209) N (%)*	*p-value*
The biggest consideration while selecting an antiplatelet strategy		$p < 0.001$
Following the latest CPGs	140 (67%)	
Consulting with patients/providing a patient-centric approach	42 (20%)	
Adopting the latest clinical evidence	27 (12.9%)	
Patients receiving DAPT therapy post-PCI		$p < 0.001$
>90% of patients receiving DAPT	180 (86.1%)	
50–90% of patients receiving DAPT	27 (12.9%)	
Recurrence of ischemic events		$p < 0.001$
Double stenting of coronary bifurcation lesion	105 (50.5%)	
Complex lesions	64 (30.5%)	
Stenting of CTO lesion	23 (11%)	
Primary PCI	17 (8.1%)	
Duration of DAPT therapy post-PCI		$p < 0.001$
>12 months	94 (45%)	
6–12 months	94 (45%)	
3–6 months	17 (8.1%)	
Up to 3 months	4 (1.9%)	

consider reducing the dose of antiplatelet in DAPT "in a few patients" due to bleeding concerns. And 63 (30.1%) of cardiologists said they "sometimes" considered reducing the dose, and 30 (14.1%) of respondents "frequently" considered, while 17 (8.1%) of the respondents "rarely" considered reducing the dose of antiplatelet in DAPT due to bleeding ($p < 0.001$).

With regard to the manner in which bleeding risk influences their decision to de-escalate (earlier vs later) the antiplatelet therapy, 83 (39.7%) of the respondents said that it influences "in few patients," followed by "sometimes" as per 72 (34.4%), then "frequently" as per 41 (19.5%) of the respondents, and lastly 13 (6.2%) said it "rarely" influenced their decision-making ($p < 0.001$) (Table 3).

Also, 128 (61%) of the respondents "strongly believe" that balancing bleeding with ischemic risk influences the choice of antiplatelet agent when treating established CAD. About 61 (29.2%) of the respondents pointed out that it does influence to "some extent," while 18 (8.6%) of the respondents said it "rarely" influenced decision-making ($p < 0.001$).

Table 3: Impact of bleeding risk in modulating DAPT therapy

Parameters	*Total N = 209 N (%)*	*p-value*
Bleeding as a risk while prescribing DAPT for secondary prevention		$p < 0.001$
In few patients	89 (42.6%)	
Sometimes	72 (34.4%)	
Frequently	33 (15.3%)	
Rarely	16 (7.7%)	
Shortening duration of DAPT due to bleeding		$p < 0.001$
In few patients	86 (41.1%)	
Sometimes	80 (38.3%)	
Frequently	31 (14.8%)	
Rarely	12 (5.7%)	
Reducing the dose of antiplatelet in DAPT		$p < 0.001$
In few patients	99 (47.4%)	
Sometimes	63 (30.1%)	
Frequently	30 (14.1%)	
Rarely	17 (8.1%)	
Influence of bleeding on the decision to de-escalate		$p < 0.001$
In few patients	83 (39.7%)	
Sometimes	72 (34.4%)	
Frequently	41 (19.5%)	
Rarely	13 (6.2%)	

De-escalation Time Frame for DAPT among Indian CAD Patients

About 75 (35.9%) of the respondents indicated up to 3 months is the perfect de-escalation time frame for Indians with high-bleeding risk, followed by 3–6 months as per 79 (35.7%), and another 52 (24.9%) of the respondents said 6–12 months and seven (3.3%) said it is >12 months ($p < 0.001$).

For medium bleeding risk, 102 (48.8%) of the respondents said 6–12 months as the perfect de-escalation time frame, while 66 (33%) said it is 3–6 months, 20 (9.6%) said it is >12 months and 18 (8.6%) of the respondents said it is up to 3 months ($p < 0.001$).

With regard to low bleeding risk, 136 (65.6%) of the respondents said that >12 months is the perfect de-escalation time frame, while 44 (21.1%) of the respondents said it is 6–12 months, 16 (7.7%) would go for 3–6 months, and 12 (5.7%) opined for "up to 3 months" ($p < 0.001$) (Fig. 1).

Use of SAPT Therapy

Regarding SAPT therapy, almost one-third of the respondents, 65 (31.1%), reported that they prescribed antiplatelet other than aspirin in 20–40% of their SAPT-eligible patients, 57 (27.3%) of the interventional cardiologists said that they prescribed it in 40–60% SAPT-eligible cases, 56 (26.8%) of the respondents prescribed in 20% and 31(14.8%) of the respondents used it in >60% of the eligible SAPT patients ($p = 0.006$).

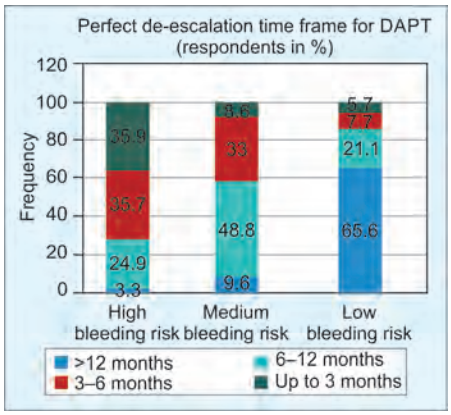


Fig. 1: Perfect de-escalation time frame for DAPT among CAD patients according to bleeding risk stratification

Choice of Antiplatelet Agents

Furtherly, 69 (33%) of the respondents said that they preferred to prescribe clopidogrel in 50–75% of SAPT-eligible patients. While 64 (30.5%) prescribed in 25–50%, 53 (25.4%) prescribed in <25%, and 23 (11%) of the respondents prescribed the drug in >75% of the SAPT-eligible patients ($p < 0.001$) (Fig. 2).

More than half of the respondents, 117 (55%), said that they prescribe ticagrelor in <25% of SAPT-eligible patients. And 39 (18.7%) of the respondents pointed out they prescribed the drug in 25–50% of cases, 27 (12.9%) of the respondents prescribed it in 50–75%, and 26 (12.4%) of the respondents used it >75% of the SAPT eligible patients ($p < 0.001$) (Fig. 3).

Considerations for SAPT Therapy

Recurrent episode/event was the "most important" consideration (CI 95%: 1.72–1.98, $p < 0.001$) as per 96 (45.9%) of the respondents, followed by bleeding risk as "fairly important" (CI 95%: 1.82–2.04, $p < 0.001$) as agreed by 85 (40.7%) of the respondents, gastrointestinal (GI) bleeding as "slightly important" (CI 95%: 2.42–2.65, $p < 0.001$) as per 102 (48.8%) of the respondents and frequency of administration as the "least important" (CI 95%: 3.23–3.47, $p < 0.001$) as per 126 (60.3%) of the interventional cardiologists who responded the survey (Fig. 4).

Recurrence of Ischemic Events

Half of the respondents, 105 (50.5%), reported that double stenting of coronary bifurcation lesions has the maximum chance of recurrence. In comparison, 64 (30.5%) said that complex lesions, 23 (11%) mentioned stenting of chronic total occlusion (CTO) lesions, and 17 (8.1%)

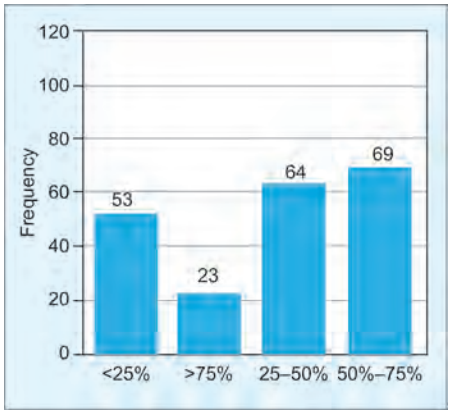


Fig. 2: Preference for prescription of clopidogrel in SAPT-eligible patients

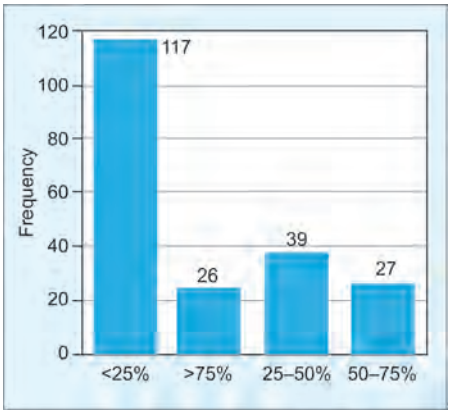


Fig. 3: Preference for prescription of ticagrelor in eligible SAPT patients

stated primary PCI has the maximum chance of recurrence of ischemic events ($p < 0.001$).

Impact of Choice of Stent on Antiplatelet Therapy

About 91 (43.5%) of respondents pointed out that their choice of antiplatelet therapy is "sometimes" influenced by the choice of stent. While 45 (21.5%) of the respondents said it "rarely" influences treatment choice, 38 (18.2%) said it "frequently" influences decision-making, and lastly, 35 (16.7%) opined it "rarely" influences the choice of antiplatelet therapy ($p < 0.001$).

Individuality and Ethnic Influences on Decision-making of Therapy

About 111 (53.1%) of the respondents reported that they consider interindividual variability in <25% of patients with responses to P2Y12 inhibitors while deciding therapy regimes. In comparison, 77 (36.8%) of respondents considered it in 25–50% of patients, and 19 (9.1%) of the respondents pointed out they only considered it in 50–70% of their patients ($p < 0.001$).

With regard to Asian paradox, the respondents believed the "Asian paradox" (for bleeding risk) is relevant to Indian patients while considering DAPT; 130 (62.2%) reported it is "sometimes" applicable to Indian patients while considering DAPT, followed by "in few patients" as per 37 (17.7%) of the respondents, "very often" as per 34 (16.3%) of the respondents, and eight (3.4%) of the respondents said it is "rarely" applicable ($p < 0.001$).

Considerations for Switching from Ticagrelor/Prasugrel to Clopidogrel

Furthermore, 134 (64.1%) of the respondents stated major bleeding events as the "most important" consideration to switching from ticagrelor to clopidogrel (CI 95%: 1.44–1.67, $p < 0.001$), adverse reactions (such as dyspnea) (CI 95%: 2.18–2.43, $p < 0.001$) as "fairly important" as per 82 (39.2%) of the respondents, need for oral anticoagulation as "slightly important" (CI 95%: 2.31–2.55, $p < 0.001$) as per 80 (38.3%) of the respondents, and creatinine levels as the "least important" (CI 95%: 3.18–3.42, $p < 0.001$) as per 113 (54.1%) of the respondents (Fig. 5).

Major bleeding events emerged as the "most important" consideration to switch from prasugrel to clopidogrel (CI 95%: 1.17–1.34, $p < 0.001$) as per 170 (81.3%) of the respondents, need for oral anticoagulation as "fairly important "(CI 95%: 2.15–2.36, $p < 0.001$) as per 117 (56%) of the respondents, creatinine levels as "slightly important" (CI 95%: 2.93–3.15) as per 81 (38.8%) of the respondents, and adverse reaction as the "least important" (CI 95%: 3.02–3.25, $p < 0.001$) as per 89 (42.6%) of the interventional cardiologists (Fig. 6).

Limitations of Newer Antiplatelet Therapies

About 73 (34.9%) of the respondents indicated that "ambiguity about dose requirements for lower body weight and elderly with prasugrel" was the major limitation of the newer antiplatelets (CI 95%: 2.03–2.32, $p < 0.001$), followed by "twice daily dosing of ticagrelor as "fairly important" (CI 95%: 2.18–2.47, $p < 0.001$) as per 62 (29.7%) of the respondents, dyspnea "slightly important" (CI 95%: 2.61–2.86) as per 83 (39.7%) of the respondents and cost as "the least important" (CI 95%: 2.51–2.83, $p < 0.001$) as per 73 (34.9%) of the respondents (Fig. 7).

Choice of Statin and Polypills in Secondary Prevention

About 85 (40.7%) of the respondents said that both atorvastatin and rosuvastatin as their choice of statin in secondary prevention, and another 62 (29.7%) of the respondents opined for rosuvastatin, and 61 (29.2%) preferred atorvastatin ($p < 0.001$).

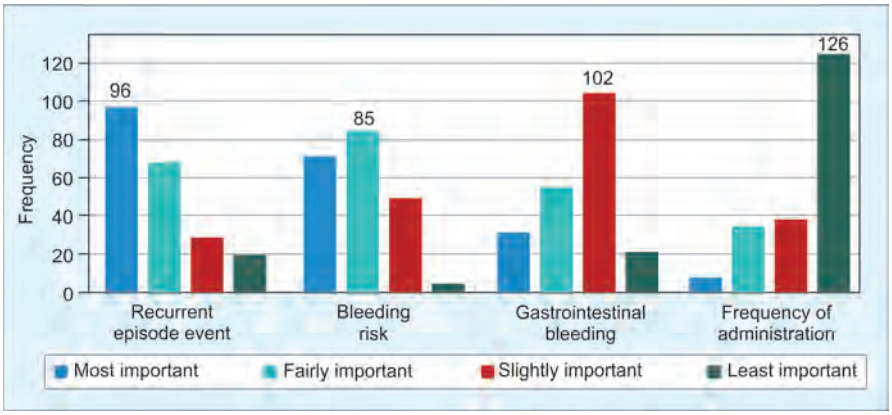


Fig. 4: Important considerations while choosing antiplatelet for SAPT therapy

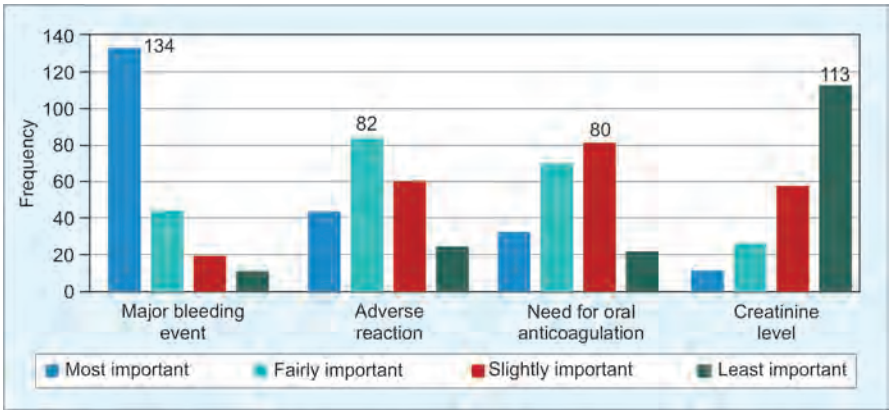


Fig. 5: Considerations while switching from ticagrelor to clopidogrel

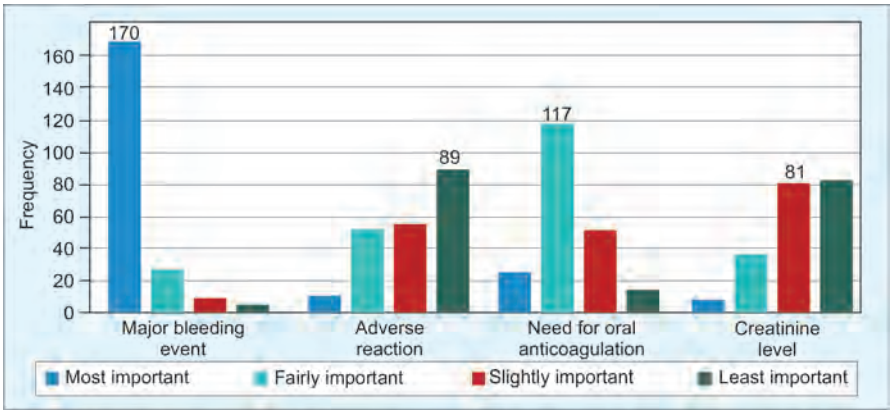


Fig. 6: Considerations while switching from prasugrel to clopidogrel

For the combination of SAPT along with a statin, "atorvastatin + clopidogrel" was the "most preferred' combination of SAPT (95% CI: 1.77–2, $p < 0.001$) as per 76 (36.4%) of the respondents, followed by "rosuvastatin + clopidogrel" as the "second preference" combination (95% CI: 2–2.24, $p < 0.001$) as per 83 (39.7%) of the respondents, atorvastatin + aspirin as the "third preference" (95%CI: 2.51–2.82, $p < 0.001$) as per 73 (34.9%) of the respondents, and "atorvastatin + ticagrelor" (95% CI: 3.01–3.26, $p < 0.001$) as the "least preferred" combination of SAPT as per 91 (43.5%) of the respondents (Fig. 8).

Indication Preference for Prescribing a Fixed-dose Combination of Atorvastatin + Clopidogrel

About 69 (33%) of the respondents indicated that management of CAD was the "most preferred" for prescribing a fixed dose combination of atorvastatin + clopidogrel (95% CI: 1.97–2.24, $p < 0.001$), while 66 (31.6%) of the respondents reported "secondary prevention of CVD" as the second preference (95% CI: 2.11–2.36, $p < 0.001$), 53 (25.4%) of the respondents indicated ACS (95% CI: 2.34–2.65, $p < 0.001$) as the third preference, and 96 (45.9%) of interventional cardiologists rated "primary prevention" as the least preferred (95% CI: 2.73–3.06, $p < 0.001$) for prescribing the fixed-dose combination (Fig. 9).

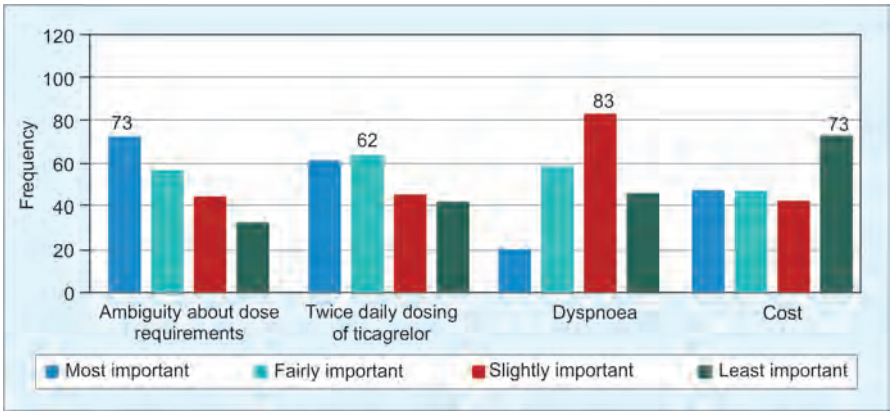


Fig. 7: Major limitations of newer antiplatelet agents

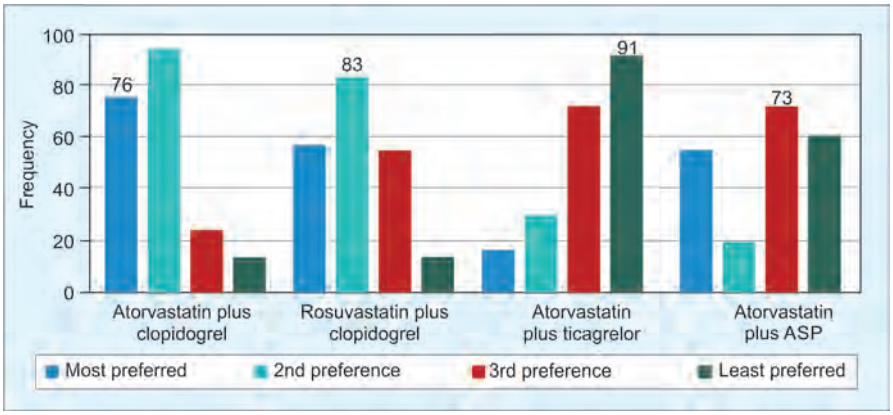


Fig. 8: Preference for the combination of SAPT along with statin

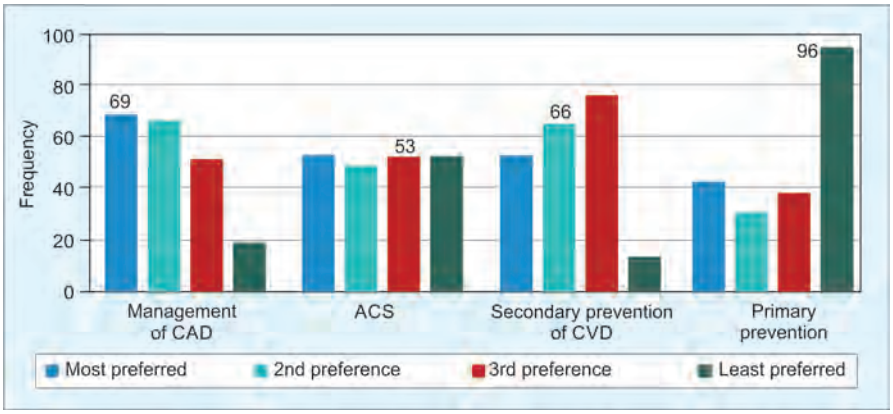


Fig. 9: Indication preference for prescribing an FDC of atorvastatin + clopidogrel

Perception Pertaining to International Guidelines

About 166 (79.5%) of the respondents shared that current international guidelines on DAPT and SAPT "somewhat" cover the Indian perspective. However, 30 (14.4%) of the respondents felt that the Indian perspective is "always" covered, while 13 (6.2%) opined that it is "rarely" covered ($p < 0.001$).

About 99 (47.4%) "strongly" believed that there is a need for India-specific guidelines on DAPT and SAPT. Another half of respondents, 98 (46.9%), also suggested that "it would be better" to have Indian-specific guidelines, and 10 (4.8%) went for "maybe" ($p < 0.001$). More than half of the respondents, 130 (62.4%), said that the current international guidance on prescribing antiplatelet therapy in established ACS is "always" friendly, and 66 (31.9%) believed that the guidelines are "sometimes" friendly ($p < 0.001$) (Table 4).

Guidelines for Determining Antiplatelet Therapies in CAD

While selecting an antiplatelet strategy for those with established ACS, 140 (67%) of the respondents reported that following the latest CPGs is their biggest consideration

Table 4: Perception pertaining to the adoption of international guidelines

Parameters	*Total (N = 209) N (%)*	*p-value*
Knowledge pertaining to guideline		$p < 0.001$
Need for Indian-specific guidelines		
Strongly	99 (47.4%)	
It would be better	98 (46.9)	
Maybe	10 (4.8%)	
Coverage of Indian perspective by international guidelines		$p < 0.001$
Somewhat	166 (79.5%)	
Always	30 (14.4%)	
Rarely	13 (6.2%)	
Friendliness of International guidelines on prescribing antiplatelet therapy		$p < 0.001$
Always	130(62.4%)	
Sometimes	66 (31.9%)	

while selecting an antiplatelet strategy in ACS. About 42 (20%) of the respondents considered consulting with patients and considering a patient-centric approach, and 27 (12.9%) of the respondents considered adopting the latest clinical evidence while choosing antiplatelet in ACS treatment ($p < 0.001$).

Discussion

The present study assessed the perspective and sought practical insights among Indian interventional cardiologists on de-escalation from DAPT to SAPT therapies in real-world settings in India.

The survey responses covered the opinions of interventional cardiologists from heterogeneous geographical locations across the country.

More than half of the respondents, 115 (55%), reported using calculator-based scoring for evaluating bleeding risk in patients who are on DAPT therapy for the management of ACS with post-PCI. Another 94 (45%) reported that they used their own clinical judgment ($p = 0.167$). This indicates that in real-world scenarios in India, bleeding risk evaluation still remains a clinical judgment in a large number of practice settings.

The study reported that the majority of respondents indicated that >90% of the patients received DAPT therapy immediately after PCI.

Despite this majority, the survey indicated that there is a small proportion of CAD patients who do not receive DAPT immediately after PCI. This proportion of patients reflected in our KAP study seems a trend to be quantitatively on the higher side than reported in related other patient-included observational studies.[34]

The factors for nonconsideration of the initiation of DAPT after PCI may include but are not restricted to suspected intracranial hemorrhage, a recent history of intracranial hemorrhage, severe thrombocytopenia, and active clinically significant bleeding.[35]

A more recently published OPTICA study provided the first-in-human evidence that P2Y12 inhibitor monotherapy directly following PCI for non-ST-segment elevation ACS is feasible without any overt safety concerns and highlights the need for randomized controlled trials (RCT) comparing direct P2Y12 inhibitor monotherapy with the current standard of care.[36]

Regarding the usual duration of DAPT therapy post-ACS, nearly half of the respondents, 94 (45%), opined that 6–12 months is the usual duration for DAPT therapy in post-ACS patients, followed by >12 months according to 94 (45%) of the respondents, 17 (8.1%) of the respondents reported it is 3–6 months, and lastly up to 3 months as per four (1.9%) of the respondents ($p < 0.001$). It indicates that Indian interventional cardiologists are prudent in considering the usual DAPT therapy duration of <12 months when needed.

More than three-fourths of respondents would consider shortening the duration of DAPT due to bleeding risk in certain patients (about 41.1% "in few patients" and 38.3% "sometimes").

Importantly, 128 (61%) of the respondents "strongly believe" that balancing bleeding with ischemic risk influences the choice of antiplatelet agent when treating established CAD. This clinical challenge remains pertinent in Indian clinical practice settings while using antiplatelet treatment in CAD patients.

Almost three-fourths of respondents would consider that bleeding risk influences decisions to de-escalate (earlier vs later) DAPT therapy in certain cases (about 39.7% "in few patients," and 34.4% "sometimes").

About 71.6% of respondents opined for <6 months (35.9% of respondents for up to 3 months and 35.7% for 3–6 months) as the perfect de-escalation time frame for Indian CAD patients with high bleeding risk (HBR).

Valgimigli et al. and MASTER DAPT investigators earlier concluded that 1 month (abbreviated DAPT) of DAPT was noninferior to the continuation of therapy for at least 2 additional months (standard DAPT) with regard to the occurrence of net adverse clinical events and major adverse cardiac or cerebral events. The abbreviated DAPT therapy also resulted in a lower incidence of major or clinically relevant nonmajor bleeding.[18]

In our KAP study, even among CAD patients receiving DAPT with "low bleeding" risk, 136 (65.6%) of the respondents said that >12 months is the perfect de-escalation time frame. The remaining respondents (~34.5%) preferred <12 months as the perfect de-escalation time frame in this group ("low bleeding" risk), indicating prudence among Indian interventional cardiologists toward possible consideration for de-escalation of DAPT and opportunity toward consideration of earlier initiation of SAPT in appropriate cases. A similar trend is observed among ~41.6% of interventional cardiologists, who suggested a perfect de-escalation time frame to be <6 months among CAD patients receiving DAPT with "medium bleeding" risk (Fig. 10).

The Academic Research Consortium for High Bleeding Risk (ARC-HBR) definition addresses an unmet need by providing a framework for evaluating treatment options for patients undergoing PCI at increased bleeding risk. A total of 20 clinical criteria were identified as major or minor by consensus, supported by published evidence (Table 5). Patients are considered to be at HBR if at least one major or two minor criteria are met.

Factors associated with an increased bleeding risk after percutaneous coronary intervention include age >75 years, comorbidities such as renal disease, liver disease and active cancer, anemia, low platelet count, stroke, intracranial hemorrhage (ICH), brain arteriovenous malformation (bAVM), bleeding diathesis, history of prior bleeding or transfusion, and iatrogenic such as the use of oral anticoagulants (OAC), nonsteroidal anti-inflammatory drug (NSAIDs), steroids, planned surgery on DAPT, recent trauma or surgery.[37]

The prevalence of HBR according to ARC-HBR criteria in studies of European and Asian populations has ranged from 30 to 50%, and the incidence of major bleeding events in the HBR groups of these studies has consistently been ≥4% at 1 year.[38–43]

Regarding SAPT therapy, almost one-third of the respondents, 65 (31.1%), reported that they prescribed antiplatelet other than aspirin in 20–40% of their SAPT-eligible patients. This implies that SAPT agents beyond aspirin are

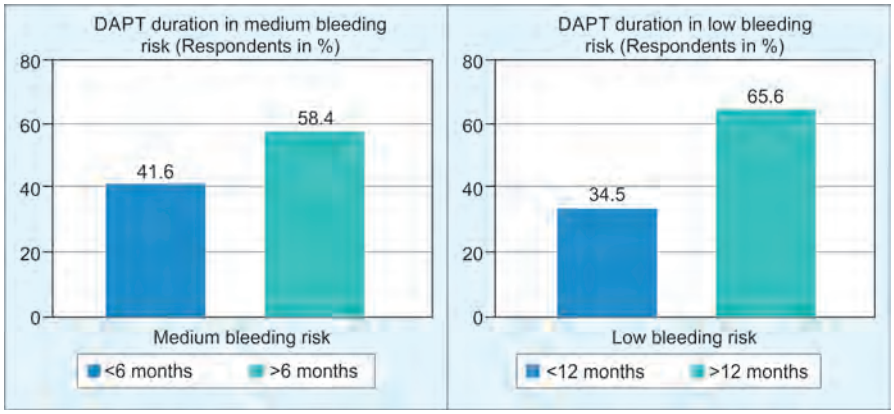


Fig. 10: Respondents preferences regarding DAPT duration in medium and low bleeding risk

Table 5: Major and minor criteria for HBR at the time of PCI

Major	*Minor*
	Age ≥ 75 years
Anticipated use of long–term oral anticoagulation*	
Severe or end–stage CKD (eGFR <30 mL/minute)	Moderate CKD (eGFR 30–59 mL/minute)
Hemoglobin <11 gm/dL	Hemoglobin 11–12.9 gm/dL for men and 11–11.9 gm/dL for women
Spontaneous bleeding requiring hospitalization or transfusion in the past 6 mo or at any time, if recurrent	Spontaneous bleeding requiring hospitalization or transfusion within the past 12 months not meeting the major criterion
Moderate or severe baseline thrombocytopenia† (platelet count <100 × 10^9/L)	
Chronic bleeding diathesis	
Liver cirrhosis with portal hypertension	
	Long-term use of oral NSAIDs or steroids
Active malignancy‡ (excluding nonmelanoma skin cancer) within the past 12 months	
Previous spontaneous ICH (at any time); previous traumatic ICH within the past 2 months; presence of a bAVM; moderate or severe ischemic stroke§ within the past 6 months	Any ischemic stroke at any time not meeting the major criterion
Nondeferrable major surgery on DAPT	
Recent major surgery or major trauma within 30 days before PCI	

bAVM indicates brain arteriovenous malformation; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; HBR, high bleeding risk; ICH, intracranial hemorrhage; NSAID, nonsteroidal anti-inflammatory drug; PCI, percutaneous coronary intervention; *this excludes vascular protection doses; †, baseline thrombocytopenia is defined as thrombocytopenia before PCI; ‡, active malignancy is defined as a diagnosis within 12 months and/or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy); §, National Institutes of Health Stroke Scale score ≥5

well-accepted among Indian interventional cardiologists in selected appropriate cases.

Clopidogrel was the most frequently prescribed antiplatelet agent, according to 69 (33%) respondents, in 50–75% of SAPT-eligible patients in the survey.

These responses seem in line with scientific evidence reported earlier in the POPular-AGE trial conducted among older patients with the non-ST-elevation ACS, where clopidogrel is a favorable alternative to ticagrelor in elderly patients with higher bleeding risk because it leads to fewer bleeding events without an increase in the combined endpoint of all-cause death, myocardial infarction, stroke, and bleeding.[44]

Furthermore, recent findings from the OPT-BRISIK trial presented at the European Society of Cardiology (ESC) 2023 suggest that an extended course of P2Y12 inhibitor monotherapy with clopidogrel for an additional 9 months was superior to DAPT with aspirin and clopidogrel for reducing clinically relevant bleeding and ischemic events.[45]

Another more recently published *post hoc* analysis of the "Harmonizing Optimal Strategy for Treatment of Coronary Artery Diseases—Extended Antiplatelet Monotherapy" trial, aimed to evaluate the benefits of clopidogrel across high-risk subgroups, concluded that the beneficial effect of clopidogrel over aspirin monotherapy was consistent regardless of clinical risk or relative ischemic and bleeding risks compared with aspirin monotherapy.[46]

Regarding the choice of antiplatelet therapy regimes, "ticagrelor + aspirin" is the preferred combination of DAPT, followed by "clopidogrel + aspirin."

Recurrence of ischemic events followed by bleeding risk are important factors when considering SAPT agents among Indian interventional cardiologists.

The survey indicated that the choice of SAPT is influenced by balancing bleeding with ischemic risk, choice of the stent, and recommendations from the latest CPGs.

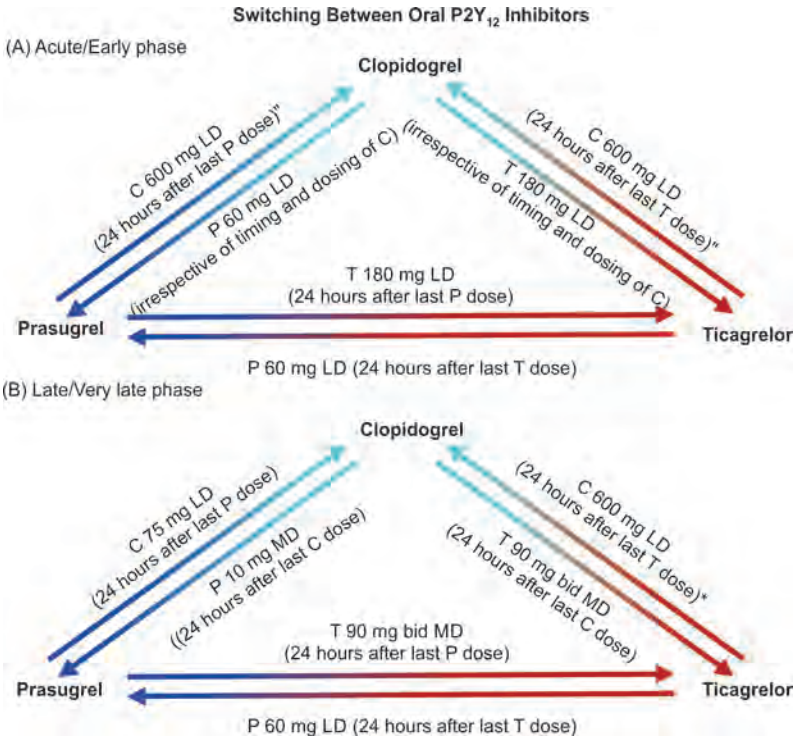
Half of the respondents, 105 (50.5%), reported that double stenting of coronary bifurcation lesions has the maximum chance of recurrence. These results seem in line with other meta-analysis evidence published by Abdelfattah et al., which included two RCTs, 10 observational studies encompassing 7,105 patients follow-up for a median duration of 42 months, reporting that for left main bifurcation PCI using second-generation drug-eluting stents (DES), a provisional stenting strategy was associated with a trend toward a lower incidence of MACE driven by statistically significant lower rates of target lesion revascularization, compared with systematic double stenting.[47]

About more than one-third (about 43.5%) of respondents pointed out that their choice of antiplatelet therapy is "sometimes" influenced by the choice of stent. This implies that the choice of the stent may not always affect the decision pertaining to the choice of antiplatelet therapy.

Drug-eluting stents (DES) were introduced in interventional cardiology and have since rapidly replaced bare metal stents (BMS). DAPT was essential to avoid potentially catastrophic stent thrombosis (ST) after stenting. Premature discontinuation of DAPT was found to be a strong predictor of ST with Sirolimus-eluting stents (SES) and Paclitaxel eluting stents (PES), the first-generation DES. Due to evidence of late and very late ST events with first-generation DES, "the longer, the better" DAPT therapy evolved into being. The second-generation DES—everolimus eluting stents (EES) and zotarolimus eluting stents and third-generation DES with biodegradable polymers (BES) are found to have lower rates of late and very late ST. A meta-analysis showed EES to have a lower risk of ST than BMS.[48] The CSI-NIC (National Interventional Council of Cardiological Society of India) data published by Kumar et al. reported 4,38,351 percutaneous coronary interventions performed in a year (2018), utilized 578,164 coronary stents and nearly 98% of stents used were drug-eluting stents. There is an increase in multivessel PCI, complex PCI, and intravascular imaging-guided precision PCI procedures in India.[49]

The survey indicates that interindividual variability with responses to P2Y12 inhibitors and Asian Paradox are applicable in some cases.

The proportion of Asian populations enrolled in landmark RCTs is substantially low, which limits the direct application of trial findings into clinical practice in Asian countries. Moreover, compared with Caucasian patients, East Asian patients are considered to have a different ischemia/bleeding propensity in response to antithrombotic therapy, known as the "East Asian paradox" (i.e., more bleeding



Figs 11A and B: Consensus recommendations on switching oral P2Y12 inhibitors; (A) Switching between oral agents in the acute/early phase; in the acute/early phase (≤30 days from the index event), switching should occur with the administration of a loading dose (LD) in most cases, with the exception of patients who are de-escalating therapy because of bleeding or bleeding concerns, in whom a maintenance dose (MD) of clopidogrel (C) should be considered; timing of switching should be 24 hours after the last dose of a given drug, with the exception of when escalating to prasugrel (P) or ticagrelor (T), when the LD can be given regardless of the timing and dosing of the previous clopidogrel regimen; *consider de-escalation with clopidogrel 75 mg MD (24 hours after last prasugrel or ticagrelor dose) in patients with bleeding or bleeding concerns; (B) Switching between oral agents in the late/very late phase; in the late/very late phase (>30 days from the index event), switching should occur with the administration of an MD 24 hours after the last dose of a given drug, with the exception of patients changing from ticagrelor to prasugrel therapy, for whom an LD should be considered; de-escalation from ticagrelor to clopidogrel should occur with administration of an LD 24 hours after the last dose of ticagrelor (but in patients whom de-escalation occurs because of bleeding or bleeding concerns, an MD of clopidogrel should be considered); *consider de-escalation with clopidogrel 75 mg MD (24 hours after the last prasugrel or ticagrelor dose) in patients with bleeding or bleeding concerns

events but fewer thromboembolic events). Coincident with consecutive RCTs in Western populations to optimize antithrombotic strategies, several such studies have now been conducted in East Asian cohorts. The clinical characteristics unique to East Asians compared to Caucasians include HBR, increased risk of hemorrhagic stroke, and GI bleeding. The plausible mechanism of the East Asian Paradox may be attributed to unique demographics, lower body weight, genetic predispositions, and differential responses to P2Y12 inhibitors. The possible optimal strategies for this population include a reduced dose regimen, short-term DAPT, and early use of P2Y12 inhibitors monotherapy.[25]

Indian phenotype differs from East Asians in having a relatively higher body mass index,[27] which is likely posing a dilemma for Indian interventional cardiologists in applying "East-Asian Paradox" evidence in clinical decision-making.

The survey also indicated that a "major bleeding event" was the most important consideration when switching from ticagrelor to prasugrel to clopidogrel.

About one-third of respondents indicated that "ambiguity about dose requirements for lower body weight and elderly with prasugrel" was a major limitation. Twice daily dosing was considered a "fairly important" limitation with the use of ticagrelor. The consensus recommendations on switching between oral P2Y12 inhibitors have been represented in Figure 11.[50]

Atorvastatin + clopidogrel is predominantly the most preferred combination of statin + SAPT for the management of CAD among the majority of surveyed Indian interventional cardiologists. Both atorvastatin and rosuvastatin were reported as the choice of statin for secondary prevention in our KAP study.

It is noteworthy that polypills containing the highest dose of atorvastatin (i.e., 80 mg) plus SAPT (aspirin or clopidogrel) are hardly available for Indian patients to allow aggressive statin dosing strategy during the initial duration of secondary prevention.

However, the findings of the secondary analysis of the LODESTAR trial, comparing rosuvastatin vs atorvastatin in patients with CAD, reported a higher risk of new-onset diabetes mellitus requiring anti-diabetic medication and the need for cataract surgery with rosuvastatin treatment compared with atorvastatin treatment.[44] Multicentric Indian studies have reported that treatment with atorvastatin 40 and 80 mg among Indian patients with ACS led to significant reductions in LDL-C and hs-CRP, with a well-accepted tolerance profile.[51]

With regard to perception regarding international guidelines, a majority, about 166 (79.5%) of the respondents shared that current international guidelines on DAPT and SAPT "somewhat" cover the Indian perspective; a significant proportion of Indian interventional cardiologists believe India-specific guidelines on DAPT and SAPT may be needed, about 99 (47.4%) strongly believed that there is a need for India-specific guidelines on DAPT and SAPT and another half of respondents 98 (46.9%) also suggest that "it would be better" to have Indian-specific guidelines.

While selecting an antiplatelet strategy for those with established ACS, 140 (67%) of the respondents reported that following the latest CPGs is their biggest consideration while selecting an antiplatelet strategy in ACS. This consideration came ahead of the patient-centric approach, further indicating a need for the development of India-specific guidelines for DAPT and SAPT, which may likely be well-accepted to optimize treatment care outcomes.

The Indian subgroup of the EPICOR Asia study published by Sawhney et al. observed a gap between international recommendations and implementation for managing ACS in Indian patients. The mortality, along with composite events of death, MI, or ischemic stroke, was highest for patients with NSTEMI. The reported CV events were similar in STEMI and NSTEMI groups. Going forward, steps need to be taken to improve the identification, diagnosis, and management of patients with ACS to improve patient outcomes.[51]

The development of Indian-specific guidelines may help address these India-

specific issues pertaining to ACS and help in effective management.

Strengths of the Study

A major strength of this study is the generalizability and diversity, as INDEPTH is a large, geographically diverse KAP survey. The study included interventional cardiologists across different regions of India, helping to cover the opinions of practicing interventionalists from heterogeneous geographical locations across the country. The present study revealed several key aspects of antiplatelet drug utilization and its applicability, in addition to improving our understanding of the myriad factors that require consideration in CAD medical management. The study also brought the need for Indian-specific guidelines regarding the use of DAPT and SAPT in CAD management.

Limitations of the Study

This study is limited by a descriptive survey, and the responses are from physician reports, which may not provide a true representation of patients' responses and also limit data on patient outcomes. The choice of treatments given for CAD may have been influenced by the presence of different comorbid conditions, yet our questionnaire was unable to detect such potential interactions. Demographic details of the respondents were not captured in the questionnaire; such details are needed to understand and analyze the factors that impact the healthcare professionals' choice of treatment. Other inevitable limitations associated with data collected from surveys that are relevant to the current study include recall bias, missing data, and overreporting of surveyed events.

Conclusion

The INDEPTH survey indicated that a majority of CAD patients received DAPT immediately after PCI, usually for 6–12 months or >12 months. In Indian real-world scenarios, bleeding risk evaluation still remains a clinical judgment in a large number of practice settings.

Indian interventional cardiologists are prudent to consider the usual DAPT therapy duration of <12 months when needed.

Clopidogrel was the most frequently prescribed antiplatelet agent in 50–75% of SAPT-eligible patients, as per the respondents of the survey. Atorvastatin + clopidogrel is predominantly the most preferred combination of statin + SAPT for the management of CAD. Secondary prevention polypills containing the highest dose of atorvastatin (i.e., 80 mg) plus SAPT (aspirin or clopidogrel) are hardly accessible in India.

Indian Perspective on De-escalation from Dual Antiplatelet Therapy to Single Antiplatelet Therapy (INDEPTH) study reemphasized that the choice of DAPT and SAPT is influenced by factors like balancing bleeding with ischemic risk, choice of stent, recurrent episodes/events, recommendations from the latest CPGs, and interindividual variability toward P2Y12 inhibitors.

International guidelines recommend 6 months of DAPT in high-bleeding risk (HBR) patients with ACS and 12 months of DAPT in non-HBR patients with ACS after PCI. In patients with non-ACS, 1–3 months of DAPT is recommended in HBR patients after PCI.[52]

Lastly, this study brought out the need for Indian-specific guidelines regarding the use of DAPT and SAPT, which may be useful.

Way Forward

A de-escalation strategy of antiplatelet therapy represents a very practical and promising strategy for reducing bleeding, ischemic risk, and recurrent episodes/events in patients with CAD. Nevertheless, available evidence presents some limitations, such as the fact that many studies have been performed on Asian and European populations, limiting the generalization of their results to other ethnicities. To this extent, the implementation of Indian-specific guidelines may play an important role. The comparative advantage of P2Y12 inhibitors such as clopidogrel, ticagrelor, and prasugrel in real-world settings is yet to be established. It may be relevant to replicate findings of POPular-AGE and LODESTAR trials in the Indian patient population.

Secondary prevention polypills containing the highest dose of atorvastatin 80 plus clopidogrel may be an interesting opportunity to consider among stakeholders responsible for optimizing accessibility to these medications.

Such studies may further facilitate evidence-based decision-making regarding determining the choice of these critical pharmacological agents in the management of CAD, thereby further optimizing long-term treatment outcomes. The development of Indian-specific consensus or guidelines in this direction may also be useful.

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CONSENSUS STATEMENT

Fortifying Micronutrient Supplementation in India: Expert Consensus by the American College of Physicians (India Chapter)

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Abstract

Micronutrients play a key role in human health, being involved in energy metabolism, immunity, cellular functioning, growth, and development. Deficiencies in micronutrients occur in individuals of all ages due to several factors, including inadequate diets, disease states, and overweight/obesity. Guidelines from the Indian Council of Medical Research (ICMR) National Institute of Nutrition (NIN) Expert Group on Nutrient Requirements for Indians (2023) have specified the Recommended Dietary Allowances (RDA) for macronutrients and micronutrients. In addition, a healthy diet is crucial for overall health and should be the first step toward addressing micronutrient deficiencies. When diet is inadequate, micronutrient supplements can be provided to compensate. An expert panel of Indian doctors, including those affiliated with the American College of Physicians, was convened to develop a pathway toward micronutrient supplementation among the Indian population. This Consensus Statement recognizes that different populations have varying needs for specific micronutrients, and ensuring adequate intake of such micronutrients can improve health outcomes. The panel provided recommendations for dietary practices and micronutrient supplementation when diet is inadequate. Addressing micronutrient deficiencies at the primary care level can prevent chronic deficiencies and their consequences. This Consensus Statement can serve as a primer for physicians to monitor and address deficiencies and thus help individuals maintain their health.

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Introduction

Micronutrients play a crucial role in human growth and development and are also required for normal functioning, energy metabolism, and immune function.[1,2] Micronutrients, including vitamins and minerals, are dietary components that do not contribute to caloric intake but are necessary for health and vital functions.[3] Micronutrient inadequacy is the intake of nutrients in lesser quantity than the estimated average requirement and can present with covert symptoms that are difficult to identify. Unidentified and untreated deficiencies could contribute to the development of chronic diseases.[4]

Malnutrition is defined by the World Health Organization (WHO) as "deficiencies or excesses in nutrient intake, imbalance of essential nutrients or impaired nutrient utilization." It encompasses undernutrition (wasting, stunting, underweight, and micronutrient deficiencies), overweight, and obesity.[5] Micronutrient deficiencies occur in obese and overweight individuals as well, driven by the consumption of calorie-rich, nutrient-deficient foods, excess adipose tissue, altered metabolism and distribution of nutrients, and increased requirements for micronutrients.[6]

Role of Micronutrients in Health

The complex process of energy metabolism in the human body requires a plethora of enzymes, and micronutrients function as cofactors for enzymes and participate in proton transfer. Micronutrient deficiencies impact cardiorespiratory function during exercise as well as submaximal work.[7] Micronutrients play a vital role in cell proliferation, growth, apoptosis, wound healing, replication, transcription, translation, gene expression, gene regulation, skeletal muscle function, neuromuscular conduction, myocardial contraction, maintenance of blood pressure, protein and nucleic acid synthesis, bone mineralization, and regulating active transmembrane transport of various cations and anions, etc.[8]

Micronutrient inadequacy can lead to specific diseases (anemia, goiter, etc.) as well as impaired learning, stunted growth, and premature death. Around 45% of deaths in children aged under 5 years can be attributed to undernutrition.[9] The complex, integrated immune system needs multiple specific micronutrients, which play vital and often synergistic roles at every stage of the immune response (Table 1). Supplementation with multiple micronutrients that have immune-supporting roles may modulate immune function and reduce the risk of infection.[1] There is, thus, a need for comprehensive nutritional care to prevent disease in the general population.

Scope of the Consensus

This Consensus Statement was developed by an expert panel of doctors (physicians, endocrinologists, diabetologists, cardiologists, and nutritionists) to develop a pathway toward micronutrient supplementation in the Indian population. This Consensus Statement takes cognizance of the fact that different populations have varying needs for specific micronutrients, and ensuring adequate intake of such micronutrients can improve health outcomes.

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Table 1: Role of various micronutrients in the human body[1]

Vitamin/mineral	*Role in the human body*
Vitamin B_1	Antioxidant; inhibits oxidative-stress-mediated stimulation of NFκB
Vitamin B_2	Antiinflammatory; cofactor for enzymes
Vitamin B_6	Regulates intestinal immunity; maintains NK cell cytotoxicity activity
Folate	Maintains NK cell cytotoxicity activity
Vitamin B_{12}	Immunomodulator for cellular immunity
Vitamin C	Maintains redox homeostasis; regenerates antioxidants to the active state
Vitamin E	A fat-soluble antioxidant that protects against free radicals enhances IL-2 production, decreases prostaglandin production
Vitamin D	Increases the oxidative potential of macrophages; reduces the expression of proinflammatory cytokines
Zinc	Maintains/enhances NK cell cytotoxicity activity; plays a role in the growth and differentiation of immune cells; enhances phagocytic activity of peritoneal macrophages
Selenium	Selenoproteins are important for antioxidant defence
Iron	Bacterial killing by neutrophils, components of enzymes critical for immune cell functioning
Magnesium	Cofactor for enzymes and stabilized nucleic acids, involved in DNA replication and repair

DNA, deoxyribonucleic acid; IL-2, interleukin-2; NFκB, nuclear factor kappa B; NK, natural killer

Understanding Micronutrient Deficiencies in India

During 2014–2016, 14.5% of the Indian population (190.7 million people) were undernourished.[2] Micronutrient deficiencies were the cause of 0.5% of deaths that occurred in 2016.[10] In addition, micronutrient deficiencies cost up to 2.5% of the gross domestic product (GDP) of India.[1]

Mineral Deficiency and Disease

Magnesium deficiency has been reported in 44% of patients with type 2 diabetes mellitus (T2DM),[11] and low serum magnesium levels are associated with poorer glycemic control,[11,12] and complications of diabetes.[11,13] Hypomagnesemia is reported in ~63% of patients with nonproliferative diabetic retinopathy (NPDR).[11] Indian patients with prediabetes have significantly lower serum levels of magnesium, selenium, and zinc compared with individuals without prediabetes. Levels of these minerals were negatively correlated with fasting plasma glucose (FPG), insulin, and insulin resistance, while glycated hemoglobin (HbA1c) correlated negatively with serum zinc and magnesium levels.[14]

Postmenopausal women with osteoporosis have low levels of serum magnesium (1.95 ± 0.44 mg/dL).[15] Levels of magnesium are indicators of the severity of asthma in adult Indians, with hypomagnesemia reported in nearly 59% of asthma patients (vs 5% of controls).[16] Selenium deficiency has been reported in adult Indians with asthma, and levels of serum selenium correlate with the severity of the disease.[17] Copper deficiency is reported in Indians with aplastic anemia,[18] and serum copper levels are significantly reduced in patients with chronic obstructive pulmonary disease (COPD).[19]

Micronutrient Deficiency in Geriatric Patients

Geriatric individuals in India have inadequate micronutrient intake, which could be attributed to the poor quality of their diets. The prevalence of inadequate intake [<100% of recommended dietary allowances (RDA)] was reported for magnesium (48%), copper (81%), chromium (89%), thiamine (33%), and niacin (88%). Nutritional inadequacy was higher among geriatric subjects of lower socioeconomic strata.[20] Vitamin D sufficiency has been reported in 22.64% of elderly individuals with coronary artery disease and in 51.04% of healthy elderly individuals.[21] Geriatric Indian women with vitamin D deficiency have an increased risk of pelvic floor disorders, and patients with urinary incontinence had significantly lower serum vitamin D levels than those without (11.26 ± 6.3 vs 14.58 ± 7.29 ng/mL, $p = 0.046$).[22]

Obese Individuals

Young obese individuals with nonalcoholic fatty liver disease (NAFLD) have significantly lower levels of serum vitamin D than controls without NAFLD (17.21 ± 6.34 vs 26.56 ± 10.63 ng/mL, $p < 0.001$) and low serum vitamin D was independently associated with the risk of developing NAFLD (odds ratio 1.52).[23] Metabolic syndrome is associated with vitamin D levels in obese Indians.[24]

Urban and Rural India

Studies on the micronutrient status of rural Indians have revealed the prevalence of vitamin B_{12} deficiency to be 42.3% without a significant difference between males and females, but females aged 45–54 years had a higher prevalence of deficiency.[25] Among urban Indians, vitamin B_{12} deficiency was noted in 35.5% of individuals. The probability of adequacy for zinc was 11%, riboflavin 37%, and thiamine 58%. Subjects with micronutrient inadequacy had a higher risk of iron-deficiency anemia and folate deficiency. Among healthy urban Indians, men were more likely to have inadequate levels of vitamin A, riboflavin, vitamin C, and zinc compared with women.[26]

Hair Loss

Nutritional deficiencies are prevalent among individuals with hair loss. Among patients with male pattern hair loss, 11.76% have zinc deficiency, and 29.41% have copper deficiency. Nearly 32% of patients with telogen effluvium have copper deficiency. In addition, more patients with telogen effluvium have iron deficiency compared to those with androgenetic alopecia.[27]

Deficiency of B Vitamins

A meta-analysis reported that folic acid deficiency is present in 41%, vitamin B_{12} deficiency in 48%, and vitamin D deficiency in 60% of Indians aged over 18 years.[9] The National Family Health Survey-5 (NFHS-5) reported anemia among 57% of women and 25.0% of men aged 15–49 years. Overall, 52.2% of pregnant women, 57.2% of non-pregnant women aged 15–49 years, and 61% of breastfeeding women were anemic. Anemia was more common in women and men in rural areas compared to urban areas (women—59 vs 54%; men—27 vs 20%).[28,29] Vitamin B_{12} deficiency is reported in individuals with NAFLD, with mean serum levels of 377.6 ± 181.43 pg/mL compared with 548.28 ± 285.7 pg/mL in non-NAFLD individuals.[30] Thiamine deficiency has been reported in 67% of patients with heart failure (mean serum levels 1.02 ± 1.65 ng/mL) who were on long-term treatment with loop diuretics.[31]

Nuances of Indian Dietary Habits Contribute to Micronutrient Deficiencies

Micronutrient deficiencies in India can be attributed to poor dietary habits and inadequate diet.[9,32] Current diets in most Indian states are lacking in 11 of the 25 essential nutrients. In almost all states, the intake of riboflavin, fiber, potassium, and vitamin A is <50% of the RDA levels. Diets in east and northeast India are deficient in more nutrients compared with diets in other zones.[33] Indian diets are predominantly cereal-based. However, cereals such as rice and wheat usually have inadequate micronutrient content (iron, calcium, vitamin A, riboflavin, and folic acid).[34,35] It is alarming that 54–70% of households consume less than the recommended dietary intake (RDI) of green leafy vegetables, milk, and milk products.[36]

Dietary patterns in India are linked to family values and cultural/religious beliefs. It is estimated that approximately one-third of the Indian population is vegetarian.[37] While vegetarians consume greater quantities of legumes, pulses, and vegetables with lower quantities of fat compared with nonvegetarians, vegetarian diets do not provide adequate quantities of vitamin B_{12}, omega-3 fatty acids, zinc, and other minerals.[9,32] Additionally, poor absorption of zinc and iron has been reported for vegetarian diets compared with nonvegetarian diets, thus contributing to deficiencies.[38,39]

Diets focusing on weight reduction coupled with improper dietary practices also lead to micronutrient deficiencies. The increased consumption of junk food and unhealthy snacking habits are also causative factors. The increased intake of processed foods, along with cereal-based food practices, are also causative factors.[9,32]

Multimicronutrient Deficiencies

Worldwide, about 2 billion people are deficient in one or more micronutrients.[1] In India, at least one, two, or three deficiencies have been reported in 41, 23, and 2.9% of pregnant women (tested for selenium, zinc, copper, iodine, vitamin B_{12}, and ferritin).[40] Hematopoiesis requires not only iron but folic acid and vitamin B_{12} as well. A study in India reported that adolescents with anemia were deficient in vitamin B_{12} but not in folate.[41] A community-based study in north India reported that iron, folate, and vitamin B_{12} deficiency was present in 67.7, 26.3, and 74.1% of pregnant women, respectively, while concomitant deficiencies of these micronutrients were reported in 16.2% of the women.[42] Another study reported that women with folate deficiency have a twofold higher prevalence of vitamin B_{12} deficiency.[43]

Association between Micronutrient Deficiency and Diseases

The causal relationship between micronutrient deficiencies and disease has been studied extensively, with the deficiencies playing crucial roles in the development of disease. Conversely, disease states are also demonstrated to cause deficiency of specific micronutrients (Table 2).[11,14–19,21,30,31,43–60]

Treatment-associated Risk of Micronutrient Deficiency

Drug-induced nutrient deficiencies can be categorized as adverse reactions (Table 3).[61,62] These deficiencies occur due to the prolonged duration of drug

Table 2: Micronutrient deficiencies leading to disease, and diseases that cause micronutrient deficiency[11,14–19,21,30,31,43–60]

Micronutrient deficiency leading to disease		
Micronutrient deficiency	Subsequent disease	
Vitamin B_1	Anemia, heart failure, and sarcopenia[31,45,47]	
Vitamin B_6	Heart failure, sarcopenia[48,49]	
Vitamin B_9	Anemia, hypertension, and obesity[43,50]	
Vitamin B_{12}	Anemia, osteoporosis, sarcopenia, and NAFLD[30,43,49,51]	
Vitamin C	Obesity[50]	
Vitamin D	Vascular function, osteoporosis, and sarcopenia[21,49]	
Vitamin E	Sarcopenia[49]	
Vitamin K	Osteoporosis, CVD, and diabetes mellitus[46]	
Cr	Diabetes mellitus[18]	
Cu	Anemia, COPD, and osteoporosis[19,52,53]	
Mg	Osteoporosis, diabetes complications, diabetes mellitus, prediabetes, and asthma[11,14–16]	
Se	Prediabetes, asthma, CVD, and obesity[10,14,17]	
Zn	Prediabetes, obesity, and osteoporosis[10,14,53]	
Disease states leading to micronutrient deficiency		
Disease	Vitamin deficiency	Mineral deficiency
Alcoholism	B_1, B_2, B_6, B_9, B_{12}, C, D[54]	Zn[54]
Chronic intestinal failure	A, B_{12}, D, E, K[55]	Mg, Fe, Zn[55]
Chronic atrophic gastritis	B_{12}, C, D[56]	Ca, Fe[56]
Chronic renal failure	B vitamins, C, D[57]	Cu[58]
Inflammatory bowel disease	B_1, B_6, B_9, B_{12}, D, K[59]	Fe, Se, Zn[59]
Liver disease	B_1, B_6, B_9, D, E[60]	Cu, Zn[60]

COPD, chronic obstructive pulmonary disease; NAFLD, nonalcoholic fatty liver disease

Table 3: Drugs and specific treatment procedures that lead to micronutrient deficiencies[61–63]

Drug/treatment	*Micronutrient deficiency*
CRRT	Copper, selenium, vitamin C, folate, thiamine, and carnitine
Proton pump inhibitors	Vitamin B_{12}
Metformin (especially chronic use and high-dose metformin)	Vitamin B_{12}
Loop diuretics	Vitamin B_1, calcium, and magnesium
Thiazide diuretics	Zinc, magnesium
Glucocorticoids	Calcium
Isoniazid	Niacin, pyridoxine
Valproic acid	Carnitine
Methotrexate, pentamidine, sulfasalazine, phenytoin, cholestyramine	Folate
Statins	Coenzyme Q10
ACE inhibitors	Zinc

ACE, angiotensin-converting enzyme; CRRT, continuous renal replacement therapy

therapy, drug–drug interactions, and disease physiology. Drugs impact nutrient levels in the body through impaired nutrient digestion, increased intestinal and/or urinary losses, decreased bioavailability, decreased storage, and impaired metabolism.[61] Additionally, renal replacement therapy (RRT) has been recognized as a cause for the loss of water-soluble vitamins, especially in the case of continuous RRT (CRRT) that lasts over 7–10 days.[63]

Current Profile of Public Health Initiatives in India

The Prime Minister's Overarching Scheme for Holistic Nourishment (POSHAN) Abhiyaan is a multiministerial effort to address malnutrition by strengthening and converging actions to support nutrition. It supports several nutrition initiatives and policies to address micronutrient deficiencies, for example, the promotion of early initiation of breastfeeding, immunization, control of childhood illness, iron and folic acid supplementation, adolescent nutrition, etc.[64]

The National Iodine Deficiency Disorders Control Programe surveys the magnitude of iodine deficiency at the district level, supplies iodized salt in place of common salt and then reassesses the magnitude of iodine deficiency after 5 years.[65] The Intensified National Iron Plus Initiative provides prophylactic iron and folic acid supplementation to six target age-groups—under five children, children 5–9 years, adolescent girls and boys, pregnant and lactating mothers, and women of reproductive age-group.[66]

Nutritional support is provided through the Public Distribution System. Under the Home-based Newborn Care (HBNC) program, an Accredited Social Health Activist (ASHA) visits newborns and their mothers at home for the first 42 days of infant life to improve postnatal care for the mother–infant. In addition, the Ministry of Health launched nationwide (IDCF), Nutritional deficiency screening among children, nutrition counseling and education at schools and villages, and food fortification is being strengthened.[64]

Age-specific Dosages of Micronutrient Supplementation for Adults

Guidelines from the Indian Council of Medical Research (ICMR) National Institute of Nutrition (NIN) Expert Group on Nutrient Requirements for Indians (2023) have specified the RDA for macronutrients and micronutrients for men and women. The micronutrient requirements are summarized in Tables 4 to 6.[67]

Table 4: Recommended dietary allowance for adult men aged >18 years (as per ICMR-NIN 2023)[67]

Micronutrient	*Sedentary work*	*Moderate work*	*Heavy work*
Vitamin A (µg/day)	460	460	460
Thiamine (mg/day)	1.4	1.8	2.3
Riboflavin (mg/day)	2.0	2.5	3.2
Niacin (mg/day)	14	18	23
Pyridoxine (mg/day)	1.9	2.4	3.1
Folate (µg/day)	300	300	300
Vitamin B_{12} (mg/day)	2.2	2.2	2.2
Ascorbic acid (mg/day)	80	80	80
Vitamin D (IU/day)	600	600	600
Magnesium (mg/day)	440	440	440
Zinc (mg/day)	17	17	17
Iron (mg/day)	19	19	19
Iodine (µg/day)	140	140	140

Table 5: Recommended dietary allowance for nonpregnant and nonlactating women aged >18–<60 years, and for pregnant and lactating women (as per ICMR-NIN 2023)[67]

Micronutrient	*Nonpregnant and nonlactating women aged >18–<60 years*			*Pregnant and lactating women*		
	Sedentary work	*Moderate work*	*Heavy work*	*Pregnant*	*Lactating 0–6 months*	*Lactating 6–12 months*
Vitamin A (µg/day)	1,000	1,000	1,000	900	950	950
Thiamine (mg/day)	1.4	1.7	2.2	2.0	2.1	2.1
Riboflavin (mg/day)	1.9	2.4	3.1	2.7	3.0	2.9
Niacin equivalent (mg/day)	11	14	18	13	16	16
Pyridoxine (mg/day)	1.9	1.9	2.4	2.3	2.16	2.07
Folate (µg/day)	220	220	220	570	330	330
Vitamin B_{12} (mg/day)	2.2	2.2	2.2	2.45	3.2	3.2
Ascorbic acid (mg/day)	65	65	65	80	115	115
Vitamin D (IU/day)	600	600	600	600	600	600
Magnesium (mg/day)	370	370	370	440	400	400
Zinc (mg/day)	13.2	13.2	13.2	14.5	14.1	14.1
Iron (mg/day)	29	29	29	27	23	23
Iodine (µg/day)	140	140	140	220	280	280

Evidence-based Micronutrient Interventions

Current Guidelines for Micronutrient Supplementation

The NIN, India, recognizes the need for adequate intake of calcium, iron, zinc, vitamin A, and antioxidants for various age groups. The NIN advises daily supplements of iron, folic acid, vitamin B, and calcium for pregnant/lactating women. Elderly individuals need more calcium, iron, zinc, vitamin A, and antioxidants to prevent

Table 6: Recommended dietary allowance for elderly individuals aged >60 years (as per ICMR-NIN 2023)[67]

Micronutrient	*Men*	*Women*
Vitamin A (µg/day)	1,000	840
Thiamine (mg/day)	1.4	1.4
Riboflavin (mg/day)	2.0	1.9
Niacin equivalent (mg/day)	14	11
Pyridoxine (mg/day)	1.9	1.9
Folate (µg/day)	300	200
Vitamin B_{12} (mg/day)	2.2	2.2
Ascorbic acid (mg/day)	80	65
Vitamin D (IU/day)	800	800
Magnesium (mg/day)	440	370
Zinc (mg/day)	17	13.2
Iron (mg/day)	19	19
Iodine (µg/day)	140	140

age-related degenerative diseases and for healthy aging.[67]

The European Society for Parenteral and Enteral Nutrition recommends that "patients receiving enteral nutrition or parenteral nutrition should receive adequate amounts of all essential trace elements and vitamins from the beginning of the period of nutritional support. Micronutrient supplements shall be provided orally or enterally if this can be done safely and effectively."[44]

Efficacy of Micronutrient Supplementation in India

There are several studies evaluating the impact of micronutrient supplementation on various populations in India, including adults, children, pregnant women, and those with specific chronic and acute diseases, etc.

Adult nonpregnant, lacto-vegetarian women receiving vitamin B_{12} 500 µg daily along with green leafy vegetables demonstrated an increase in serum levels of vitamin B_{12} within 2 weeks and a decrease in total homocysteine concentrations. This improvement was not reported for women receiving only green leafy vegetables.[68]

In a study of 75 individuals with T2DM receiving vitamin B_{12} and folate [alone or in combination, in addition to the standard oral antidiabetic drug (OAD)] for 8 weeks, an improvement in HbA1c was noted compared with patients receiving only OAD. A clinically meaningful decline in HbA1c (0.5%) was noted for 68 and 79% of patients receiving vitamin B_{12} and vitamin B_{12} plus folate, respectively, compared with 42% of patients receiving only OAD. Glycemic control was associated with improved insulin sensitivity and increased serum adiponectin levels.[69]

Among vitamin D-deficient T2DM patients with simvastatin-induced impaired exercise performance, vitamin D (60,000 IU once-weekly for 12 weeks) increased skeletal muscle mitochondrial content from 3.6 to 12.1% and increased skeletal muscle citrate synthase activity by 16.7%.[70] Adults with prediabetes and insufficient vitamin D also benefit from supplementation (60,000 IU weekly for 8 weeks followed by 60,000 IU monthly along with 1,250 mg of calcium carbonate), with higher levels of serum vitamin D, lower FPG, postprandial glucose (PPG), tumor necrosis factor α (TNF-α), and interleukin-6 (IL-6) compared with prediabetic vitamin D-deficient individuals receiving only calcium carbonate. Vitamin D supplementation also reduced the rate of progression to diabetes (10.9% vs 26.5%) and increased the rate of reversion to normoglycemia (41.8% vs 20.4%) compared with calcium carbonate supplementation.[71]

Patients with T2DM who received vitamins B, C, and E for 5 years had a slower rate of the development of diabetic retinopathy and improved levels of reactive oxygen species (ROS), superoxide dismutase, and malondialdehyde (MDA). In addition, levels of advanced glycation end (AGE) products and vascular endothelial growth factor (VEGF) also improved.[72]

Vitamin C supplementation improves cognition in postmenopausal women, resulting in significantly improved delayed verbal recall, naming, and repetition scores after 12 weeks and a significant decrease in β-amyloid levels.[73] Vitamin C plays a role in improving lung function in healthy adults aged over 35 years, which could be related to the antioxidant potential that could protect against pulmonary diseases. Almost 6 weeks of vitamin C supplementation (250 mg daily) led to an improvement in peak expiratory flow (PEF) and percent-predicted PEF.[74]

Vitamin C, in combination with collagen type II and glucosamine, is beneficial among adults with tendinopathies. About 6 months of supplementation with the combination led to a reduction in mean visual analog scale (VAS) scores compared with patients in the placebo group.[75] Supplementation of vitamins C and E along with exercise leads to an improvement of lipid profile among young Indian males. There was suppression of hemolysis and an improvement in inflammatory markers and lipid parameters.[76]

Efficacy of Multivitamin-mineral Supplementation

Role of Micronutrients in Healthy Aging

Micronutrient deficiency is an established cause of reduced cognition, especially among elderly individuals. Deficiencies of vitamins B_1, B_9, and C, calcium, magnesium, and zinc lead to a decrease in short-term memory, confusion, visual difficulties, disorientation, and loss of concentration, among various other impacts.[77]

A proprietary multivitamin-mineral (MVM) supplement has been evaluated for its impact on cognitive function in older adults (vs cocoa extract supplement). Daily use of the MVM significantly improved global cognition, particularly in patients with a history of cardiovascular disease (CVD) for up to 2 years. Improvement of executive function and memory was also noted with the use of MVM.[78] The COcoa Supplement and Multivitamin Outcomes Study Web (COSMOS-Web) ancillary study reported that daily MVM supplementation improved the Modified Rey Auditory Verbal Learning Test (ModRey) immediate recall memory from 7.1 to 7.81 after 1-year, and the effect was sustained for over 3 years.[79] In the COSMOS for the Mind (COSMOS-Mind) study, daily MVM supplementation slowed the decline of incidents of mild cognitive impairment.[80]

The Age-related Eye Disease Study (AREDS) assessed the impact of MVM supplementation on the development and progression of opacities of the lens among adult participants. MVM supplementation led to a 16% reduction in any lens opacities (median follow-up, 6.3 years) and a 25% reduction in nuclear opacity events,[81] which is in line with the findings of the Linxian Cataract Study, which demonstrated a 36% reduction in the prevalence of nuclear cataracts after 5–6 years of treatment.[82]

Multivitamin-mineral Supplementation and Cancer

The role of MVM supplementation in the prevention of chronic disease has been widely debated, with evidence ranging from protective action to possible harm. The Physicians' Health Study II evaluated the impact of MVM supplementation on the incidence of cancer (excluding nonmelanoma skin cancer) among over 14,000 male physicians. After a mean follow-up of 11.2 years, there was an 8% reduction in the incidence of total cancer in the MVM group compared with the placebo group and an 18% reduction in the incidence of total cancer among men aged 70 years and over. The impact was stronger for secondary prevention of cancer among participants with a history of cancer at baseline compared with participants with no history of cancer.[83]

Multivitamin-mineral Supplementation and Fertility

Oxidative stress is a major cause of male infertility, with antioxidants proposed to be a treatment option.[84] Studies have demonstrated an improvement in semen parameters such as diminished DNA damage, as well as improved antioxidant potential, sperm count, and sperm motility.[85] A recent study compared the effect of antioxidant coenzyme Q10 with the MVM supplement on semen parameters of 130 men with idiopathic oligoasthenospermia. Both treatment groups had improved sperm concentration, progressive motility, total motility, antioxidant capacity, and sperm DNA fragmentation (SDF). However, the MVM supplement scored over coenzyme Q10 for sperm motility, antioxidant capacity, and SDF.[84]

Potential Side Effects and Risks Associated with Supplementation with Higher Doses

Dietary supplements are commonly consumed across the world, both on prescription and over-the-counter.[86] When used for the treatment of deficiency states, vitamin and mineral supplements are well-tolerated since dosing is derived from clinical research. Adverse effects occur due to long-term use, drug–drug interactions, and drug-disease interactions.[87] There is a fallacy among consumers that vitamin supplements are safe.[88] Water-soluble vitamins such as vitamin B_6 can cause neurotoxicity and photosensitivity at doses over 500 mg/day, while elderly patients may experience pyridoxine-associated chronic sensory polyneuropathy.[86] Moderate-to-high doses of vitamin B_3 are associated with peripheral vasodilation, and vasodilation in the eye can cause reversible toxic cystoid macular edema.[87]

Vitamin E at doses over 400 IU/day can cause an increase in all-cause mortality.[89] Doses of 800–1200 mg/day can result in bleeding, and doses above 1200 mg/day can result in diarrhea, weakness, blurred vision, and gonadal dysfunction.[86] The Heart Outcomes Prevention Evaluation (HOPE) reported that patients with vascular disease or diabetes mellitus who received vitamin E 400 IU daily for 7 years had a 13% higher risk of heart failure and a 21% higher risk of hospitalization for heart failure compared to those who did not receive supplementation.[90]

Excess consumption of vitamin A (25,000 IU/day) during pregnancy can lead to birth defects, while children can suffer adverse effects at doses of 1,500 IU/kg/day.[91] Vitamin A can alter bone metabolism and can cause hypercalcemia, profound weight loss, and liver disease.[92] An increased risk of hip fractures and osteoporotic hip fractures has been reported among postmenopausal women who consumed vitamin A supplements for 18 years.[93]

In conclusion, formulations of vitamin/mineral supplements must contain the appropriate balance of micronutrients and should provide micronutrients within the RDA recommended for the Indian population, as per Indian guidelines. Commercially available formulations provide a comprehensive blend of vitamins and minerals, along with botanicals, to meet the specific needs of specific populations with micronutrients within RDA levels that are generally considered safe for long-term use. Vitamins and minerals at high doses can be considered drugs, and therefore, regular monitoring through blood profiling is necessary to ensure the safety of the prescribed treatment in patients who are prescribed therapeutic doses of vitamins.

Specialty Nutrients

Boswellia Extract

Boswellia serrata, which has been used in traditional medicine, contains boswellic acid, which has significant antiinflammatory activity. 3-acetyl-11-keto-beta-boswellic acid (AKBA) exhibits the strongest inhibitory action on 5-lipoxygenase (5-LOX),[94,95] and acts synergistically with β-boswellic acid.[96] Patients with osteoarthritis (OA) who receive oral *Boswellia serrata* extract (BSE) have improved pain and stiffness after 120 days of treatment. An improved knee joint gap and reduced serum levels of high-sensitivity C-reactive protein (hsCRP) are also reported.[96] BSE treatment reduces pain, Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain, and WOMAC stiffness and improves joint function.[95]

Grape Seed Extract

Grape seed extract (GSE) contains several biologically active components that display antioxidant, antiinflammatory, antiapoptotic, antinecrotic, and cardioprotective effects.[97] The cardioprotective effect has been demonstrated through antiatherogenic effects among patients with asymptomatic carotid plaques or abnormal carotid intima-media thickness (CIMT) in a placebo-controlled study (mean maximum CIMT, –5.8%; plaque score, –33.1%) after 24 months, and a lower incidence rate of transient ischemic attack (27.27 vs 28.21%) and rehospitalization for unstable angina (36.36 vs 43.59%).[98]

Hyaluronic Acid

Hyaluronic acid (HA), a naturally occurring mucopolysaccharide, is abundant in the extracellular matrix and pericellular matrix. It contributes to the elastoviscosity of the joint synovial fluid and facilitates the lubrication of joints and muscles.[99] HA at a dose of 60 mg daily for 4 months reduces pain and improves step-up and step-down function in patients with knee OA and synovitis. A dose of 200 mg daily for 8 weeks significantly improves total WOMAC score in patients with knee OA.[100]

Pomegranate Extract

Pomegranate peel extract (PPE) is rich in phenolic compounds which exhibit antioxidative, antitumor, antiinflammatory, neuroprotective, antiviral, and antibacterial activities.[101] Oral administration of fermented pomegranate extracts for 8 weeks reduces oxidative stress and improves moisture, brightness, elasticity, and collagen density of the skin.[102] Obese and overweight individuals who consume pomegranate extract for 30 days have a significant reduction in serum glucose, insulin, total cholesterol, and low-density lipoprotein cholesterol and a significant increase in plasma malondialdehyde (MDA), IL-6, and hs-CRP.[103] Patients with NAFLD who are administered pomegranate extract for 12 weeks have improved liver function, reduced IL-6 levels, and increased total antioxidant capacity (TAC).[104]

Omega-3 Fatty Acids

Eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids are omega-3 fatty acids that have beneficial effects on the cardiovascular system by increasing mitochondria β-oxidation and exerting antiarrhythmic and antithrombotic effects. Omega-3 fatty acids improve endothelial and vasomotor function and lower blood pressure.[105,106] Omega-3 fatty acid supplementation reduces the risk of CV mortality by 7%, nonfatal myocardial infarction (MI) by 13%, coronary heart disease events by 9%, major adverse cardiovascular events (MACE) by 5%, and revascularization by 9%.[105]

Biotin

Biotin is a cofactor for carboxylases that are required for the synthesis of keratin, thus contributing to the growth of hair and nails.[107,108] Low biotin levels are reported in 38% of women experiencing hair loss.[109] Among patients with telogen effluvium who received biotin supplementation for 3 months, 51.5% demonstrated improved hair growth. This was particularly evident for individuals who had deficient serum biotin levels before supplementation. Biotin supplementation also improves hair health in children with uncombable hair.[107]

Probiotics and Prebiotics

Prebiotics are nondigestible, fermentable food ingredients, predominantly fibers that stimulate the growth of gut microorganisms (such as lactobacilli and bifidobacteria).[110] Probiotics are "live microorganisms which, when administered in adequate amounts, confer a health benefit to the host" that inhibit the colonization of the intestine by pathogenic bacteria and enhance the intestinal barrier to improve the immune function of the host.[111,112] The gut microbiome plays a role in intrinsic primary afferent neuron excitability and modulates the release of biologically active peptides from enteroendocrine cells. This can

influence mood, blood pressure, sleep cycle, etc. Metabolites of the gut microbiome have immunomodulatory functions, stimulate the autonomic nervous system, and regulate brain development by influencing the homeostasis of microglia.[112] Adults aged 18–60 years with irritable bowel syndrome (IBS), when treated with *Bacillus*, coagulant Unique IS2 along with standard care, experience a significant reduction in bloating, vomiting, diarrhea, abdominal pain, and stool frequency.[113]

Melatonin

Melatonin (5 methoxy-N-acetyl tryptamine) is a hormone secreted by the pineal gland primarily after sundown. Peak melatonin levels are achieved between 2 and 4 AM, and serum concentrations at night are typically 80 and 120 pg/mL (vs 10–20 pg/mL during the day). Melatonin is a crucial regulator of the sleep-wake cycle.[114] Middle-aged patients with insomnia who receive melatonin for 4 weeks have improved total sleep time, percentage of rapid eye movement, and early morning wake time.[115] Among nonsmoking, nonpregnant, shift-worker female nurses, melatonin significantly decreased sleep onset latency and increased sleep quality compared with placebo. Melatonin supplementation reduces daytime sleepiness among night shift workers and increases sleep duration by up to 20 minutes per day.[116]

L-theanine

L-theanine (γ-glutamylethylamide) has a structure that resembles L-glutamic acid and is isolated from green tea (Camellia sinensis). It acts on glutamate receptors and may have a partial coagonistic effect on the N-methyl-D-aspartate receptor.[117] L-theanine exerts neuroprotective effects that improve sleep quality and reduce cognitive abnormalities, which may occur due to the release of glutathione from astrocytes. A synergistic effect with γ-aminobutyric acid (GABA) could improve sleep quality and duration.[118] Supplementation with L-theanine decreases stress-related symptoms, including depression, anxiety traits, and sleep disturbances, along with a significant reduction in the use of sleep medication. Cognitive function, including verbal fluency and executive function, improved after 4 weeks of L-theanine administration.[117]

Collagen: Undenatured Collagen II

The dominant collagen present in articular cartilage is type II collagen. Supplementation of type II collagen may prevent progressive damage to cartilage and aid in the healing of cartilage among patients with OA. Oral tolerance to antigens, amelioration of the T cell-mediated attack on articular cartilage, and suppression of IL-17 associated receptor activator of nuclear factor kappa B ligand (RANKL) expression of clusters of differentiation 4+ T cells is achieved in response to oral supplementation with undenatured type II collagen (UC II).[119,120] Among Indian patients with OA, UC II intake is associated with a reduction in pain, stiffness, and improved functional mobility, which can improve the quality of life. It reduces WOMAC pain by 95.5%, WOMAC stiffness by 60%, and WOMAC physical function by 80%.[120,121]

Gingko Biloba

Gingko biloba (*G. biloba*) contains bioactive terpenoids, flavonoids, polyphenols, and organic acids, which have antiinflammatory, antioxidative, and antiapoptotic effects. Beneficial effects of *G. biloba* include improvement in memory, cognition, hypertension, dyslipidemia, insulin resistance, and cardiovascular disorders. It also improves mood and quality of life and decreases stress. Thus, *G. biloba* has a wide range of beneficial effects that could impact several chronic conditions associated with aging.[122]

Addressing Micronutrient Deficiencies in India: Expert Consensus

There is a need to ensure that recommended levels of micronutrients are maintained in all individuals, especially those who are at risk of developing diseases due to deficiency states. Micronutrient supplementation is also essential as supportive therapy for acute and chronic diseases, as well as during recovery and healing. There is a need to focus on risk groups such as children aged <5 years, individuals in lower socioeconomic strata who lack food security, women of the reproductive age-group, pregnant women, and elderly individuals. Each of these groups may have a specific requirement for a micronutrient or a combination of micronutrients, and therapy should be tailored to suit the target group.

The need for nutrient supplementation does not take away from the importance of a well-balanced diet as the foundation for good health and nutrition. However, it is essential to recognize that gaps in nutrition may require supplementation to ensure that the correct balance of nutrients is provided. These micronutrient supplements can also compensate for dietary practices that are inadequate in terms of vital nutrients.

Balancing Nutrient Intake Through Diet

Micronutrient deficiencies typically arise from diets lacking diversity in food groups or from disease to infections. Long-term food-based strategies can effectively prevent these deficiencies sustainably for most of the population.[123] Commercially cultivated cereal, pulse, and oilseed varieties often lack vital nutrients due to nutrient-poor soils or the crops themselves. Unfortunately, these major food crops do not provide the essential micronutrients for normal human growth. To combat nutritional deficiencies, identifying genes and quantitative trait loci related to essential nutrients and integrating these into elite breeding lines may be helpful.[124]

Micronutrient intakes vary significantly between diet inadequacy, Indian dietary patterns, losses due to food processing/cooking, and food impurities (Table 7).[32]

Do Traditional Indian Diets Meet the Guideline Requirements?

Traditional dietary practices, including the "Thali" (plate) concept, emphasize combinations (grains, lentils, vegetables, dairy, spices, prebiotics and probiotics, and fats) that are local and seasonal. These practices ensure that all the necessary food groups are provided and comply with evidence-based recommendations. Techniques for the preparation, cooking, and preservation of food impact the glycemic index (GI) and nutrient availability. A few traditional ways to lower GI and improve the nutritional value of meals include[125]:

Table 7: Causes of inadequate micronutrient intake *via* poor diets[32]

Causes	*Causative features*
Daily diet inadequacy	Vegetarian diets may lack essential omega-3 fatty acids, vitamin B_{12}, and minerals due to reduced bioavailability in plant sources Inadequate consumption due to weight-reduction diets, dietary imbalances, and unhealthy eating habits Increased consumption of junk food leads to unhealthy snacking habits, eating disorders, emotional and/or physiological stress
Micronutrient loss in food	Farming techniques and food processing results in plant micronutrient loss Cooking leads to a loss of vitamins (25–40%)

- Use whole grains (unpolished, coarse, long grain, and aged).
- Include slow-digesting carbs with high amylose and soluble fiber (e.g., pulses and barley).
- Combine meals with protein, fiber, and healthy fats.
- Opt for resistant-starch-rich foods and preparation methods.
- Use acidic ingredients like lemon, vinegar, or tamarind.
- Choose slightly unripe fruits to control GI since the GI increases as the fruit ripens.

Expert Consensus

Adults (Men and Nonpregnant/ Nonlactating Women)

- Food group recommendations to meet the estimated average requirements (EAR) of different nutrients for Indian adult men and nonpregnant and nonlactating women are described in Table 8.
- It is essential to make smart food choices from a diverse range of food groups, obtaining all the necessary nutrients in appropriate quantities.
- An individual should incorporate a daily intake of a minimum of 300 gm of vegetables (50 gm of green leafy vegetables, 200 gm of other vegetables, and 50 gm of roots and tubers). It is advisable to regularly consume 100 gm of fresh fruits.
- High-calorie vegetables and fruits are to be restricted for overweight/obese subjects.
- Adults leading a sedentary lifestyle should aim for around 25 gm of visible fat in their diet, whereas those engaged in strenuous physical work may need 30–40 gm of visible fat.
- Limit salt intake to 6 gm per day.

For effective removal of pesticide residues from food products, follow these methods:

- Wash: Use cold water or a 2% saltwater solution
- Blanch: Briefly treat prewashed vegetables in hot water or steam
- Peel: Remove surface pesticides by peeling fruits and vegetables
- Cook: Use methods like pressure cooking, frying, and baking for animal products. Boil milk at high temperatures to destroy persistent residues.

Elderly Individuals (Age >65 Years)

- It is recommended to limit daily oil intake to 20 gm and to avoid the use of butter, vanaspati, and coconut oil.
- Consumption of protein-rich foods like pulses, toned milk, egg whites, and nutrient-rich options containing calcium, micronutrients, and fiber is recommended.
- Besides cereals and pulses, an intake of 200–300 mL of milk and milk products and 400 gm of fruits and vegetables daily for fiber, micronutrients, and antioxidants are suggested.

Micronutrient Supplementation

Expert Consensus

Adults (men and nonpregnant/nonlactating women) aged 18–65 years and elderly individuals aged >65 years:

- In adult men and nonpregnant/nonlactating women, if micronutrient deficiencies persist despite adequate dietary interventions, a combination of vitamins and minerals is recommended for men and nonpregnant/ nonlactating women aged 18–65 years old.
- A combination MVM is recommended to be taken daily.
- The combination pill should contain essential vitamins, including vitamins A, D, E, and B (B_1, B_2, B_3, B_6, B_9, B_{12}), and vitamin C, and minerals, including copper, selenium, zinc, and magnesium in the correct proportions based on established RDA according to Indian standards.
- Regular monitoring through blood profiling is necessary to ensure the safety of the prescribed treatment in individuals who are prescribed therapeutic doses of vitamins.

Community Awareness and Healthcare Practitioners on Micronutrient Supplementation

Expert Consensus

- Healthcare practitioners (HCPs) should advocate the importance of MVM to various risk groups (children, elderly, obese, those with chronic disease, postsurgical patients, and postillness) and, subsequently, to all patients based on their individual needs.
- Healthcare practitioners (HCPs) should make it a routine to inquire regarding adherence to MVM among all patients during consultation, regardless of indication. This would serve as a reminder to patients.
- Awareness camps can be conducted for specific deficiencies such as iron, folate, vitamin D, and vitamin B_{12}. Screening for these deficiencies at such awareness camps would identify persons who require supplementation.

Table 8: Suggested food groups for a balanced diet to meet EAR of different nutrients

Parameter	*Men*		*Women*	
	Sedentary	*Moderate*	*Sedentary*	*Moderate*
Body weight (kg)	65	65	55	55
Cereals/millets (gm)	270	390	200	280
Pulses and beans (gm)	90	130	65	95
Green leafy vegetables (gm)	100	100	100	100
Vegetables (gm)	200	200	200	200
Roots and tubers (gm)	100	100	100	100
Fruits (gm)	100	100	100	100
Nuts (gm)	40	45	30	40
Milk (mL)	300	300	300	300
Fats and oils (gm)	25	30	20	25
Energy (kcal) obtained from these food groups	~2,080	~2,680	1,660	~2,125
Crude protein (gm) obtained from these food groups	75	90	57	72

EAR, estimated average requirements

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Conflict of Interest

Dr Atul Sharma is on Haleon India's payroll.

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CASE REPORT

Hemophagocytic Lymphohistiocytosis: A Rare Complication of Acute Hepatitis E Infection

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive hematological disorder caused by uncontrolled activation of cytotoxic T-cells (CTL), natural killer (NK) cells, and macrophages leading to hyperinflammation and cytokine storm. The clinical course is characterized by high-grade fever, cytopenia, and multiorgan dysfunction. HLH is classified as either primary/familial or secondary, the latter being most often triggered by infections, malignancies, and autoimmune disorders. Viral infections are commonly known to cause HLH with Epstein–Barr virus (EBV), cytomegalovirus (CMV), influenza virus, adenovirus, and parvovirus being most often implicated. Hepatitis E virus (HEV) has infrequently been reported to cause HLH with less than five cases being reported in the literature. We report a case of a young man who presented with hepatitis E-associated HLH.

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Case Description

A previously healthy, 26-year-old gentleman presented with complaints of high-grade fever for 4 days accompanied by yellowish discoloration of eyes for 2 days. He also complained of generalized abdominal pain and three episodes of vomiting on the day of admission. He denied a history of alcohol intake and the use of complementary medication. On general physical examination, his temperature was 101°F, pulse rate 114/minute, and blood pressure 98/68 mm Hg. Other significant findings included conjunctival pallor, scleral icterus, liver, and spleen palpable 2 and 4 cm below the costal margin, respectively.

Laboratory investigations were significant for pancytopenia, hyperbilirubinemia, elevated lactate dehydrogenase (LDH), aspartate and alanine aminotransferase, serum triglycerides, and serum ferritin (Table 1).

In view of the abdominal pain, vomiting, icterus, and fever, a diagnosis of viral hepatitis was considered and serological tests for hepatitis A, B, C, and, E were ordered and he tested positive for immunoglobulin M (IgM) anti-hepatitis E virus (HEV) antibodies, 1.232 IU/mL (normal < 0.417 IU/mL). As no cause of pancytopenia was apparent, a bone marrow examination was performed and it showed significantly increased hemophagocytic activity (Fig. 1). The patient's history, physical examination, and laboratory tests were consistent with a diagnosis of hemophagocytic lymphohistiocytosis (HLH) as per the HLH-2004 criteria of the histiocyte society.[1] In addition, his HScore was 198 points which is 80–88% predictive of HLH.[2] Serological tests for cytomegalovirus (CMV), Epstein–Barr virus (EBV), parvovirus B19, human immunodeficiency virus 1 and 2, COVID-19, dengue, and malaria were all negative. Blood and bone marrow cultures for bacteria and fungi, and serum procalcitonin were also negative. Cross-sectional imaging of his chest, abdomen, and pelvis did not reveal any abnormalities.

Given the temporal association with HLH and no alternate explanation for his clinical findings, acute hepatitis E infection was identified as the most probable triggering event. The patient received supportive care in the intensive care unit and corticosteroids (dexamethasone, 10 mg/m^2/day) were added once the diagnosis of HLH was confirmed. This led to a resolution of fever on day 2 of therapy. The serum ferritin reduced to 1,369 mcg/L (from 21,926 mcg/L) and there was an improvement in his blood counts and liver function by day 3 of therapy. He made a full recovery and was discharged from the hospital on day 12 of admission.

Table 1: Laboratory investigations

	At presentation	*At discharge*	*Normal range*
Hemoglobin	101 gm/L	131 gm/L	120–150 gm/L
White blood count	1.8 × 10^9/L	4.5 × 10^9/L	4–10 × 10^9/L
Absolute neutrophil count	0.4 × 10^9/L	1.6 × 10^9/L	2.5–6 × 10^9/L
Platelet count	106 × 10^9/L	201 × 10^9/L	150–300 × 10^9/L
Total bilirubin	9.7 mg/dL	1.6 mg/dL	0.6–1 mg/dL
Conjugated bilirubin	6.8 mg/dL	0.9 mg/dL	<0.3 mg/dL
Aspartate aminotransferase	460 U/L	82 U/L	<40 U/L
Alanine aminotransferase	198 U/L	38 U/L	<40 U/L
Serum creatinine	1.1 mg/dL	0.9 mg/dL	0.7–1.3 mg/dL
LDH	676 U/L	350 U/L	<250 U/L
Serum ferritin	21,926 mcg/L	1,369 mcg/L	30–300 mcg/L
Serum triglycerides	630 mg/dL	188 mg/dL	<150 mg/dL
Prothrombin time	16 seconds	13 seconds	10–13.6 seconds
Activated partial prothrombin time (aPTT)	44 seconds	27 seconds	26–32 seconds
Serum fibrinogen	2.1 gm/L	2.8 gm/L	1.5–3.5 gm/L

Discussion

The HLH is a life-threatening disorder caused by the inability of the immune system to restrict the stimulatory effects of an immune trigger. There is an uncontrolled, pathological activation of cytotoxic T-cells (CTL), natural killer (NK) cells, and macrophages that causes uninhibited cytokine production leading to multiorgan dysfunction and if untreated, death.[1]

In adults, malignancies, autoimmune disorders, and infections are the most

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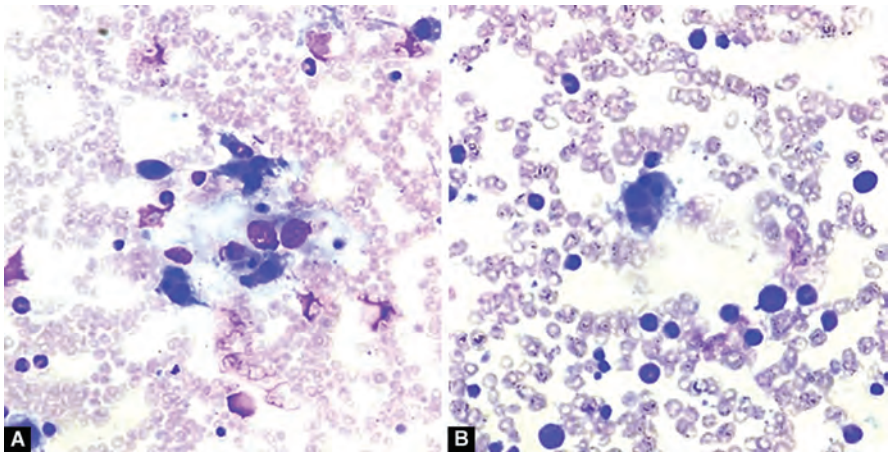

Figs 1A and B: Bone marrow aspirate; May–Grünwald Giemsa stain. (A and B) Cellular marrow with normal hematopoietic elements and increased histiocytes with hemophagocytic activity

Table 2: HLH associated with hepatitis E infection

Serial number	*Age*	*Sex*	*Serum ferritin (mcg/L)*	*Serum triglycerides (mg/dL)*	*Serum fibrinogen (gm/L)*	*HLH-2004 criteria fulfiled*	*Treatment*	*Outcome*	*Reference*
1	40	F	26,200	285	2.82	6/8	Dexamethasone + etoposide	Death	10
2	46	F	1,281	–	1.34	5/8	Methylpredniso-lone	Death	11
3	20	M	13,578	316	3.24	6/8	Dexamethasone	Death	12
4	6	F	1,923	548	–	5/8	Dexamethasone	Death	13
6	26	M	21,926	630	2.1	5/8	Dexamethasone	Alive	Present case

common triggers of HLH. DNA viruses like EBV, CMV, herpes simplex virus, adenovirus, and intracellular organisms like leishmania and tuberculosis are most often implicated.[3] Hepatitis E is the most common cause of acute viral hepatitis in the world and usually causes a self-limiting disease in the immunocompetent population.[4] The diagnosis is usually established by the detection of HEV RNA by reverse transcription polymerase chain reaction (RT-PCR) or detection of anti-HEV antibodies using commercially available kits which are highly specific (99.6%) for the virus.[5] Despite causing >20 million infections each year, hepatitis E has rarely been associated with HLH with only five cases having been reported in the literature (Table 2).[6–10]

The diagnosis of HLH in adults is difficult to establish due to the overlap of symptoms with more common disorders like sepsis and disseminated intravascular coagulation. There is also no standard diagnostic test for HLH. A combination of the HLH-2004 diagnostic criteria and the patient's clinical history is often used to establish the diagnosis. The criteria suggested by the histiocyte society include fever, splenomegaly, cytopenias affecting ≥2 cell lines (hemoglobin ≤90 gm/L, neutrophil count ≤ 0.1 × 10^9/L, platelets ≤ 100 × 10^9/L), hypertriglyceridemia (≥265 mg/dL) and/or hypofibrinogenemia (≤1.5 gm/L), hyperferritinemia (≥500 mcg/L), hemophagocytosis in the bone marrow, spleen, or lymph nodes, low/absent NK cell activity, and soluble CD25 level ≥2400 IU/L. Fulfilment of five or more out of eight criteria is diagnostic of HLH but this is validated for use only in familial/primary HLH. Furthermore, assays for NK cell cytotoxicity are rarely available in resource-constraint settings and limit the usefulness of these diagnostic criteria.[6]

In the absence of such specialized tests, serum ferritin, a widely available test can be used to support a diagnosis of HLH. Extreme hyperferritinemia (≥25,000 mcg/L) is frequently associated with HLH, infections, and cytokine release syndrome. Fauter et al. found that a serum ferritin level ≥13,405 mcg/L was associated with a 76.4% sensitivity and 79.3% specificity for the diagnosis of HLH.[7] Another study found serum ferritin levels ≥10,000 mcg/L to be characteristic of HLH with >90% sensitivity and specificity.[6] Our patient also had a significantly raised serum ferritin level (21,926 mcg/L). Though not a part of any diagnostic criteria, serum LDH has also been associated with an increased likelihood of HLH, albeit with a lower specificity than serum ferritin (57%).[7]

The treatment of HLH is three-pronged, the rapid institution of supportive care, identification, and treatment of the underlying trigger, and suppression of the cytokine storm. There is no consensus regarding the optimal treatment of adults and therapy is tailored as per the HLH-triggering factor. Since the mean age of HLH in adults is close to 50 years, the HLH-2004 protocol which has dramatically improved survival in primary HLH may lead to increased toxicity in this population.[8] It is recommended that infection-triggered HLH be usually treated with a short course of corticosteroids with or without intravenous Ig (IVIg) and etoposide be reserved for severe HLH with imminent organ dysfunction.[6] Our patient was treated with single-agent dexamethasone and made a full recovery within 2 weeks. The corticosteroid dose was gradually tapered and stopped over the next 2 weeks. IVIg could not be administered because of financial constraints.

Our case underscores the need to consider hepatitis E as a possible cause of secondary HLH. The diagnosis must be suspected in patients who present with or develop cytopenia during the course of their illness. Maintaining a high index of suspicion is critical as delays in diagnosis and institution of therapy can prove to be detrimental.

Declaration of Patient Consent

Yes.

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CASE REPORT

A Curious Case of Autoimmunity, Pancytopenia, and Disseminated Intravascular Coagulation

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Abstract

History and examination: A 21-year-old female patient presented to us with severe low back pain for 4 months. On examination, patient was afebrile, with severe pallor, and tenderness in both sacroiliac (SI) joints. Patient was being admitted and evaluated, and during the course of evaluation, developed severe headache, which was severe in intensity and associated with nausea and projectile vomiting.

Initial investigations: An X-ray of the bilateral SI joints revealed inflammation, and the antinuclear antibody (ANA) turned out to be 4+ with pancytopenia and raised lactate dehydrogenase (LDH), but the liver function tests were normal. Rest of the rheumatological profile was unremarkable. During the course of the evaluation, she developed a severe headache, which, on imaging, showed presence of cerebral edema with chronic subdural hematoma, and a concomitant coagulopathy workup revealed evidence of disseminated intravascular coagulation (DIC).

Discussion: Taking the whole picture into consideration, a malignant process in the body was suspected, and serum tumor markers carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and cancer antigen 125 (CA-125) were sent, all of which were raised. Validating the clinical clue was the bone marrow biopsy done for pancytopenia, which revealed malignant epithelial infiltration. A contrast-enhanced computed tomography (CECT) thorax and whole abdomen were done to find out the primary, which showed a neoplastic mass at the gastroesophageal junction along with bony metastases in the vertebrae and left adrenal. Tissue from the primary lesion was taken for histopathological examination (HPE) through upper gastrointestinal endoscopy. Although HPE revealed grade III poorly differentiated stomach adenocarcinoma, the patient had succumbed to the disease process by the time the diagnosis came to light.

Conclusion: In short, this case perfectly illustrates how solid organ malignancies might be a mimicker of multisystem disorders, thereby delaying diagnosis and worsening the prognosis even further.

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Introduction

Delayed diagnosis due to absence or paucity of classical symptoms is one of the key prognostic factors in cancers and is a feature of adenocarcinoma in the young.[1] Gastric cancer (GC) usually presents in middle and old age, between 50 and 70 years, with 50% of the freshly diagnosed stomach cancer patients aged >74 years.[2] Local symptoms predominate, and GC is generally associated with a dismal prognosis unless localized at the time of diagnosis. However, 2–8% of GCs are reported in young persons (<41 years), called young adult GCs; they pursue an aggressive course, frequently with less prominent local features and masquerade as a different disease altogether, baffling clinicians[3]. We describe a 21-year-old female who presented with low back pain, had strongly reactive antinuclear antibody (ANA), pancytopenia with features mimicking hemolytic anemia, disseminated intravascular coagulation (DIC), developed cerebral edema before an incidental diagnosis of gastric carcinoma could be achieved, with an extremely poor outcome.

Case Description

A woman aged 21 years presented with severe low back pain for 4 months. She was pale, afebrile, with tenderness in both sacroiliac joints that was incapacitating. An X-ray of both sacroiliac (SI) joints showed inflammation features, warranting consideration of connective tissue disease. Her ANA titer was strongly reactive (+++) with an immunofluorescence assay. Blood tests revealed anemia [hemoglobin (Hb) of 6.6 gm/dL], thrombocytopenia (platelet count 75,000), indirect hyperbilirubinemia (2.6 with 0.6 mg/dL direct bilirubin), markedly elevated alkaline phosphatase level (1256 U/L), normal γ-glutamyl transferase (GGT) 93 U/L, altered aspartate aminotransferase (AST) [AST 87 U/L and alanine aminotransferase (ALT) 23 U/L]. Peripheral smear showed erythrocytes were microcytic hypochromic with anisocytosis, reactive lymphocytes were seen occasionally, and thrombocytopenia was confirmed on the smear. Further tests showed elevated reticulocyte count (5.45%) but a low reticulocyte proliferation index of 1.7 (hypoproliferative), highly raised lactate dehydrogenase (LDH) (1294 U/L), normal complement C3 (125 mg/dL) and C4 level (40.2 mg/dL), negative rheumatoid factor, normal level of serum parathyroid hormone (37.22 pg/mL), and a negative direct Coombs test. A complete ANA profile revealed a negative anti-dsDNA antibody and weakly reactive for autoantibodies against proliferating cell nuclear antigen (PCNA). This effectively ruled out systemic lupus erythematosus or rheumatoid arthritis (Table 1).

While she was being evaluated in the hospital, one day, she had a severe headache, making her very restless and disabling her from sleeping all night. A noncontrast CT scan of the brain showed diffuse cerebral edema with bilateral frontotemporoparietal (Fig. 1) chronic subdural hemorrhage. Her coagulation profile at this stage revealed prothrombin time (PT) was 14.8 seconds (control 10.9 seconds), activated partial thromboplastin time (aPTT) was 36.8 seconds (control 21.9 seconds), international normalized ratio (INR) of 1.39, and fibrin degradation product (FDPs) 1600 ng/mL. These findings indicated the development of DIC. She received 3 units of fresh frozen plasma and 2 units of packed red blood cell transfusion along with other supportive care. Over the course of her admission, she became drowsy, and her Glasgow Coma Scale score gradually deteriorated to E1M5V1. Her pupils

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Table 1: Summary of investigations[1]

Serial no.	*Parameter*	*Value*
1.	Hb	6.6 gm/dL
2.	Mean corpuscular volume	66 fL
3.	Platelet	75,000/mm^3
4.	White blood cells	3,200/mm^3
5.	Reticulocyte proliferation index	1.7 (hypoproliferative)
6.	Total serum bilirubin	2.6 mg/dL
7.	Direct serum bilirubin	0.6 mg/dL
8.	AST/ALT	87/23 U/L
9.	ALP	1256 U/L
10.	GGT	93 U/L
11.	LDH	1294 U/L
12.	C3	125
13.	C4	40.2
14.	Rheumatoid factor	Negative
15.	Serum parathormone	37.22 pg/mL
16.	DCT	Negative
17.	ANA	4+
18.	ANA profile	Weakly positive anti-PCNA, rest negative.

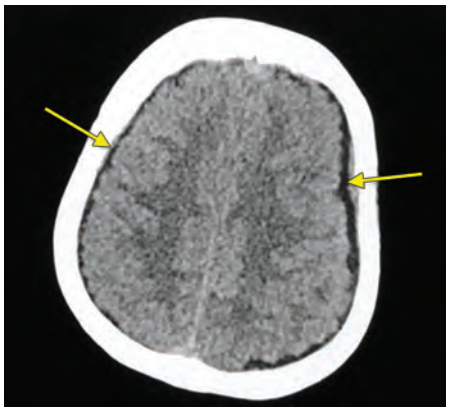
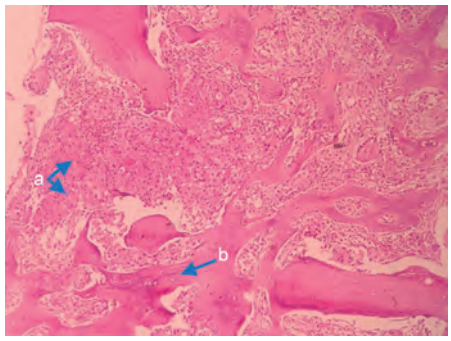


Fig. 1: Noncontrast CT scan of the brain shows diffuse cerebral edema with a thin layer of chronic bilateral frontotemporoparietal subdural hemorrhagic collection

were 3 mm bilaterally and sluggishly reacting to light, with both plantar reflexes going up.

Having developed a DIC and having positive ANA with an unclear etiology, the occult malignant disease was thought of, and blood tests for several common tumor markers were done. The blood levels of carcinoembryonic antigen (CEA) (42.53 ng/mL), carbohydrate antigen 19-9 (CA19-9) (51.11 U/mL), and CA-125 (48.4 U/mL) were markedly raised (Table 2).

In view of significant unexplained alterations in reticulocyte count along with the predominance of hematological changes, bone marrow aspiration and trephine biopsy were carried out. The bone marrow aspiration showed deposits of malignant epithelial cells in clusters, and trephine biopsy showed sheets of malignant epithelial cells infiltrating



Figs 2A and B: (A) Sheets of malignant epithelial cells; (B) Infiltrating the bone marrow interstitium [hematoxylin and eosin (H&E) stained; 40×]

the marrow interstitium (Fig. 2), indicating metastatic carcinoma with overall reduced hematopoietic cellularity of all three cell lines. The epithelial origin of the cells was confirmed by immunohistochemistry staining with cytokeratin.

In search of the primary tumor, we did an ultrasound of the whole abdomen, which revealed a hypoechoic mass in the upper portion of the epigastrium and mild hepatomegaly with normal echotexture of the liver; this was followed up by a contrast-enhanced CT scan of the thorax and whole abdomen, which revealed an irregularly heterogeneously contrast-enhancing wall thickening at gastroesophageal junction having diffuse luminal irregularity with multifocal perigastric and retroperitoneal lymphadenopathy indicating a possibility of gastroesophageal junction neoplasm along with metastatic deposits in the T3, T6, T8-S1 vertebral body and left adrenal gland (Figs 3 and 4). A positron emission tomography scan could not be done due to affordability issues. Finally, an upper gastrointestinal endoscopy was done, which confirmed a proximal gastric neoplastic mass, from which biopsy samples were taken. Eventually, the patient succumbed on the 12th day of her admission. An autopsy was not done in view of negative consent for the same by family members; however, the biopsy report that arrived later

Table 2: Summary of investigations[2]

Serial no.	*Parameter*	*Value*
1.	PT/control	14.8/10.9 seconds
2.	aPTT/control	36.8/21.9 seconds
3.	INR	1.39
4.	FDP	1600 ng/mL
5.	CEA	42.53 ng/mL
6.	CA-19-9	51.11 U/mL
7.	CA-125	48.4 U/mL

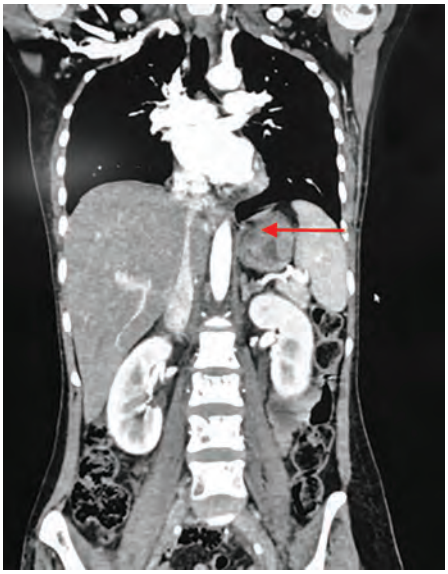


Fig. 3: Contrast-enhanced computed tomography (CECT) of the thorax and abdomen shows a neoplastic mass at the gastroesophageal junction

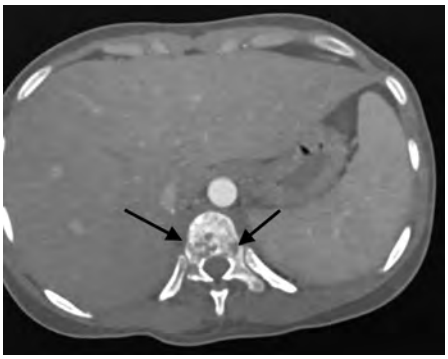


Fig. 4: Lumbar vertebrae show lytic lesions, most probably due to metastatic deposits (cross-sectional view in CECT abdomen)

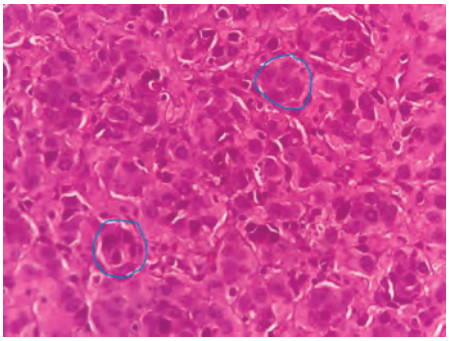


Fig. 5: Hematoxylin and eosin (H&E) stained section of the gastric tumor shows the presence of malignant epithelial cells in acini and clusters (40×)

proved it to be a grade III poorly differentiated adenocarcinoma of the stomach (Fig. 5).

Case Discussion

Uncommon and rare presentations of common diseases are the greatest challenges in medicine, not only as an academic curiosity but also to raise the alarm early for diagnosis and improved outcomes. Solid organ malignancies with a usual late onset are too frequently diffusely metastatic and multisystem in presentation when they occur at a disproportionate early age, worsening the outcome. The patient we report here had a GC diagnosis that was preterminal and hence inconsequential in targeted care because of the absence of local symptoms, baffling bone disease due to metastasis, positive markers of autoimmunity with hemolysis and DIC.

Gastric cancer (GC) is the fourth most common cancer worldwide, and effective care with surgery and neoadjuvant chemotherapy is largely dependent on early diagnosis. This patient had no gastrointestinal symptoms at all. She complained of severe lower back pain for the last four months, which was later discovered to be due to metastasis in the bone. In the last 2 decades, 40% of patients with GC present with metastasis and 12% of all metastasis occurs in the bone.[4]

There are several aspects of the case that make it worthy of mention. First, the low back pain, along with her young age and strongly reactive ANA, misled us in the first place, making us consider connective tissue disorder. It is important to note that significant and clinically consequential ANA reactivity in GC has not been reported so far. The diagnostic booby trap was widened in the context of a finding of elevated levels of LDH along with anemia and thrombocytopenia. This raised the possibility of immune hemolysis, but other features were absent. LDH and tumor markers CEA, CA19-9, and CA-125 were also elevated due to the underlying gastric carcinoma. Poorly differentiated adenocarcinoma and high levels of LDH, CEA, and CA19-9 are shown to be poor prognostic factors of gastric carcinoma.[5]

Second, she suddenly developed a severe headache, which, on a noncontrast CT scan of the brain, revealed diffuse cerebral edema with bilateral chronic subdural hematoma without midline shift. There have been very few reported cases of GC presenting with a bilateral subdural hematoma, and it is indeed a very unusual presentation of GC.[6,7] The coagulation profile revealed raised PT, aPTT, INR, and FDP. All of these proved she developed an acute DIC. GC patients with DIC are rare but carry the risk of severe complications resulting in a dismal prognosis.[8]

Third, widespread bone metastasis was all too evident and worsened the prognosis further. She had markedly elevated alkaline phosphatase (ALP) (1256 U/L). Bone marrow aspiration and trephine biopsy showed infiltrative malignant cells of the epithelial type in the bone marrow along with a reduction of all three hematological cell lines, confirming a case of diffuse metastatic malignancy with unknown primary. The low back pain and tenderness in SI joints were probably due to metastasis to the bones. DIC associated with metastatic malignant bone marrow involvement, like our patient, is a rare complication of gastric carcinoma.[9]

The net 1-year survival rate for stage IV GC is 21.4% (CI: 20–22.9) for females in the UK.[3]

Conclusion

In conclusion, one must remember that neoplastic cells can wreak havoc with our immune system. A clinician must always consider the diagnosis of occult malignancy, particularly intraabdominal visceral malignancies like GC, in patients presenting with a combination of bizarre features like bone pain, cytopenia, false positive ANA, and bleeding manifestations.

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CASE REPORT

A Rare Case of *Pseudomonas putida* Bacteremia in a Patient with Cirrhosis of Liver

Vishal R Shriwastav[1*], Pravin Rathi[2], Khwaja Aminoddin Siddiqui[3]

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Abstract

Pseudomonas putida (*P. putida*) is a rare pathogen that primarily causes nosocomial infection. It is usually seen in immune dysfunction or immunocompromised patients and patients with invasive medical devices. Here, we present a rare case of *P. putida* bacteremia in a patient with cirrhosis of the liver.

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Background

Pseudomonas putida (*P. putida*) is a gram-negative, rod-shaped bacterium. *P. putida* is a rare pathogen that primarily causes nosocomial infection. To date, only a few cases of *P. putida* bacteremia in adult patients have been reported. Case reports describe a range of conditions due to *P. putida* bacteremia, including pneumonia,[1,2] catheter-related bloodstream infections (CRBSI),[1–4] and skin and soft tissue infections.[5]

Cirrhosis is well-known immunocompromised state due to associated immune dysfunction. However, *P. putida* bacteremia in cirrhotic patients has not been reported until now. We present a rare case of *P. putida* septicemia in cirrhosis of the liver patient.

Case Description

A 61-year-old man was diagnosed with alcohol-associated liver disease leading to cirrhosis of the liver in 2017 (Fig. 1). He underwent transjugular intrahepatic portosystemic shunt (TIPSS) in the same year for the management of complications of cirrhosis. Later in the course, he developed generalized weakness and altered sensorium in the form of disorientation to place and person. He was diagnosed with hepatic encephalopathy and treated for the same; subsequently, he improved and was discharged from the hospital. The patient became febrile and also developed one episode of generalized tonic-clonic convulsion. He was evaluated with a magnetic resonance imaging (MRI) scan of the brain, which showed ischemic changes in the left gangliocapsular region. He was treated with levetiracetam and clopidogrel. He was discharged in stable condition. Again, within 1 day of discharge, patient developed a high-grade fever with which he presented to our institution for the first time.

On physical examination, he was febrile and malnourished, while blood pressure, respiratory rate, and oxygen saturation were normal. On laboratory evaluation, leukocytosis, low hemoglobin, and high bilirubin were evident.

Fever profile including dengue antibody, malarial antigen, leptospira antibody, and urine routine microscopy were normal. Computed tomography (CT) scan of the chest showed minimal bilateral pleural effusion without any evidence of pulmonary infection. Ultrasonography (USG) of the abdomen with TIPSS Doppler revealed changes of chronic liver parenchymal disease with normal TIPSS Doppler.

Hemoglobin	8.90 gm/dL (NS1)
White blood cell	11600/mm^3
Platelets	Adequate
Total bilirubin/direct bilirubin	4.4/3.0 mg%
Serum glutamic oxaloacetic transaminase/serum glutamic pyruvic transaminase	43/26 µ/mL
Creatinine	1.10 mg%
Procalcitonin	1.43 ng/mL
C-reactive protein	77.10 mg/L

Simultaneously, BLOOD BACTEC and urine culture were sent before initiating antimicrobial therapy. Empiric antibiotics with cefepime plus tazobactam were initiated; however, patient did not respond to antibiotics, and the fever remains persistent. BLOOD BACTEC result revealed growth of *P. putida*, while urine culture was sterile. The *P. putida* isolate was sensitive to aztreonam, doripenem, meropenem, amikacin, colistin, cefoperazone/sulbactam, ceftazidime, and ciprofloxacin, while it was intermediate sensitive to levofloxacin and resistant to piperacillin/tazobactam, ticarcillin/clavulanic acid, and trimethoprim/sulfamethoxazole. According to the antibiotic sensitivity result, he was initiated on parenteral aztreonam. Subsequently, a CT abdomen was done, which revealed changes of liver cirrhosis with TIPSS *in situ* and bulky left kidney with multiple hypoenhancing areas within, probably suggestive of pyelonephritis. He recovered from fever within 72 hours of starting aztreonam. Antibiotic therapy with aztreonam was continued for 10 days, followed by oral ciprofloxacin for 10 days on discharge.

Discussion

Pseudomonas putida (*P. putida*) is not a very common cause of bacteremia, with only a few cases reported in the literature. Yoshino et al. described a series of five cases of *P. putida* bacteremia; out of five patients, three were cases of CRBSI, one case of indwelling biliary

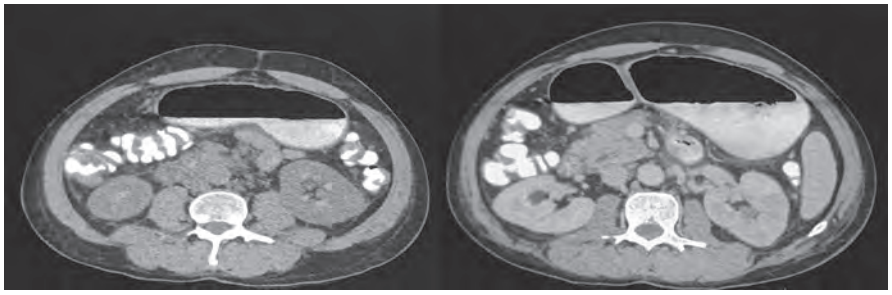

Fig. 1: Computed tomography (CT) of the abdomen

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drainage tube-related cholangitis, and one case of cholecystitis.[3]

The current case of *P. putida* bacteremia is probably due to pyelonephritis. As previously noted, most patients with infections due to *P. putida* had indwelling medical devices or an underlying immune-dysfunction state. Cirrhosis is a state of altered immune response that predisposes to various infections; the most common culprits are gram-negative bacteria. Reduced intestinal motility and increased intestinal permeability lead to increased bacterial translocation, an important contributor to cirrhosis-associated immune dysfunction (CAID).[6] CAID is acquired alteration of both innate and acquired immunity[7] and results in systemic inflammation as well as immunosuppression. CAID, there is an impaired synthesis of acute-phase proteins, deficiencies of the complement system, and decreased number of receptors that are meant to recognize antigens. Negative changes are evident in the field of cell responses, for example, changes in the quantities of monocytes and macrophages generated as well as changes in their capabilities to phagocytose and chemotaxis. Impaired humoral response results in the distorted synthesis of particular antigen categories.[8] Due to their altered cellular and humoral immune response, patients with cirrhosis are more likely to develop spontaneous bacterial infections, hospital-acquired infections, and infections caused by uncommon pathogens. Once an infection develops, it predisposes to the development of complications like shock, acute on chronic liver failure, acute kidney injury, hepatic encephalopathy, etc.[9]

Conclusion

Cirrhosis of the liver leads to immune dysfunction state, predisposing to various typical and atypical infections. A high index of clinical suspicion and appropriate cultures for both typical and atypical organisms need to be considered for timely diagnosis and effective management of infection while maintaining appropriate antibiotic stewardship.

Credit Authorship Contribution Statement

Shriwastav Vishal Ramchandra—data collection and original draft preparation.

Pravin Rathi—editing and critical review of the manuscript.

Khwaja Aminoddin Siddiqui—manuscript review.

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Jaccoud Arthropathy: A Pictorial Perspective

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A 55-year-old woman with a known case of systemic lupus erythematosus (serositis, hematological, and cutaneous involvement) was diagnosed at 37 years of age and presented with complaints of symmetric polyarthritis affecting metacarpophalangeal (MCP) and proximal interphalangeal (PIP) of the hands with a deformity for 5 years. She was on treatment with steroids, antimalarials, and azathioprine. On examination, she had Z-deformity of thumb, ulnar deviation of fingers, MCP subluxation, and swan-neck deformities that were reducible with manipulation (Figs 1 and 2). X-ray helped clinch the diagnosis (Fig. 3). Jaccoud arthropathy is a nonthreatening, long-lasting joint condition characterized by the relaxation and elongation of structures and tendons around the joints in the hands and/or feet. The resulting deformities are painless, can be adjusted through manipulation, and do not hinder normal movement. This arthropathy does not involve ongoing inflammation of the joints. Jaccoud's arthropathy is not frequently observed in Western countries. However, it holds clinical importance because its presence necessitates additional investigation to identify possible underlying causes such as rheumatic diseases, systemic lupus erythematosus around 5% and other conditions such as Sjögren syndrome, scleroderma, dermatomyositis, psoriatic arthritis, vasculitis, ankylosing spondylitis, mixed connective tissue disease, and pyrophosphate deposition disease. Fortunately, this arthropathy has the potential to be corrected or improved.

Learning Points

- This arthropathy does not involve ongoing inflammation of the joints.
- The deformities are painless, "correctable" with manipulation, and do not cause functional impairment, unlike other erosive arthritis.

Fig. 1: Z-deformity of thumb, ulnar deviation, MCP subluxation, and swan-neck deformities are present

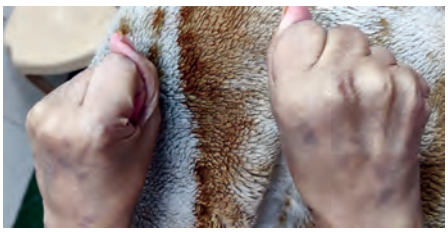

Fig. 2: Showing the reducible nature of these deformities, leaving no or minimal functional impairment

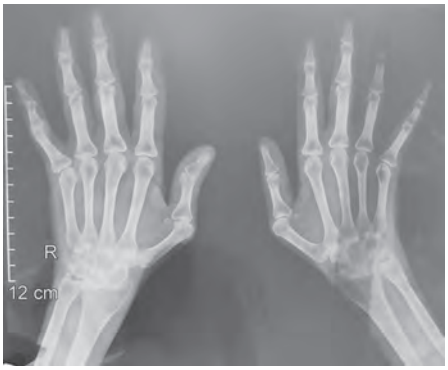

Fig. 3: A radiograph shows the deformities, but there is no erosion, which would be expected in a patient with rheumatoid arthritis with similar hand deformities

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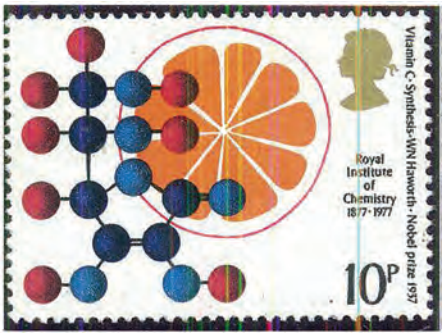
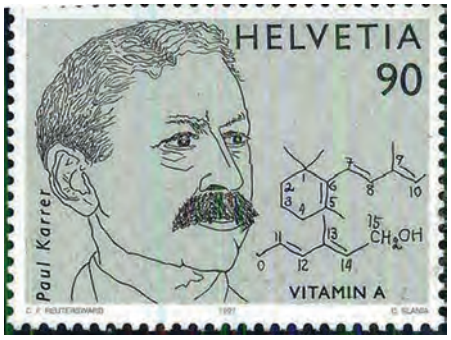
Synthesizing Vitamins: Karrer and Howard

J V Pai-Dhungat



Royal Institute of Chemistry honors Howard for the discovery of ascorbic acid and orange Stamp-GB, 19**



Paul Karrer and structure of vitamin A; Stamp Switzerland, 1997

Microcrystals of ascorbic acid; Germany, 2012

The Nobel Prize in Chemistry 1937 was divided equally between Walter Norman Haworth "for his investigations on carbohydrates and vitamin C" and Paul Karrer "for his investigations on carotenoids, flavins, and vitamins A and B_2."

Paul Karrer (1889–1971) was born in Moscow to Swiss parents and was brought to Switzerland at the age of 3 in 1892. He attended the University of Zurich, working as an assistant to Alfred Werner. After obtaining his PhD in 1911, he returned to Zurich as a Professor of Chemistry and was promoted to Director of the Chemical Institute Zurich in 1919.

Karrer's most important work was concerned with plant pigments, particularly the yellow carotenoids, which are related to the pigment in carrots. He not only elucidated the chemical structure of the carotenoids but also showed that some of these substances are transformed into vitamin A. His work in this field led to the establishment of the correct formula for β-carotene, the chief precursor of vitamin A, in 1930. This was the first time that the structure of a vitamin or provitamin had been established. Later, he extended his research to other vitamins and synthesized vitamin B_2 (riboflavin) in 1935 and vitamin E (tocopherol) in 1938. His important contributions to the chemistry of the flavins led to the identification of lactoflavin as part of the complex originally thought to be vitamin B_2.

Paul Karrer died in 1971, at the age of 82, in Zürich.

Walter Norman Hayworth (1883–1950), a British chemist, was educated at the University of Manchester and did graduate work at the University of Gottingen. He studied under Wallach and obtained his doctorate in 1910. Much of his research was done on sugars. He devised a ring form to represent the sugar molecule, which became its accurate form and became more useful in describing chemical reactions. Howard worked on vitamin C, which is related in structure to simple sugars and was one of the first to synthesize it in 1934. He suggested the name "ascorbic acid" for the vitamin, which is now universally accepted.

Hayworth was knighted in 1947. He died in 1950 at the age of 67.

Professor of Medicine (Retired), Department of Medicine, Topiwala National Medical College and Bai Yamunabai Laxman Nair Charitable Hospital; Honorable Physician, Bhatia Hospital, Mumbai, Maharashtra, India

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Tissue Biopsy to the Rescue: The Art of Modern Medicine

Rahul Kumar[1], Pooja Khosla[2], Vinus Taneja[3], Manuj Sondhi[4]

[1]DNB Trainee; [2]Senior Consultant; [3]Associate Consultant; [4]Clinical Assistant, Department of Internal Medicine, Sir Ganga Ram Hospital, Delhi, India

Sir,

The importance of tissue biopsy in making a diagnosis is well established. As practicing clinicians, every now and then, we stand at a crossroads where we need microbiological/histopathological evidence to guide us further. Even though clinical judgment takes precedence, tissue diagnosis is equally important in today's era. We are writing this to emphasize the same in a clinical scenario that we recently encountered. A 54-year-old male with a known case of type II diabetes presented with low-grade fever and pain in the right thigh for 2 months, which aggravated on walking. The patient gave a history of fracture of the right proximal femur 20 years back in a road traffic accident, which was treated with an Illizarov fixator. On examination, the patient was conscious, oriented, and hemodynamically stable. Systemic examination was normal. On local examination of the right thigh, there were no signs of inflammation. An X-ray of the right femur was done, and it revealed a healed fracture. In view of persistent pain at the fracture site, magnetic resonance imaging (MRI) of the right proximal thigh was done, which showed osteomyelitis of metaphyses of the right femur with sinus formation and extension into adjacent muscles (Fig. 1). Initial blood work was normal. Inflammatory markers were raised. A diagnosis of osteomyelitis of the right femur was made. A strong suspicion of tubercular osteomyelitis was made considering the long duration of illness with low-grade fever, no acute signs of inflammation, and normal blood parameters. Debridement and curettage were done, and samples were sent for microbiological and histopathological examination. Both pus and tissue cultures revealed *Citrobacter brakii*. Tissue and pus Mycobacterium GeneXpert and Ziehl–Neelsen staining for acid-fast bacilli were negative. Biopsy revealed pyogenic osteomyelitis. The patient was treated with 6 weeks of IV carbapenems and is currently doing well on regular follow-up.

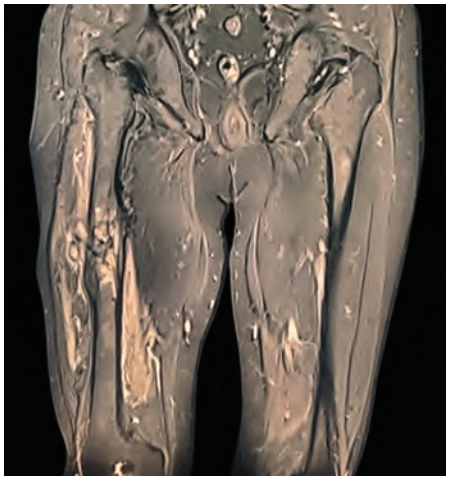

Fig. 1: Magnetic resonance imaging (MRI) thigh showing osteomyelitis of metaphyses of the right femur with sinus formation and extension into adjacent muscles

India is an endemic country for tuberculosis.[1] A patient presenting with this history and baseline investigations would have been started on empirical antitubercular therapy had the tissue biopsy not been done. However, this one correct step helped save the patient from months of empirical therapy and pointed us in the right direction of treatment. This case classically describes how modern medicine has revolutionized the diagnostic skills of a clinician. Even in resource-limited countries, an attempt should be made to obtain tissue diagnosis to improve the overall management and outcomes of patients. Tissue biopsy, being an invasive procedure, can have complications, adversely affecting the outcome of the case, particularly in malignant tumors.[2] Therefore, it should be done with proper planning in conjunction with a multidisciplinary team and appropriate prebiopsy imaging.[3]

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Supraventricular Tachycardia: An Uncommon Cause of Chronic Cough

Ambika Sharma[1], Kanhaiya Lal Meena[2], Raghuveer Singh[3]

[1]Assistant Professor; [2,3]Junior Resident, IRD Hospital, SMS Medical College, Jaipur, Rajasthan, India Supraventricular Tachycardia: An Uncommon Cause of Chronic Cough

Sir,

We report a case of cardiac arrhythmia-induced chronic cough that was managed by radiofrequency ablation (RFA) of a slow pathway.

A 16-year-old girl complained of having a dry cough for 5 years, which was off and on initially but later was persistent for 7 months. The cough was short but multiple times in a minute. Her daily, repeated, and frequent coughs were highly upsetting to her and were interfering with her schoolwork. She reported that after slight exertion, her breath would get short. Her appetite had decreased over the past 5 months, and she lost 5 kg of weight. She occasionally complains of palpitations as well.

She didn't experience any bowel or bladder issues, fever, frequent colds, syncopal episodes, or chest pain. She also says she has never had gastric reflux disease or acid peptic disease. No complaints of throat and ear problems. She made no mention of any serious previous illnesses. She was initially treated by an ear, nose, and throat specialist for the aforementioned complaints, and antihistamines inhaled nasal corticosteroid spray, and proton pump inhibitors were started. Computed tomography (CT) of the paranasal sinus and fiberoptic laryngoscopy were done, and the results were normal. With these medications, the patient did not feel any better. She later visited a pulmonologist, where she underwent a spirometry and chest X-ray investigation. The chest X-ray was normal, but spirometry results were unacceptable due to coughing. The patient was started on the line of bronchial asthma and on inhalers (inhaled corticosteroids and inhaled long-acting β-agonists) and antitussive cough syrups. Even after taking her medication continuously for 5 months, her coughing problem did not get better.

With all the above history, patients presented to us in our patient department. Upon physical examination, the patient displayed a pulse rate of 160/minute (regular, normovolemic) with a pulse oximeter saturation of 100%, a respiratory rate of 16/minute, and a blood pressure of 104/68 mm Hg. She was afebrile and comfortable during an examination except for intermittent but frequent short coughs. A head-to-toe and respiratory system examination revealed no remarkable findings. Bilateral vesicular breath sounds were detected during chest auscultation without any added sounds. The cardiovascular examination was unremarkable, except for the presence of tachycardia. After 15 minutes of rest, the patient was reevaluated and showed a heart rate of 110/minute. However, due to slight mobility and continued coughing, the pulse rate increased to 160/minute. Supraventricular tachycardia (SVT) was thought to be the primary cause of her chronic cough.

Further investigations were conducted, including an electrocardiogram (ECG) that showed sinus tachycardia (Fig. 1) and a normal two-dimensional echocardiogram (ECHO). Routine blood tests, such as complete blood counts, liver and kidney function tests, and thyroid profiles, were all normal. Additionally, chest X-rays and CT chest with virtual bronchoscopy showed no abnormalities. A cardiologist was consulted, and an electrophysiology study was conducted. The basal ECG was normal, except for sinus tachycardia, with a rate of 140/minute. No manifest preexcitation was found. During V pacing, VA conduction was concentric and decremental until 350. Although no sustained tachycardia was induced, slow pathway modification was performed due to the presence of ECHO, AH jump, recurrent palpitation, and cough. Successful RFA of the slow pathway region was performed at the M2–M1 junction. After a 30-minute wait and vigorous stimulation protocol, no tachycardia was induced. Following the procedure, the patient's condition improved significantly, and her heart rate remained stable at 75 beats/minute (Fig. 2). The cough completely disappeared. At the 3- and 6-month follow-ups, no complaints recurred, and the patient remained asymptomatic.

Supraventricular tachycardia (SVT) is an arrhythmia that arises above the bundle of His and results in heart rates of >150 beats/minute. It has an electrophysiologic basis of reentry or automaticity. Palpitations, pulsations in the neck, discomfort in the chest, dyspnea, hyperventilation, lightheadedness, and anxiety are common SVT symptoms. Cough, chest pain, diaphoresis, nausea, presyncope, and syncope are uncommon symptoms that SVT patients may experience.[1]

Some cases of ventricular arrhythmia and supraventricular arrhythmia have been documented in the literature when they occur with the symptom of coughing, which may first be mistaken for a respiratory tract condition. The authors hypothesized two potential reasons for the arrhythmia that caused cough in these patients: increased pulmonary artery blood flow generating ventricular arrhythmia and anatomically close contact between phrenic nerve and atrium causing the supraventricular arrhythmia.[2–4]

After ruling out other potential causes, the chronic cough was completely alleviated by RFA. This case also emphasizes the importance of careful physical examination in diagnosing the disease on time. A similar case in the past was reported where a man was diagnosed with cardiac arrhythmia after 15 years of cough symptoms.[5]

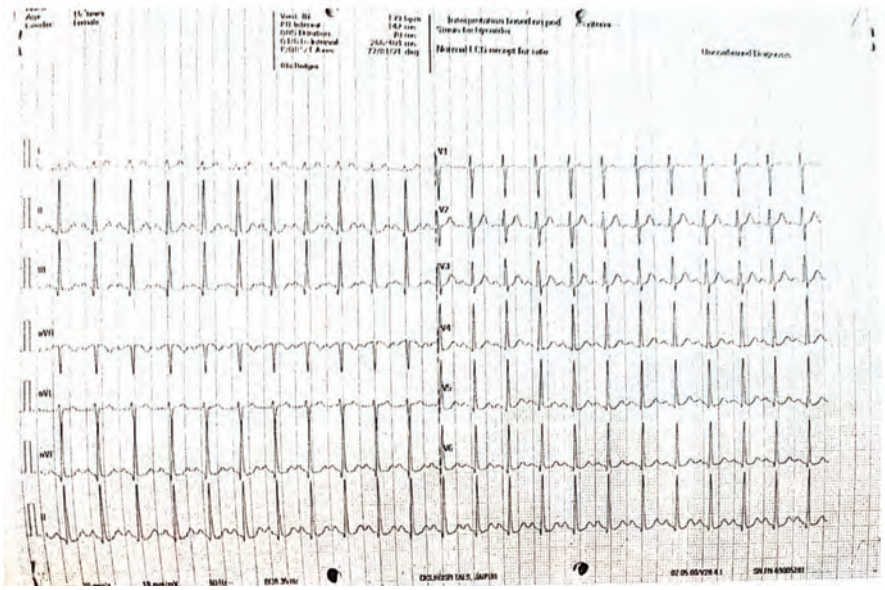

Fig. 1: Electrocardiogram (ECG) showing sinus tachycardia with a heart rate of 150/minute

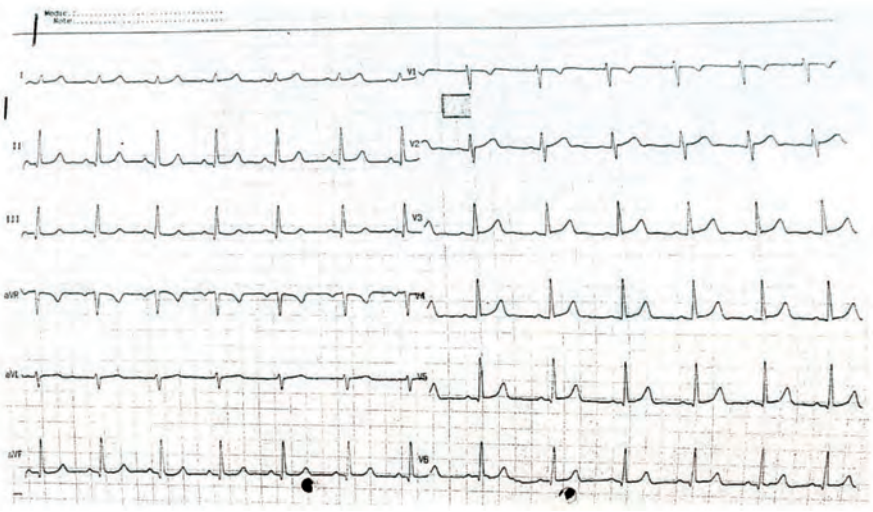

Fig. 2: Postradiofrequency ablation (RFA) ECG showing improvement in heart rate (75/minute)

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Letter to Editor in Response to Article "Diagnostic Approach to Extrapulmonary Tuberculosis by Cartridge-based Nucleic Acid Amplification Test" Published in J Assoc Physicians India 2023; 71(6):34–37

Madhu Sudan Barthwal[1], Sachin Dole[2], Aman Barthwal[3]

[1]Professor and HOD; [2]Professor, Department of Respiratory Medicine; [3]Senior Resident, Department of Anesthesiology, Dr DY Patil Medical College, Hospital & Research Centre, Dr DY Patil Vidyapeeth (Deemed to be University), Pune, Maharashtra, IndiaLetter to Editor in Response to Article

We read with interest an article titled "Diagnostic Approach to

Extrapulmonary Tuberculosis by Cartridge-based Nucleic Acid Amplification Test" published in Journal of the Association of Physicians of India.[1] We have the following comments to offer:

- Authors have compared cartridge-based nucleic acid amplification test (CBNAAT) results with Ziehl–Neelsen smear, fluorescence microscopy smear, and culture on Löwenstein–Jensen media to find out the sensitivity and specificity of CBNNAT. Ideally, CBNAAT should be compared with culture as a gold standard, but extrapulmonary tuberculosis (EPTB), being a paucibacillary disease, has a low yield on culture. To overcome this issue, authors should have compared the diagnostic yield of CBNAAT with the composite reference standard, which is defined by clinical, radiological, laboratory, and histopathological findings and treatment response to antituberculosis therapy at the end of 6 months.[2,3]
- The present study seems to convey that CBNAAT alone can lead to the diagnosis of EPTB and has not at all emphasised the role of other modalities of investigation which need to be considered for the diagnosis of EPTB. Diagnosis of EPTB requires a composite approach comprising of clinical and radiological examination, smear examination, cytology, histopathology, acid-fast bacillus (AFB) culture and CBNAAT of tissue aspirate and biopsy. Since the sensitivity and specificity of CBNAAT against culture varies significantly for lymph nodes, cerebrospinal fluid, and pleural fluid, relying solely on CBNNAT can lead to false positive and false negative results.[4] As per the guidelines for EPTB in India,[4] CBNAAT should be used as an additional test to conventional smear microscopy, culture and cytology in fine needle aspiration cytology specimens.
- Authors have mentioned that CBNAAT was introduced for rapid diagnosis of pulmonary tuberculosis and as a replacement for sputum microscopy. Undoubtedly, CBNAAT has revolutionized the rapid diagnosis of tuberculosis, but in no way has this test replaced sputum microscopy. Sputum microscopy remains an essential part of not only the initial diagnosis but also for monitoring response to treatment and for determining cure.[5]
- Authors have mentioned that CBNAAT also detects nontuberculous *Mycobacterium* (NTM). This is not correct since CBNAAT can detect only *Mycobacterium tuberculosis*. In fact, CBNAAT has excellent positive predictive value in the setting of AFB smear-positive but CBNAAT-negative specimens for distinguishing tuberculous from nontuberculous mycobacteria (>95%).[6]
- In the discussion, it has been mentioned that the usage of CBNAAT in the diagnosis of EPTB has been low because of a lack of awareness, and have supported this by quoting references from before 2013. This statement does not seem to be true since World Health Organization introduced CBNAAT for the diagnosis of EPTB in 2013, and since then, it has been widely used in the National Tuberculosis Elimination Program and by private doctors.

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API Announcement

Elections of API, ICP and PRF

(Full details circular No. 1 & 2/2024)

Election for Governing Body of API, Faculty Council of ICP and Board of PRF are announced for following posts:

Governing Body of API:
President-Elect: One; Vice President: One; Hon. General Secretary: One; Elected Members: Six

Faculty Council of ICP:
Dean-Elect: One; Vice Dean: One; Jt. Secretary HQ: One; and Elected Members: 4 posts

Board of PRF:
Board members: Two
Separate nominations must be submitted for each post.

Requirements for eligibility contest of election to the Governing Body of API

1. **President Elect:** To contest for the post of President Elect the candidate should be a life member of API for at least 10 years and have completed at least two full terms of 3 years each in any elected position in the Governing Body.
2. **Vice President and Hon. General Secretary:** To contest for the post of Vice President and Hon. General Secretary, the candidate should be a life member of API for at least 5 years and should have completed at least one continuous full term of 3 years in any elected position in the Governing Body.
3. **Governing Body Member:** To contest for the post of Member of the Governing Body, continuous membership of the Association of at least 3 years is mandatory.

Requirements for eligibility contest of election to Board of PRF

Board Member: A Member of API for at least 10 years with research experience and having 5 research publications in peer reviewed indexed journals.
The members contesting for the PRF election must attach copies of the Research Papers as mentioned above is mandatory.

Nominations shall be made on prescribed forms stating the office for which nominations are filled. The nominations for API/PRF posts shall be proposed by one valid member and seconded by another valid member of API and duly signed by them and shall also be signed by the candidate signifying his/her willingness to stand for election and serve on the Governing Body if elected.

Requirements for eligibility for the contests of election to ICP

***Dean Elect*:**
i. A member of API for at least 15 years and
ii. A Founder Fellow or a Fellow of the College of 7 year standing and
iii. Any person who has held the position of President/Secretary of API or served as Vice Dean for one full term or elected member of the Faculty Council for one term.

***Vice – Dean*:**
i. A member of API for at least 12 years and
ii. A Founder Fellow or a Fellow of the College of 5 year standing and
iii. Any person who has held the position of Secretary of API or has been a Jt Secretary from HQ for one full term or a member of the Faculty Council.

Elected Members: A member of API for at least 10 years and a Founder Fellow or a Fellow of the college of 3 years standing.
Nominations shall be made on prescribed forms stating the office for which nominations are filled. The nominations for ICP posts shall be proposed by one valid Founder Fellow/Fellow and seconded by another valid Founder Fellow/Fellow of ICP and duly signed by them and shall also be signed by the candidate signifying his/her willingness to stand for election and serve on the Faculty Council of ICP if elected.

A member shall not contest simultaneously for more than one post (i.e., President-Elect, Vice-President, Hon. General Secretary; Member of the Governing Body) (Dean-Elect; Vice Dean; Joint Secretary HQ and Elected Members of Faculty Council) and also (Board members of PRF) Post means not only an office-bearer but also member of the Governing Body of API or Faculty Council of ICP or Board of PRF.
Every member is supplied with a nomination form. The nomination form completed in all respects should reach the API Office not later than 31st May 2024. For every post on the Governing Body/Faculty Council/Board of PRF, the nomination must be accompanied by a sum of Rs. 7500/- + 1350/- (GST) (Rupees eight thousand eight hundred fifty only) nonrefundable in the form of Demand Draft payable at Mumbai. The nomination paper NOT accompanied by the Bank Draft of Rs. 8850/- will be deemed invalid.

Important
Canvassing in any form should not be done by the candidate for the election. Instead, they are requested to send a short bio-data NOT MORE THAN 200 words along with the nomination paper which will be printed and circulated along with the ballot paper. Excess of bio-data beyond the first two hundred words shall be deleted. Canvassing in any form or in favor of the candidate shall not be permitted.
THE CANDIDATE WILL HAVE TO CERTIFY AND SIGN THAT THE INFORMATION PROVIDED IN HIS/HER BIODATA IS CORRECT.
The results will be declared at the end of counting of votes and announced in the subsequent issue of JAPI. The report will be placed before the Governing Body for intimation.

DEAD LINES OF ELECTION PROCEDURE

Last date to receive the nomination at API Office	31st May 2024
Last date for withdrawal	20th June 2024
Last date to receive ballot papers at API Office	31st August 2024

Dr. Agam Vora
Hon. General Secretary

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