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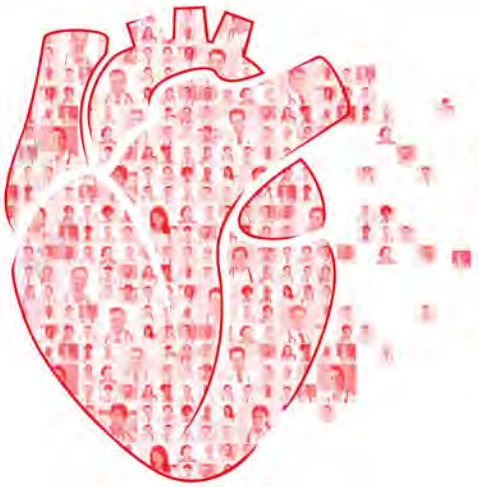

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Telmisartan Tablets

Round the clock, Action 'n' Protection

Composition: **Telvas 40** Each tablet contains : Telmisartan IP 40 mg,Telvas- 80 Each tablet contains : Telmisartan IP 80 mg, Telvas20 Each tablet contains : Telmisartan IP 20 mg **Indication:** Hypertension - Treatment of essential hypertension in adults. Cardiovascular prevention - Reduction of cardiovascular morbidity in adults with: manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or type 2 diabetes mellitus with documented target organ damage. **Dosage and Administration:** Essential hypertension : The effective dose is 40 mg once daily. Some patients may already benefit at a daily dose of 20 mg. In cases where the target blood pressure is not achieved, the dose of telmisartan can be increased to a maximum of 80 mg once daily. Cardiovascular protection : The recommended dose is 80 mg once daily. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Second and third trimesters of pregnancy. Biliary obstructive disorders. Severe hepatic impairment. The concomitant use of Telmisartan with aliskiren containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 mL/min/1.73 m2). **Warnings And Precautions - 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** 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. Periodic determinations of serum electrolytes to detect possible electrolyte imbalances should be considered 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. Telmisartan should be initiated at low doses and titrated slowly in these patients. Impaired Renal Function as a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function should be anticipated 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 an effect similar to that seen with ACE inhibitors should be anticipated. **Dual Blockade of the Renin-Angiotensin-Aldosterone System**: 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, combined use of drugs from different classes of RAS inhibitors should be avoided. Blood pressure, renal function and electrolytes in patients on Telmisartan and other agents that affect the RAS should be closely monitored. Aliskiren must not be co-administered with Telmisartan in patients with diabetes. Concomitant use of aliskiren with Telmisartan in patients with renal impairment (GFR <60 mL/min/1.73 m²) must be avoided. **Nonclinical Toxicology:** Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no evidence of carcinogenicity when Telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m² basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of Telmisartan. These same doses have been shown to provide average systemic exposures to Telmisartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day). Genotoxicity assays did not reveal any Telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with Salmonella and E. coli (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test. No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m² basis, the MRHD of Telmisartan. This dose in the rat resulted in an average systemic exposure (Telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day). **Use In Specific Populations: Nursing Mothers:** It is not known whether Telmisartan is excreted in human milk, but Telmisartan was shown to be present in the milk of lactating rats. **Pediatric Use:** Safety and effectiveness of Telmisartan in pediatrics has not been established. Thus, the drug is not recommended in pediatrics. **Geriatric Use:** No dose adjustment is needed in elderly patients

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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. 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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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Images are for illustration purpose only.

Abbreviations: ARB, angiotensin II receptor blocker, ACE, angiotensin-converting enzyme, BP, blood pressure, MACE, major adverse cardiovascular events

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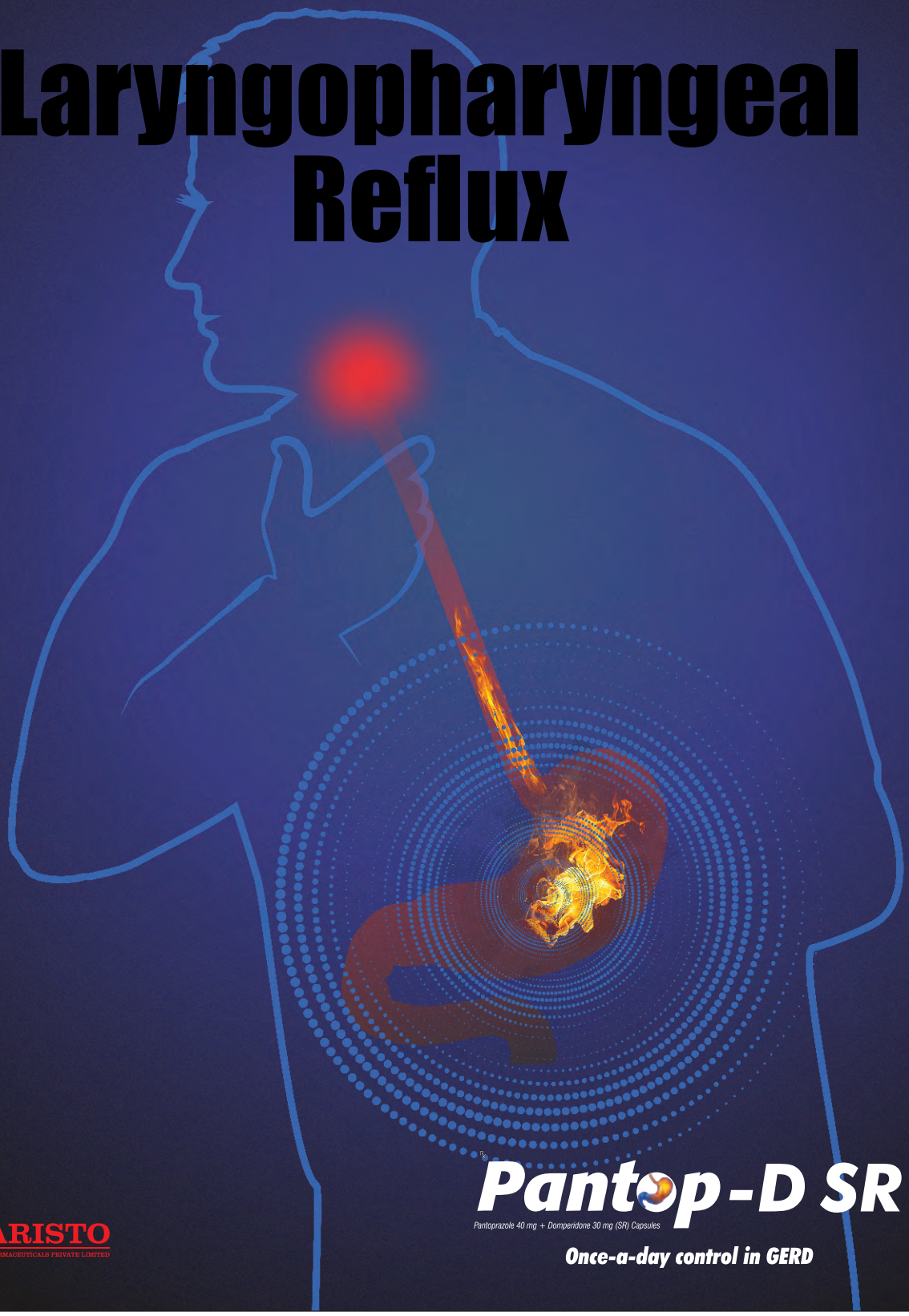

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EDITORIAL

Empowering Physicians for Holistic Wellness in Diabetes Management through Mind–Body Medicine: Implications of the Psycho-Neuro-Immuno-Endocrine/Enteric Concept in Diabetes

Vaishali Chetan Deshmukh[1*], Manoj Chadha[2]

The psycho-neuro-immuno-endocrine/enteric (PNIE) axis is a fundamental concept in neuroscience, integral to the neuroendocrine system (NES). It encompasses the interactions between behavior, neurology, endocrinology, gut biology, and the immune system. These interactions regulate crucial metabolic processes like glucose, lipid, and protein metabolism, blood pressure, and various homeostatic functions, including blood pressure regulation, thermogenesis and pulmonary hypoxia detection.

Diabetes as a Dysfunction of the Psycho-neuro-immuno-endocrine/enteric Axis

While the physical damage diabetes causes to the body is well-known,[1] the impact on the mind, which is an abstract function of the brain, is also significant. It is a well-established fact that mental health issues often underlie physical ailments. The mind influences behavior, which in turn affects hormone levels, impacting immunity, brain function, cardiovascular health, and overall physiological well-being.[2]

Chronic conditions often trigger a maladaptive stress response, activating the hypothalamus–pituitary–adrenal (HPA) axis and leading to diseases like metabolic syndrome, type II diabetes, atherosclerosis, hypertension, dementia, and depression.[3] This vicious cycle of the mind affecting the PNIE axis, and the PNIE axis influencing metabolism and homeostasis, initiates a process called allostasis, which precedes many noncommunicable diseases (NCDs).

The dysfunction of the PNIE axis in diabetes is evident from the fact that one in five adults with type II diabetes experiences depression,[4] and one in three experiences diabetes distress.[5] Autonomic dysfunction, manifesting as symptoms like palpitations, breathlessness, dry mouth, and fatigue, is common in diabetes. This neurological and immunological dysfunction forms the basis of hormonal and autonomic imbalances, which are central to diabetes, stress, and other excessive fat-related metabolic disorders (EFRMDs).

These imbalances also affect mental health by inducing chronic inflammation, marked by elevated levels of C-reactive protein and cytokines like TNF-a, IL-1b, and IL-6.[6] Chronic inflammation is a known risk factor for atherosclerosis and coronary artery disease (CAD).[7] and it may increase the risk of coronary heart disease (CHD) associated with depression.[8] Diabetes, a major metabolic stress disorder, is strongly linked to stress, high cortisol levels, and a heightened risk of ischemic heart disease and cardiovascular death. Additionally, endothelial dysfunction, sympathetic activation, and increased platelet activity further elevate the risk of cardiovascular disease (CVD).[9] In addition, a common genetic vulnerability has been discovered through twin studies, which suggests that a common, genetically influenced biological pathway contributes to the risk of depression and heart disease, which is inturn linked with autonomic dysfunction, pain, and the serotonergic system (Fig. 1).[10]

Interactions Between Brain, Behavior, Hormones, and Metabolism

The nervous system maturation modulates the nonendocrine behavioral effects of hormones. The neural mechanism that supports these actions over time is called brain plasticity (neuroplasticity). Hormones act as epigenetic factors and influence behavior through the plasticity processes which are a result of two main effects: organizing tissue effects affecting cellular architecture and its activating effect later in life.

Mind–Body Medicine in Diabetes

Mind–body medicine (MBM) is an evidence-based, self-care intervention that is affordable, easy to practice at home, and empowering. It combines traditional knowledge—such as yoga, meditation, and spirituality—with modern psychology and medicine to promote whole-body health, from prevention, treatment to recovery. MBM practices induce a positive psychological state, which has been shown to regulate the PNIE axis, improve neuroplasticity, enhance outcomes and quality of life, and reduce diabetes complications.

In addition to psychological benefits, MBM offers physical benefits such as increased flexibility and improved blood and oxygen supply. Positive mental health and MBM practices provide deep relaxation and well-being, suppress the emotional brain, activate the logical brain, and help the body and mind heal from trauma and pain while building resilience. These practices effectively "turn off" the sympathetic nervous system (SNS) and stress response while "turning on" the parasympathetic nervous system, allowing the body to rest.

Evidence Supporting Mind–Body Medicine in Diabetes

The efficacy of MBM in diabetes has been demonstrated in small patient populations through behavioral health group visits that utilize the biopsychosocial model to successfully modulate glycemic targets.[12]

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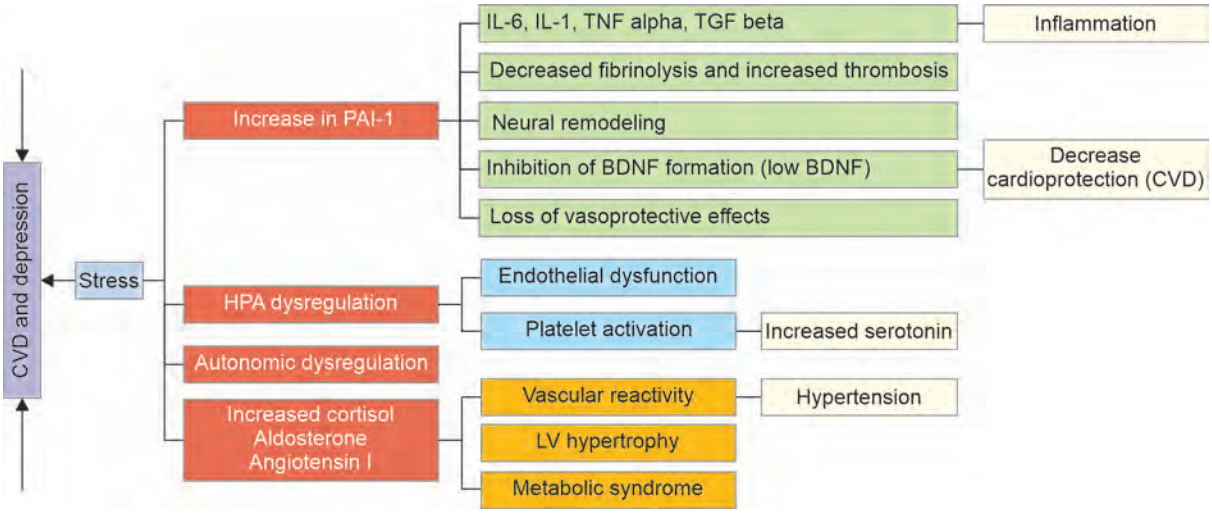

Fig. 1: Complex psycho-neuro-immune-endocrine interactions that influence the biobehavioral basis of CVD, depression, dysautonomia, inflammation, endothelial dysfunction, and thrombosis in diabetes which functions as a metabolic stressor. BDNF, brain-derived neurotrophic factor; CHD, coronary heart disease; HPA, hypothalamic-pituitary-adrenal axis; IL, interleukin; PAI, plasminogen activator inhibitor; TGF, transforming growth factor; TNF, tumor necrosis factor (adapted from Vaccarino et al.[11])

These interventions have been effective in alleviating "diabetes distress" among patients.

A randomized controlled trial among Asians showed superior glycemic control in patients who practiced a specific form of mind–body exercise, such as Tai chi.[13] Another similar trial showed significant improvements in C-peptide levels among the Tai chi group compared to other interventional and control groups.[14] These findings suggest that MBM practices are beneficial for patients with type II diabetes.

A network meta-analysis of randomized trials further supports the positive effects of various mind–body exercises on glycemic and lipid metabolism, showing sustained improvements in triglycerides and glycated hemoglobin levels.[15] A systematic review and meta analysis by Vinod Kumar et al. has shown evidence to conclude that Yoga can be considered as adjunct to medication in treatment of diabetes.[16]

Conclusion

This editorial highlights the critical importance of assessing and regulating the PNIE axis in chronic diseases, including diabetes. There is an urgent need to raise awareness among doctors, patients, and their families about the significance of mental health and MBM in improving outcomes and well-being for all people with diabetes irrespective of complications or psychological ailments. MBM techniques are flexible and adaptable, making them accessible to individuals of all ages and in various environments.

Even a slow, regular practice of 5–10 minutes daily can significantly enhance the mind–body connection, improve glycemic control, reduce oxidative stress, and enhance overall health. High-quality studies and randomized controlled trials are needed to further explore the clinical benefits of various MBM practices in diabetes.

Psycho-neuro-immuno-endocrine/enteric concept-based MBM forms an important component of integrated and holistic health in NCDs and is now included as a part of the curriculum at all medical colleges in India. Our team dedicates 4 days annually to the "mind–body medicine"—SYNAPSE workshop, which has been successfully implemented for the past 5 years, to train doctors and patients to improve their mental health and, consequently, their health outcomes. This editorial emphasizes the necessity of addressing the mental health of diabetes patients and their caregivers in the current era.

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ORIGINAL ARTICLE

An Epidemiological Study on Magnitude of Selected Components of Metabolic Syndrome and Its Risk Factors among First-year MBBS Students

Arkaprava Dasgupta[1*], Kakali Das Sarkar[2], Adwitiya Das[3]

Received: 21 June 2023; *Revised:* 05 September 2023; *Accepted:* 05 September 2023

Abstract

Background: Previous research has suggested that the prevalence of risk factors for cardiometabolic diseases is higher in South Asians, with premature presentation common in this subpopulation.

Aim: To explore this further, we assessed the prevalence of metabolic syndrome (MetS) components and risk factors among young adults.

Methods: This was a cross-sectional, epidemiological, institution-based study conducted at the Medical College in Eastern India. The study aimed to assess the demographic, physical, and biochemical risk factors for MetS among first-year medical students using a predesigned, pretested, semistructured questionnaire. The relationship between socio-demographics and other characteristics of MetS was calculated by using Chi-squared tests and unpaired *t*-tests. A *p*-value ≤ 0.05 was significant with a 95% confidence interval (CI). The logistic regression method was applied to find out the strength of the association of sociodemographics and other characteristics with MetS.

Results: The study included 150 first-year medical undergraduate students (mean age of 18.5 ± 0.4 years), comprising 68% males. Among students who were smokers, consumed alcohol, and had excessive junk food, salt, and red meat, the risk of MetS was significantly greater ($p < 0.00001$). The logistic regression revealed that history of smoking [adjusted odds ratio (AOR) 5.32, 95% CI (3.31–9.02)] and history of alcohol intake [AOR 6.23, 95% CI (2.45–8.62)] were significantly associated with greater odds of MetS.

Conclusion: In young adults, the risk of premature cardiovascular disease can be reduced by focusing on the early identification and prevention of risk factors for MetS. Context-specific, cost-effective, and feasible interventions to reduce identified risk factors are the need of the hour.

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Introduction

Metabolic syndrome (MetS) contributes considerably to cardiovascular disease (CVD) risk.[1] Studies have suggested a significant influence of age on MetS and CVD association.[2] South Asians have been reported to have greater rates of cardiometabolic abnormalities compared with other ethnicities and are categorized as an insulin-resistant phenotype.[3] It is strongly associated with MetS, with premature presentation being common in this subpopulation.[4,5]

To explore this further, we assessed the prevalence of MetS components and its predisposing factors among young adults.

Methods

Study Design

The current study was a cross-sectional, epidemiological, institution-based study conducted at the Physiology Department of a medical college in Eastern India. The study aimed to assess the demographic, physical, and biochemical risk factors for MetS among first-year undergraduate medical students using a predesigned, pretested, semistructured questionnaire adopted from the World Health Organization (WHO) STEPwise approach to noncommunicable disease (NCD) risk factor surveillance (STEPS).

The study included all undergraduate medical students enrolled in the first year at the medical college who provided written consent for participation. Students who could not be approached for data collection or biological sample collection on three consecutive attempts were excluded from the study.

Sample Size

The prevalence was taken as 22% based on published literature. The sample size was calculated using this formula as follows:

$$N = \frac{z_\alpha{}^2 * p * q}{d^2}$$

Where, N = sample size, p = prior prevalence = 0.22144 – 146, $q = 1 - p = 0.78$, $z = 1.96$ (considering 95% confidence level), d = relative error—10%,

$$N = \frac{1.96 * 1.96 * 0.22 * 0.78}{(10\% \text{ of } 22)^2}$$

$$= 136$$

Considering the possible nonresponse rate was 10% of the sample size, the total sample size was 136 + 13.6 = 149.6 ≈ 150.

Sampling Design

Among the 250 first-year MBBS students, 150 students were selected using a simple random sampling technique with the help of a computer-generated random number table.

Primary and Secondary Objectives

The sociodemographic data obtained included age, type of family, and family history of NCD (obesity, hypertension, diabetes). The risk factors assessed for MetS included diet, addiction, physical activities, blood pressure [diastolic pressure and systolic blood pressure (DBP/SBP)], pulse rate, anthropometric variables [body mass index (BMI)], plasma glucose profile [fasting plasma glucose (FPG)], and lipid profile [high-density lipoprotein cholesterol (HDL-C), triglycerides (TG)].

Ethics Committee

The study was approved by the Institutional Ethics Committee.

Statistical Analysis

Data were entered in a Microsoft (MS) Excel spreadsheet. The calculation was done using Statistical Package for the Social Sciences (SPSS) 20.0 and MS Excel. Descriptive statistics were expressed as mean ± standard deviation (SD) and proportion (%). The association between sociodemographics and other

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characteristics of MetS was calculated using Chi-squared tests and unpaired *t*-tests. A *p*-value ≤ 0.05 was considered significant with a 95% confidence interval (CI). The logistic regression method was applied to determine the strength of the association of sociodemographics and other characteristics with MetS.

Sociodemographic and other variables were categorized as categorical variables, with one category serving as the reference.

Results

The study included 150 students from the first-year MBBS program, with a mean age of 18.5 ± 0.4 years and 68% males. The demographic details are depicted in Table 1.

Approximately, 37.3% of participants were overweight, and almost a similar proportion, 38.7%, were centrally obese (Tables 2 and 3).

Table 1: Demographic variables, clinical and biochemical parameters

Variable	*Overall n (%)*
Male	102 (68%)
Female	48 (32%)
Nuclear family	118 (78.6%
Joint family	32 (21.4%)
Socioeconomic status	
I (upper)	35 (23.3%)
II (upper-middle)	91 (60.7%)
III (middle)	14 (9.3%)
IV (lower-middle)	6 (4.0%)
V (lower)	4 (2.7%)

Table 2: Demographic, clinical, and biochemical characteristics of study subjects

Variable	*Overall (mean ± SD)*
Anthropometric parameters	
Height (cm)	165.4 ± 9.6
Weight (kg)	64.7 ± 12.2
BMI (kg/m^2)	23 ± 3.8
Clinical Assessment	
SBP (mm Hg)	122 ± 11
DBP (mm Hg)	77 ± 7
Pulse rate (minute)	77 ± 8
Laboratory investigations	
Fasting plasma glucose (mg/dL)	93 ± 10
TG (mg/dL)	106 ± 26
HDL (mg/dL)	45 ± 4

BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides

Blood pressure (BP) was elevated in 14.6% of participants. The fasting plasma glucose (FPG) and triglycerides (TGs) were elevated in 19.3% and 17.3% of participants, while high-density lipoprotein (HDL) was low in 22%. Almost an equal proportion of participants were smokers (33%) and consumed alcohol (31.3%). Among smokers, >50% reported taking more than 10 cigarettes per day. The dietary habits regarding fruit, vegetable, and red meat consumption were unsatisfactory in 61–80% of participants. Of the 150 participants, 57.3, 53.3, and 36% had a family history of MetS components: obesity, hypertension, and diabetes. Nearly 90% of participants did not exercise regularly.

Association between Demographic Variables and Metabolic Syndrome

In the present study, the overall prevalence of MetS was 16.7% (as per IDF criteria). Although the proportion of females with MetS was higher than that of males, the difference was not statistically significant (Table 4). Similarly, whether the student belonged to a nuclear or joint family did not affect their risk of MetS. Among students who were smokers and consumed alcohol, excessive junk food, salt, and red meat, the risk of MetS was significantly greater (Table 4). Lower consumption of fruits and vegetables and lack of exercise were not associated with a higher risk of MetS in this group of participants.

The logistic regression revealed that a history of smoking [adjusted odds ratio (AOR) 5.32, 95% CI (3.31–9.02)] and a history of alcohol intake [AOR 6.23, 95% CI (2.45–8.62)] were significantly associated with greater odds of MetS (Table 5).

Discussion

The current cross-sectional epidemiological study in young participants found MetS in 16.7%. The National Health and Nutrition Examination Survey (NHANES) data from 2011 to 2016 reported a prevalence of 19.5% among those aged 20–39 years.[6] Earlier studies in urban Indian young adults found a lower prevalence, ranging from 3.6 to 8.7%, based on different criteria by the International Diabetes Federation (IDF),

Table 3: Proportion of subjects with features and risk factors for MetS

Variable	*Overall n (%)*
Anthropometric parameters	
Overweight/obese (BMI ≥23 kg/m^2)	56 (37.3%)
Central obesity (waist circumference >90 cm in males and >80 cm in females)	58 (38.7%)
Clinical assessment	
Elevated BP (SBP/DBP ≥130/85 mm Hg)	22 (14.6%)
Laboratory investigations	
Elevated FPG (≥100 mg/dL)	29 (19.3%)
Elevated TGs (≥150 mg/dL)	26 (17.3%)
Decreased HDL (<40 mg/dL in males/<50 mg/dL in females)	33 (22%)
Lifestyle factors	
Smoking habit (≥6 months)	50 (33.33%)
• <5 cigarettes	13 (26%)
• 5–10 cigarettes	11 (22%)
• >10 cigarettes	26 (52%)
Alcohol consumption (≥1 in a week for the last 6 months)	47 (31.3%)
Diet (unsatisfactory)	
• Fruit consumption (<3 days/week)	110 (73.3%)
• Vegetable consumption (<5 days/week)	120 (80%)
• Extra salt consumption with food	92 (61.3%)
• Regular fast food and/or junk food consumption (>1 day/week)	115 (76.7%)
• Red meat consumption (>1 day/week)	101 (67.4%)
Family history	
• Obesity	86 (57.3%)
• Hypertension	80 (53.3%)
• Diabetes	54 (36%)
No exercise	135 (90%)

BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides

Table 4: Association between demographic variables and MetS

Variable	*MetS n (%)*	*χ^2 at df 1*	*p-value*
Male	15 (14.7%)		
Female	10 (20.8%)	0.882	0.347
Nuclear family	20 (17.2%)		
Joint family	5 (15.4%)	0.032	0.858
Nonsmokers	7 (7.3%)		
Smokers	18 (35.7%)	20.184	0.00001
No alcoholism	8 (7.7%)		
Alcoholism	17 (36.8%)	18.75	0.00001
Satisfactory fruit consumption	6 (15.1%)		
Unsatisfactory fruit consumption	19 (17.3%)	2.54	0.9
Satisfactory vegetable consumption	6 (20.0%)		
Unsatisfactory vegetable consumption	19 (16.0%)	0.54	1.5
Satisfactory salt consumption	3 (6.2%)		
Excess salt consumption	16 (23.3%)	16.02	0.01
Satisfactory fast-food consumption	2 (6.8%)		
Excess fast-food consumption	23 (19.7%)	34.38	0.00
Satisfactory red meat consumption	1 (2.4%)		
Excess red meat consumption	25 (25.0)	39.09	0.001
Regular physical activity	1 (8.3)		
No physical activity	24 (17.6)	1.2	0.27

BP, blood pressure; FPG, fasting plasma glucose; HDL, high density lipoprotein cholesterol; TG, triglycerides

Table 5: Logistic regression shows an association between different factors and MetS

Variable	*MS n (%)*	*AOR (95% CI)*	*p-value*
Male	15 (14.7%)	1.86 (0.86–3.66)	0.06
Female	10 (20.8%)		
Nuclear family	20 (17.2)	1.01 (0.49–1.20)	0.96
Joint family	5 (15.4)		
Nonsmokers	7 (7.3)	5.32 (3.31–9.02)	0.00
Smokers	18 (35.7)		
No alcoholism	8 (7.7)	6.23 (2.45–8.62)	0.002
Alcoholism	17 (36.8)		

AOR, adjusted odds ratio; BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; HDL, high density lipoprotein cholesterol; TG, triglycerides

National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), and Indian consensus.[7–9] Our findings support and encompass the results of previous studies, indicating that MetS is not infrequent among younger adults. Similar to the prevalence data reported in the NHANES study, our study found no significant differences in MetS prevalence based on the sex of the participants.[6]

High BP is mostly associated with dietary salt intake.[10] In our study, a significant proportion of participants consuming excess dietary salt had MetS compared to those who did not. Previous studies in young Asian adults have shown that the mean salt intake is twice that recommended by various international guidelines.[11] A prevalence of elevated BP in participants with MetS was found in this study, which was comparable to data published earlier.[7] Additionally, a positive correlation was established not only between salt intake and high blood pressure but also between BMI and body fat proportion.[12]

High FPG and high TGs may be attributed to various lifestyle factors described earlier, such as diet, sedentary lifestyle, and addictions like smoking and alcohol consumption. Smoking induces an increase in insulin-antagonistic hormones, resulting in elevated triglyceride levels and impaired fasting glucose.[13] In our study, smokers had five-fold greater odds of MetS. Previous studies in young adults in their 20s and 30s have shown that the risk of dyslipidemia is significantly higher in smokers than in nonsmokers.[14]

Previous clinical evidence suggests that the prevalence of risk factors for cardiometabolic diseases is relatively greater in Indians and evident prematurely compared to the European population.[15] Apart from the ethnicity factor, rapid lifestyle changes in the past decade have also contributed to the higher prevalence of MetS-associated risk factors.[16] These include excessive consumption of calorie-dense foods, poor intake of fiber-rich vegetables and fruits, and increasing automation and sedentary lifestyle. In addition to these environmental and dietary factors, smoking and alcohol abuse significantly contribute to the increased risk of MetS among young adults.

Individual MetS component risk factors, such as smoking and alcohol consumption, are linked to MetS among young Indian adults. The relatively high prevalence of MetS in younger adults is alarming, as it implies prolonged susceptibility to cardiovascular risk factors and an increased risk of diabetes and CVD. Consequently, it impacts younger adults in their most productive age span.

Thus, the emerging global picture has become increasingly concerning in recent years due to a precipitous, untimely rise in cardiometabolic abnormalities among younger generations. This trend could be attributed to rapid globalization, resulting in a complete lifestyle change over the last few decades among adolescents and young adults. Hence, it is worthwhile to scrutinize sociobiological factors that may contribute to cardiometabolic abnormalities leading to MetS in this age-group.

Conclusion

In younger adults, susceptibility to premature CVD can be decreased by focusing on the early identification and prevention of risk factors for MetS. Context-specific, cost-effective, and feasible interventions to mitigate identified risk factors are the need of the hour.

Limitations

The study results are based on a limited sample size, so generalization of the findings is difficult, and confirmation in a larger population may be necessary. An important factor among medical students is the stress of the course, which may also influence individual components of MetS but was not assessed.

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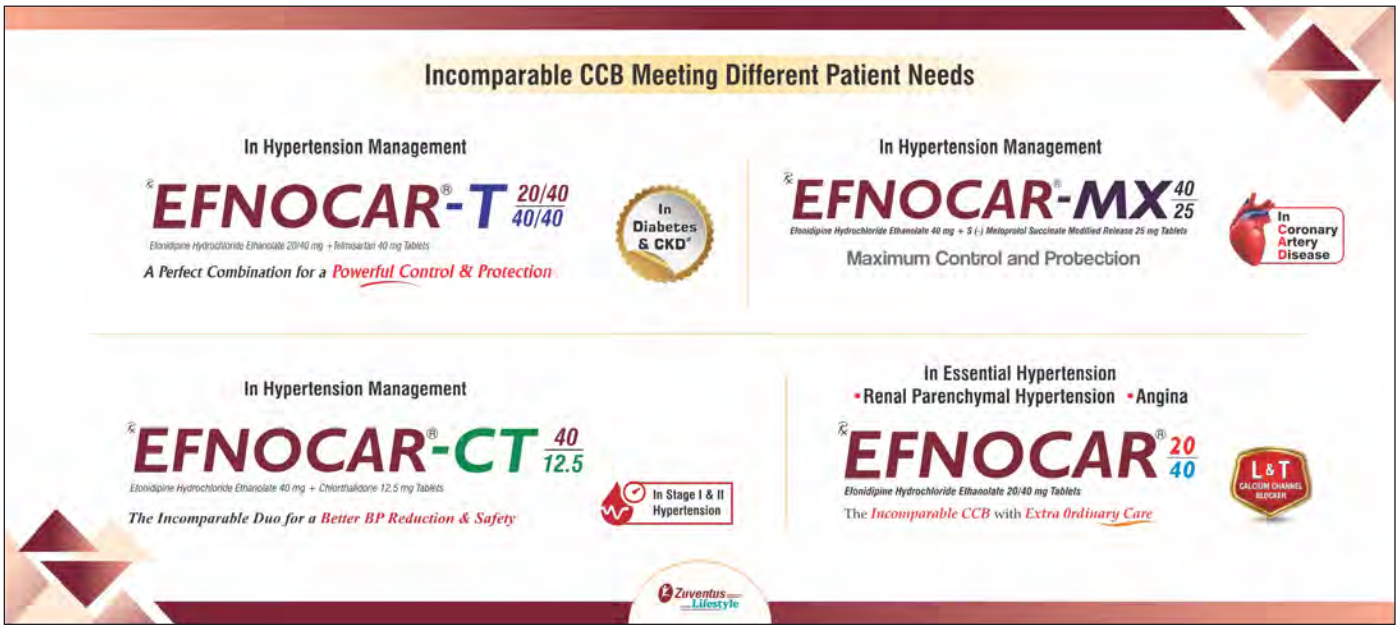

ORIGINAL ARTICLE

Comparison of Basal Core Promoter Region Mutation and Precore Mutation among Monoinfected Hepatitis B Virus and Coinfected Hepatitis B Virus with Human Immunodeficiency Virus Patients

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Abstract

Objectives: Hepatitis B virus (HBV) has a partially double-stranded circular deoxyribonucleic acid (DNA) that replicates through reverse transcription, producing an intermediate ribonucleic acid (RNA). This replication process has a high chance of error, leading to several mutations in the genome. According to several studies conducted worldwide, the classical basal core promoter (BCP) double mutation (A to T at nucleotide 1762 and G to A at nucleotide 1764) in the BCP region and the mutation in the precore (PC) region (G to A at nucleotide 1896) of HBV DNA have a strong correlation with advanced liver disease. The present study aims to compare the role of BCP and PC mutations among two groups of patients: monoinfected HBV (acute and chronic) and coinfected HBV–HIV patients.

Methodology: Thirty cases from each group of monoinfected (acute = 15 and chronic = 15) and coinfected patients were subjected to BCP and PC mutation identification by PCR-RFLP, confirmed by sequencing. The prevalence of BCP and PC mutations between the two groups was then compared statistically.

Results: The BCP mutation among chronic HBV and HBV–HIV coinfected patients was 66.67 and 19.23%, respectively, while the PC mutation among chronic HBV and HBV–HIV patients was 8.34 and 23.07%, respectively. Both mutations were higher among hepatitis B e antigen (HBeAg)-negative subjects. HBV/D was the major genotype among the BCP and PC mutant subjects.

Conclusion: The BCP mutants in our study had a high percentage of HBeAg negativity, low DNA levels, and mildly elevated ALT levels, mimicking inactive carriers. BCP mutants have a strong association with chronic liver diseases, so identifying chronic inactive HBV patients harboring the BCP mutant is necessary, and they require a close follow-up regimen.

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Introduction

Cirrhosis of the liver and hepatocellular carcinoma (HCC) are life-threatening conditions with several risk factors, among which chronic hepatitis B virus (HBV) infection is one of the most important factors.[1–3] Immune-mediated injury to the liver caused by the virus is thought to be the main pathogenesis of chronic liver diseases among chronically HBV-infected patients. Additionally, several mutants of this virus may contribute to the pathogenesis of liver damage.[4–7]

Seroconversion from hepatitis B e antigen (HBeAg) positive to HBeAg negative was previously considered a good prognosis. However, in some patients, even after seroconversion, hepatocellular carcinoma (HCC) or cirrhosis of the liver was observed. It was later found that the basal core promoter (BCP) region double mutation, A to T at nucleotide 1762 and G to A at nucleotide 1764, is also associated with HBeAg seroconversion.[8,9] Additionally, the most common mutation in the precore (PC) region, a G to A transition at position 1896 (G1896A), creates a premature stop codon at codon 28. This mutation halts HBeAg translation, but the virus's replicative ability remains the same. Thus, these precore mutants and BCP mutants fall under the group of HBeAg-negative chronic hepatitis B carriers. Patients harboring these mutants characteristically exhibit an absence of HBeAg in the serum, lower HBV DNA levels (usually $\leq 10^5$ IU/mL), and fluctuations in aminotransferase levels.[10]

Several studies have shown a strong correlation between BCP and PC mutations and disease progression to liver cirrhosis and HCC.[11–15] According to studies, antiviral therapy in patients with an HBeAg-negative profile lowers the HBV DNA level more readily than in patients with a positive HBeAg. However, the group of HBeAg-negative patients harboring BCP and PC mutants may not respond well to short-term antiviral therapy and may require long-term follow-up and treatment.[16]

Human immunodeficiency virus (HIV) infection, an immunocompromised condition, has a significant impact on the pathogenesis of HBV-related liver disease. Limited information is available regarding HBV genome mutations in patients with HIV–HBV coinfections.

The aim of our study was to compare the prevalence of BCP and PC mutations between two cohorts of HBV monoinfected and HBV–HIV coinfected patients and to determine the association of these mutations with varying disease severity among these two cohorts.

Methodology

Hepatitis B-infected cases (HBsAg positive) of all age groups and both sexes attending the School of Tropical Medicine, Kolkata, were included in this study. Patients infected with other hepatitis viruses (HAV, HCV, and HEV) were excluded from the study. Collected samples were transported to the microbiology laboratory for tests and analysis. Ethical clearance was obtained from the Institutional Ethics Committee of the School of Tropical Medicine, Kolkata.

HBV monoinfected patients (acute: $n = 15$ and chronic: $n = 15$) and HBV–HIV coinfected patients ($n = 30$) were included in our study. Acute cases were selected based on HBsAg positivity for <6 months and anti-IgM HBcAb positivity. Chronic cases were selected

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based on HBsAg positivity for >6 months, while coinfected cases were selected based on HBsAg positivity for >6 months among the HIV-positive patients (irrespective of antiretroviral therapy).

HBV DNA was extracted from the blood samples using the QIAamp DNA Blood Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. The S gene of HBV and the complete basal core promoter/precore (BCP/PC) (nucleotides 1742–1900 from the EcoRI site) region were amplified by nested PCR. Promega Taq DNA polymerase (Promega, Madison, WI) was used for the amplification reaction. After PCR amplification, a portion of the amplified PCR mixture of the complete basal core promoter/precore region was subjected to restricted fragment length polymorphism (RFLP) gel electrophoresis. Further, amplicons were directly sequenced using the Prism Big Dye Kit and ABI 3130xl Genetic Analyzer (Applied Biosystems, Foster City, United States). All the sequences were aligned and corrected using the BioEdit v7.1.3.0 software. Polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) was used for genotyping of the HBV. Statistical analysis was performed using Microsoft Excel and GraphPad Prism (version 4.0.3). *p*-values < 0.05 were considered statistically significant.

Results

Among the 60 patients, 52 (86.67%) were males and 8 (13.34%) were females. A high percentage of males was observed in all the cohorts (Table 1). The median age of the study population was 32 years (range 16–60 years). However, the median ALT level was significantly higher among the acute HBV patients (268.72 U/L, IQR 75–2588 U/L) compared to the chronic HBV (58 U/L, IQR 19–148; *p*-value < 0.0001) and HBV/HIV coinfected subjects (56 U/L, IQR 22–186; *p*-value < 0.0001).

HBV DNA positivity among HBV/HIV coinfected samples was 93.34%, while it was 86.67% in the chronic HBV group and 66.67% in the acute group. The median HBV DNA load among the HBV/HIV coinfected cases (5.01 $\log_{10}$ copies/mL, IQR 2–7.65 $\log_{10}$ copies/mL) was significantly higher compared to both acute (2.68 $\log_{10}$ copies/mL, *p*-value 0.0004) and chronic HBV (3.75 $\log_{10}$ copies/mL, *p*-value 0.004) infected cases. However, there were no significant changes in HBV viremia between chronic and acute patients (*p*-value 0.16). Data for the HBeAg status was available for all the study participants in the chronic and coinfected groups, while data was available for only 10 participants in the acute group. Similarly, the HBeAg positivity rate was higher in the coinfected group (63.34%) compared to the other two groups, as shown in Table 2.

The major genotype found among our study subjects was genotype HBV/D (35/51, 68.63%), followed by HBV/A (11/51, 21.57%) and HBV/C (5/51, 9.80%). Intergroup comparison between the different cohorts also revealed similar findings, with the predominance of HBV/D in each of the groups. Moreover, we found that the distribution pattern of HBV/A and HBV/C was quite similar in both acute and chronic HBV groups, while it varied in the HBV–HIV coinfected patients, where the prevalence of HBV/C was considerably low. In our study, the precore mutation was not associated with genotype HBV/A, whereas in HBV/HIV coinfected patients, both HBV/D (2/4, 40%) and HBV/C (2/4, 40%) were found to be the predominant genotypes among the BCP mutant groups.

Among the DNA-positive subjects, the complete basal core promoter (BCP) and precore (PC) region of the HBV genome could be successfully amplified for 8 isolates out of 10 in the acute group (80%), 12 isolates out of 13 in the chronic group (92.30%), and 26 isolates out of 28 in the coinfected group (92.86%).

It was observed that the frequency of BCP double mutation was significantly higher in the chronic population compared to the HBV/HIV coinfected group (66.67 vs 19.23%, *p*-value 0.004) (Table 3). Interestingly, a complete reverse pattern was observed for the precore mutation, which was considerably higher in coinfected subjects compared to chronic ones (23.07 vs 8.34%). However, this difference was statistically insignificant (*p*-value 0.275). On the other hand, none of the acute subjects harbored either the BCP double mutations (A1762T/G1764A) or the precore mutation (G1896A).

The different variables, including age, sex, ALT, HBV DNA, and HBeAg status, were compared between subjects harboring BCP

Table 1: Baseline characteristics of all the study participants

Variables	*Acute HBV (n = 15)*	*Chronic HBV (n = 15)*	*HIV/HBV (n = 30)*
Age in years Median (IQR)	30 (24–59)	32 (16–60)	32 (21–54)
Male, *n* (%)	10 (66.67)	14 (93.34)	28 (93.34)
ALT in U/L Median (IQR)	268.72 (75–2588)	58 (19–148)	56 (22–186)

IQR, interquartile range

Table 2: Virological characteristics of our study population

Variables	*Acute HBV n = 15*	*Chronic HBV n = 15*	*HIV/HBV n = 30*
HBV DNA positivity *n* (%)	10 (66.67)	13 (86.67)	28 (93.34)
HBV DNA load (Log_{10} copies/mL) Median (IQR)	2.68 (2–4.28)	3.75 (2.10–5.35)	5.01 (2–7.65)
HBeAg positivity, *n* (%)	3 (30)	6 (40)	19 (63.34)

p-value ≤ 0.16, for comparison of HBV DNA load between acute and chronic HBV group; *p*-value = 0.004, for comparison of HBV DNA load between chronic HBV and coinfected HBV/HIV group; *p*-value ≤ 0.0004, for comparison of HBV DNA load between acute HBV and coinfected HBV/HIV group; *p*-value = 0.7, for comparison of HBeAg positivity rate between acute and chronic HBV group; *p*-value = 0.06, for comparison of HBeAg positivity rate between acute HBV and coinfected HBV/HIV group; *p*-value = 0.14, for comparison of HBeAg positivity rate between chronic HBV and coinfected HBV/HIV group

Table 3: Identification of BCP A1762t/G1764a double mutation and precore G1896a mutation

Variable	*Acute HBV n = 8*	*Chronic HBV n = 12*	*HBV/HIV n = 26*
BCP double mutation A1762T/G1764A, *n* (%)	–	8 (66.67)	5 (19.23)
Precore mutation G1896A, *n* (%)	–	1 (8.34)	6 (23.07)

double mutations and wild-type strains (Table 4). It was found that there was no significant difference in median age between these two groups (33 vs 31 years, *p*-value 0.74). In addition, there was a minor elevation in the ALT levels of the mutant subjects (68 vs 59 U/L, *p*-value 0.48). However, this elevation was not significant in our settings. On the contrary, though not statistically significant, median HBV DNA levels were considerably lower in the mutant subjects compared to the wild-type ones (3.92 $\log_{10}$ copies/mL vs 4.655 $\log_{10}$ copies/mL, *p*-value 0.13). As expected, the proportion of patients with HBeAg-positive status was significantly lower among the patients with BCP double mutation (69.23 vs 30.77%, *p*-value 0.008). This indicates that the presence of these mutations severely compromises the expression of HBeAg.

The different variables, including age, sex, ALT, HBV DNA, and HBeAg status, were again compared between subjects harboring the PC mutation and wild-type strains (Table 5). It was found that there was no significant difference in median age between these two groups (32 vs 37 years, *p*-value 0.068). In contrast to the BCP mutant, the median ALT level among the PC mutant (49 U/L) was slightly lower than the wild-type strains (68 U/L). However, this difference was not statistically significant (*p*-value 0.26). Also, though not statistically significant (*p*-value 0.60), median HBV DNA levels were lower in the mutant subjects (4.4 $\log_{10}$ copies/mL, IQR 2.79–5.24 $\log_{10}$ copies/mL) compared to the wild-type ones (4.575 $\log_{10}$ copies/mL, IQR <2–7.65 $\log_{10}$ copies/mL). As expected, PC mutations were harbored by a significantly higher proportion of HBeAg-negative population (14.29 vs 85.71%, *p*-value 0.03). This indicates that the presence of these mutations also severely compromises the expression of HBeAg.

Table 4: Comparison of baseline characteristics among wild type variant and BCP mutant variant

Variable	*HBV wild variant (N = 33)*	*HBV BCP mutant (N = 13)*
Age in years, median (IQR)	33 (21–60)	31 (16–57)
Male gender, *n* (%)	29 (87.88)	12 (92.30)
ALT, U/L, median (IQR)	59 (22–2588)	68 (19–186)
DNA load, $\log_{10}$ copies/mL, median (IQR)	4.655 (<2–7.65)	3.92 (2.1–6.34)

Table 5: Comparison of baseline characteristics among wild type variant and precore mutant variant

Variables	*HBV wild variant (N = 39)*	*HBV precore mutant (N = 7)*
Age in years, median (IQR)	32 (16–60)	37 (31–54)
Male gender, *n* (%)	34 (87.18)	7 (100)
ALT, U/L, median (IQR)	68 (19–2588)	49 (33–70)
DNA load, $\log_{10}$ copies/mL, median (IQR)	4.575 (<2–7.65)	4.4 (2.79–5.24)

Discussion

Major demographic characteristics of our study population show an overall high percentage of male gender (86.67%) with a male-to-female ratio of 6.5:1. A study done by Chachá et al.[17] corroborates with our findings, while some studies showed equal gender distribution among the HBV monoinfected cases.[18] The median age of the study population was 32 years (range 16–60 years), a finding that corroborates with other studies.[19–22] According to previous studies, a higher frequency of BCP double A1762T/G1764A mutations was found in HBV genotype C patients.[23] However, in our study, this mutant was more prevalent in the chronic HBV group infected with HBV genotype D (50%), followed by HBV/C (37.5%) and HBV/A (12.5%). This finding corroborates with the study done by Taghavi et al.[24] However, the mutation among the coinfected HBV/HIV group was equal (40%) in patients with circulating HBV/D and HBV/C genotypes, followed by genotype HBV/A (20%).

Genotype HBV/D was predominantly associated with precore mutation in our study (85.71%), which is similar to other studies.[24–26]

Both BCP (69%) and PC (86%) mutations were found to be significantly higher among the HBeAg-negative cohorts. BCP double mutation was significantly higher among the chronic HBV isolates (66.67%) than the coinfected HBV/HIV isolates (19.23%). This finding corroborates with studies done in different parts of the world. Lower HBV quasispecies diversity was found in HBV/HIV coinfected patients when compared to HBV monoinfected patients.[27,28] It was assumed, in a subsequent study, that the absence of immune pressure in an immunocompromised state might be the reason the HBV isolates retain their wild-type characteristics.[29] In contrast, in our study, precore mutation was found to be higher among the coinfected subjects (23.07%) than the chronic HBV patients (8.34%). However, this finding was not statistically significant. According to a 3-year prospective study done by Cassino et al., precore region mutation might be genotype-dependent in its frequency but not on HIV coinfection.[30] In subsequent studies, it has been reported that the genotype HBV/D is most frequently associated with precore mutation. Probably, as in our study, the frequency of genotype HBV/D was higher among the coinfected group, precore mutation was found to be higher among this group. According to several studies done in subsequent years, BCP double mutation has a relevant association with the development of chronic liver disease like HCC and cirrhosis. Comparison of biochemical and virological profiles among BCP mutant groups and wild-type variant cohorts in our study shows no significant differences in ALT levels and DNA loads. Surprisingly, DNA load was lower among the mutant groups than the wild-type variant. Similar findings were shown in a study done on Chinese patients, where necroinflammation and fibrosis were present despite persistently normal serum ALT levels and low viral load with BCP mutations.[31]

Several studies have demonstrated that patients who harbored precore mutations were more predisposed to chronic liver diseases than those with the wild-type infection.[15,32] Recent meta-analysis[33] indicated that precore mutation is a predisposing factor for HCC, especially among Asians.[29] Our findings corroborate with a study done in Iran, where there were no significant differences in demographic data and liver enzyme levels between patients with mutations and those without mutations.[34] Similarly, a study done in Morocco[35] showed no significant difference in the HBV DNA level between patients with and without the precore mutation. It thus implied that G1896A had no effect on viral replication.[34,36,37] However, it is very difficult to draw a conclusion on the relevant association of PC mutation with chronic liver disease from our small study population.

Conclusion

The predominant genotype in our study was found to be HBV/D in the eastern part of India. Our study showed that the BCP mutation was significantly higher among the monoinfected chronic HBV patients, the immunocompetent group, than the coinfected HBV/HIV patients. Additionally, as the isolates with BCP mutations in our study had a high percentage of HBeAg negativity, low DNA levels, and mildly elevated ALT levels, they mimicked inactive carriers. BCP mutants have a strong association with chronic liver diseases, so identifying the chronic

inactive HBV patients harboring the BCP mutant is necessary, and they require a close follow-up regimen.

Our study concluded that BCP and PC mutations in HBeAg-negative CHB patients can mimic inactive carriers. Detection of BCP and PC mutations can, therefore, aid in the early initiation of treatment for this subset of CHB patients, potentially resulting in less progression to cirrhosis and HCC.

Limitations

The small sample size makes it very difficult to draw a conclusion on the relevant association of PC mutation with chronic liver disease.

The lack of long-term follow-up makes it difficult to draw a direct conclusion regarding the association of mutations with HBeAg-negative individuals harboring PC and BCP mutations in causing CLD or HCC.

Ethical Approval

Taken.

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ORIGINAL ARTICLE

DiSi Survey: Use of Generic DPP4i–SGLT2i Fixed-dose Combinations in Indian Clinical Practice

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Abstract

India has a high burden of patients with diabetes mellitus (DM). Challenges to managing type 2 diabetes (T2DM) in India are unique. Indian T2DM patients do not just present with DM alone, but with clustering of cardiovascular (CV) risk factors like hypertension (HTN), dyslipidemia, and obesity. Furthermore, Indian patients also have lesser baseline beta-cell function compared to global reference populations. In India, various cost-effective, generic, fixed-dose combinations (FDC) of dipeptidyl peptidase 4 inhibitors (DPP4i) with sodium-glucose cotransporter 2 inhibitors (SGLT2i) are available for the management of T2DM. However, to the best of our knowledge, scant surveys have studied the clinical practice nuances regarding the use of these FDCs in Indian settings. Hence, we designed and conducted a knowledge, attitude, and practice (KAP) survey to study the attitude and practice of Indian physicians with regard to patient population and placement of generic DPP4i–SGLT2i FDCs. Our survey showed that in India, patients often present with a high baseline HbA1c. From a glycaemic control perspective, DPP4i-SGLT2i FDCs are preferred in treatment-naïve patients with HbA1c >8% and those with HbA1c >8.5% despite metformin monotherapy. Also, 85% physicians observed a reduction in SGLT2i associated GUTIs with use of DPP4i-SGLT2i FDCs or concomitant use of these agents. Part of these survey findings were presented at the American Diabetes Association (ADA) 2024 Congress held in Orlando, Florida.

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Background and Aim

India is home to 101 million patients with diabetes mellitus (DM).[1] The Indian phenotype of patients with type 2 diabetes mellitus (T2DM) is associated with clustering of cardiovascular (CV) risk factors, increased insulin resistance, and reduced beta-cell function.[1,2] In India, various cost-effective, generic, fixed-dose combinations (FDC) of dipeptidyl peptidase 4 inhibitors (DPP4i) with sodium-glucose cotransporter 2 inhibitors (SGLT2i) are available for the management of T2DM. However, to the best of our knowledge, scant surveys have studied the clinical practice nuances regarding the use of these FDCs in Indian settings. Hence, we designed and conducted a knowledge, attitude, and practice (KAP) survey to study the attitude and practice of Indian physicians with regard to patient population and placement of generic DPP4i–SGLT2i FDCs. Generic FDCs commonly available in India at the time of the survey were vildagliptin–dapagliflozin (Vilda–Dapa), sitagliptin–dapagliflozin (Sita–Dapa), and linagliptin–dapagliflozin (Lina–Dapa). Part of the findings from this survey were presented at the American Diabetes Association (ADA) 2024 Congress held in Orlando, Florida.[3]

Methods

We designed a KAP survey questionnaire with 6 key questions to decipher clinical practice perspectives relevant to the usage of DPP4i–SGLT2i FDCs. Questions pertained to the clinical practice burden of newly diagnosed, treatment-naive patients presenting with high baseline HbA1c of >8%, and patients presenting in clinic with HbA1c >8.5% despite being on metformin monotherapy. Questions also pertained to the clinical placement of these FDCs, preferred FDC combinations, and the effect of FDC on SGLT2i-related genitourinary tract infections (GUTI). The survey was conducted over 4 days in November 2023 at an Indian Medical Congress. Convenience sampling was used to reach out to at least 150 respondents *via* both physical as well as online Google forms. Descriptive statistics were used, and data was analyzed using MS Excel 2019.

Results

In total, 185 practicing doctors from different states of India completed the survey. About 48% of respondents (n = 89) reported that in their clinical practice, >40% of their newly diagnosed, treatment-naive patients present with a baseline HbA1c >8% (Fig. 1A). Also, 52% (n = 97) of physicians reported that in their practice settings, >40% of patients present with HbA1c >8.5% despite metformin monotherapy. From the available generic DPP4i–SGLT2i FDCs in India, 36.2% of respondents (n = 67) preferred Sita–Dapa as their FDC of choice. About 12.9% (n = 24) of respondents preferred Lina–Dapa, while 15.1% (n = 28) of respondents gave equal preference to Sita–Dapa and Lina–Dapa FDCs since both sitagliptin and linagliptin have established evidence for CV safety. Only 9.7% (n = 18) of clinicians preferred Vilda–Dapa, while 25.9% (n = 48) of respondents preferred all three available FDCs equally in their clinical practice.

From a glycemic control perspective, 65.9% (n = 122) of respondents preferred DPP4i–SGLT2i FDCs for all three scenarios, namely (Fig. 2A):

- Treatment-naive patients with contraindication/intolerance to metformin and HbA1c >8%.
- Uncontrolled on metformin monotherapy with HbA1c >8.5%.
- As add-on to insulin.

About 60.5% (n = 112) respondents prescribe these FDCs due to all four clinical reasons namely (Fig. 2B):

- Cardiovascular benefits of SGLT2i are an added advantage in Indian population (since Indian patients often have clustering of multiple CV risk factors).
- Targets multiple pathways in ominous octet.
- Fixed-dose combinations promotes weight loss.
- Significantly lesser risk of hypoglycemia than sulfonylurea (SU) based FDCs.

A total of 85% of respondents (n = 158) noted a reduction in the incidence of SGLT2i associated GUTI with the use of DPP4i–SGLT2i FDCs or concomitant use of DPP4i with SGLT2i (Fig. 1B).

Discussion

The Indian phenotype is associated with clustering of CV risk factors like hypertension

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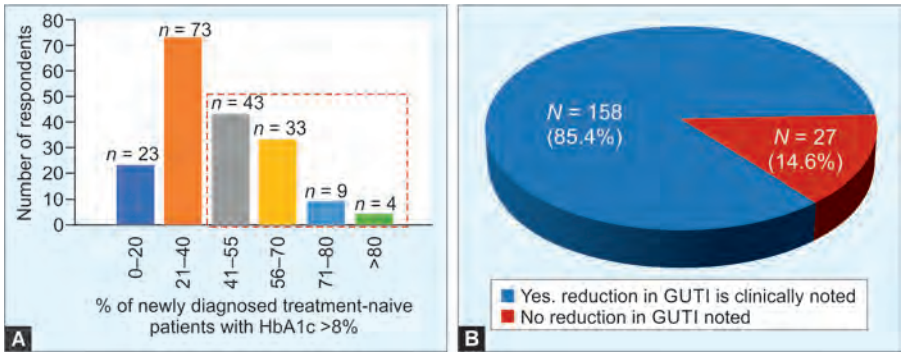
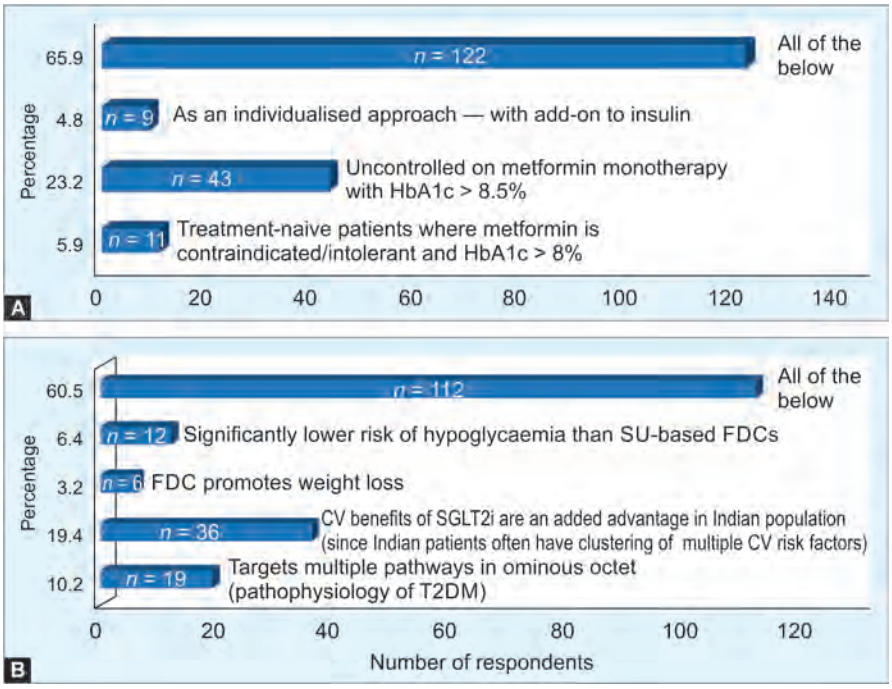


Figs 1A and B: (A) Percentage of newly diagnosed treatment naive patients with HbA1c >8% in individual clinicians practice—dotted red line shows that 48% respondents (n = 89) reported that >40% of their newly-diagnosed, treatment-naive patients present with a baseline HbA1c >8%; (B) Number (and percentage) of respondents who noted reduction of SGLT2i associated GUTI with concomitant administration of DPP4i or DPP4i–SGLT2i FDC—158 respondents (85.4%) noted reduction in their clinical practice



Figs 2A and B: (A) Clinical placement of DPP4i–SGLT2i FDC from glycemic control perspective; (B) Reasons other than glycemic control for prescribing DPP4i–SGLT2i FDC

(HTN), dyslipidemia, and abdominal obesity, ultimately leading to early atherosclerotic cardiovascular disease (ASCVD) compared to Caucasian populations.[1,4] Hence, management of T2DM in India warrants early consideration of therapies that confer CV protection (e.g., SGLT2i) at the time of diagnosis itself. Studies have demonstrated that in global reference populations, patients with diabetes have already lost approximately 50% of their β-cell mass at the time of diagnosis itself.[5] This phenomenon is furthermore relevant for Indian T2DM patients, since the South Asian phenotype has reduced baseline β-cell function compared to other population groups.[2] This further underscores the need for considering agents that preserve β-cell function (e.g., DPP4is) early in the course of diabetes.

Our pan-India survey also highlights that patients with T2DM often present with a high baseline HbA1c in the physician's office. Current guidelines recommend initiating dual-combination therapy when the target HbA1c is >1.5% compared to baseline HbA1c.[6] This correlates with the findings of our survey, with respondents placing this combination for treatment-naive patients with HbA1c >8% or those uncontrolled on metformin monotherapy with HbA1c >8.5%.

Fadini et al. conducted an analysis of the Food and Drug Administration Adverse Event Reporting System (FAERS) pharmacovigilance database. They noted a 26% reduction in GUTIs in patients receiving DPP4i concomitantly with SGLT2i compared to those receiving SGLT2i alone. Intriguingly, this effect was not noted when SU were concomitantly given with SGLT2i.[7] A study conducted by DeFronzo et al. also demonstrated a similar trend toward reduction in genital tract infections and urinary tract infections in patients on empagliflozin plus linagliptin compared to linagliptin alone.[8,9] This correlates with our survey findings, whereby 85% of physicians clinically noted a reduction in SGLT2i-associated GUTIs with the use of DPP4i–SGLT2i FDCs or concomitant administration of both agents. Larger studies with DPP4i–SGLT2i aimed at studying GUTI frequency as the primary endpoint will provide valuable evidence on the same. Key limitations of our survey are that we did not include renal endpoints in our questions and also did not include innovator empagliflozin-linagliptin as a reference in our questionnaire (since our survey only focused on key generic FDCs commonly available at the time of the survey). An additional methodology-related limitation also includes the risk of sampling bias.

Conclusion

Indian clinical practice faces a significant burden of T2DM patients who present with high baseline HbA1c. Generic DPP4i–SGLT2i FDCs are preferred in treatment-naive patients with HbA1c >8% and those with HbA1c >8.5% despite being on metformin monotherapy. The FDCs are also prescribed for the extra glycemic benefits that they confer. Most physicians (85%) observed a reduction in SGLT2i-associated GUTIs with the use of DPP4i–SGLT2i FDCs or concomitant administration of both agents. Further well-designed studies may be conducted to confirm this interesting finding.

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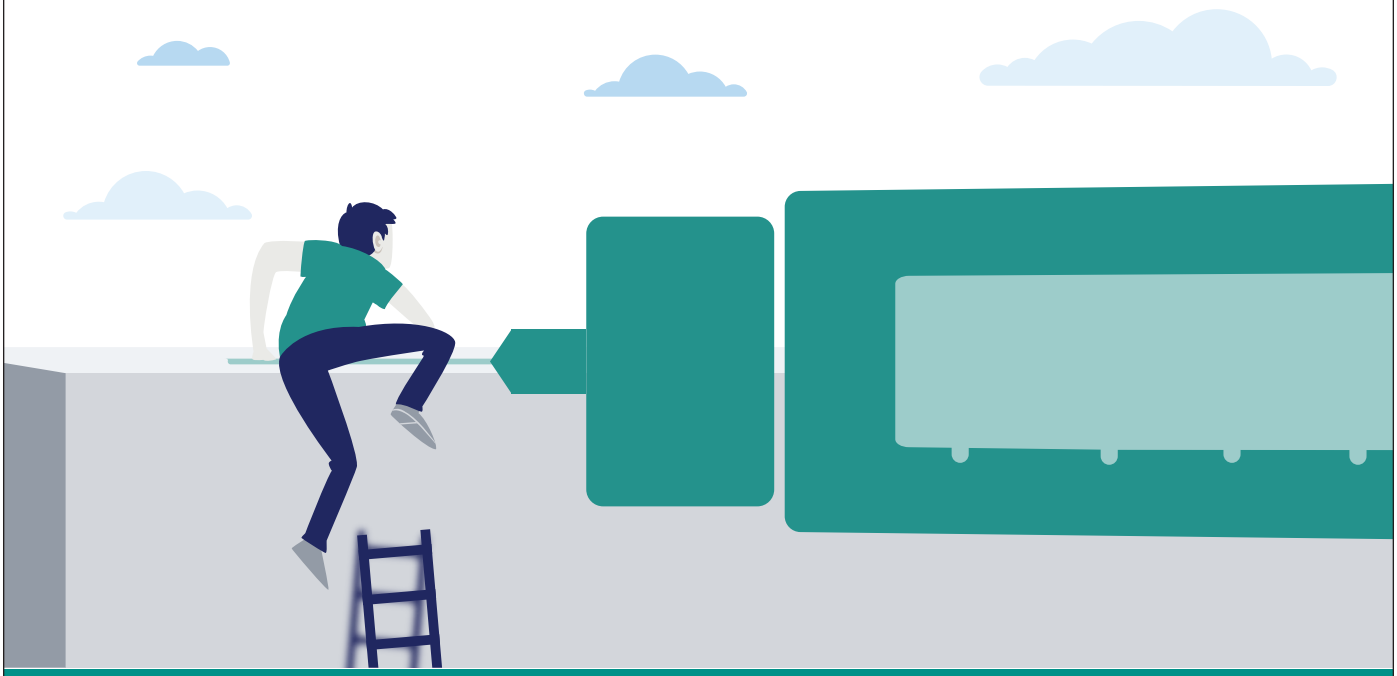

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Reference : 1. Sharma SK *et al.* Prevalence of Primary Non-adherence with Insulin and Barriers to Insulin Initiation in Patients with Type 2 Diabetes Mellitus – An Exploratory Study in a Tertiary Care Teaching Public Hospital. *European Endocrinology.* 2020;16(2):143–7

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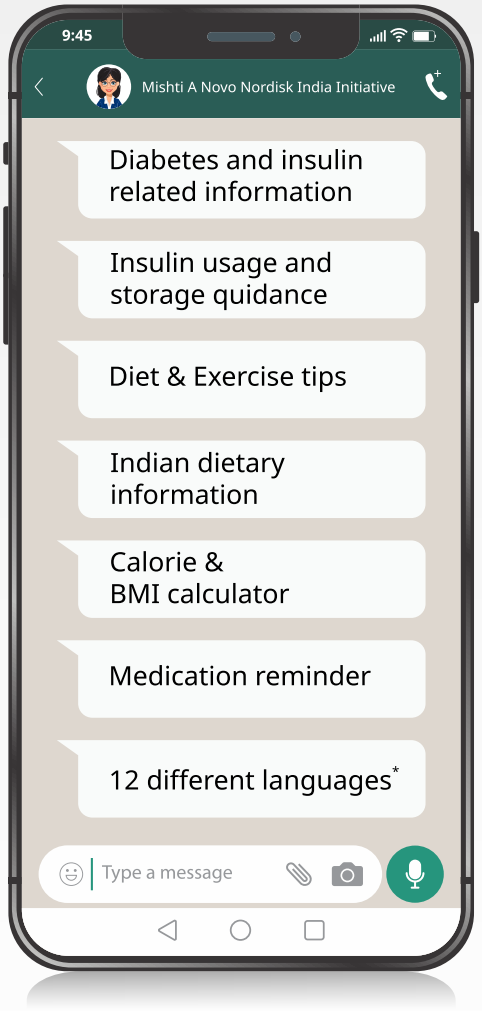

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ORIGINAL ARTICLE

Peak Inspiratory Flow Rate as a Prerequisite for Prescription of Inhaler Devices: A Cross-sectional Study

Spandan Biswas[1], Jai Kishan Karahyla[2*], Sameer Singhal[3], Tushar Nehra[4], Ajit Yadav[5]

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Abstract

Inhaler therapy has become the mainstay of treatment in obstructive airway diseases. Although patients, and to a certain extent doctors also, were not initially comfortable with inhalation devices, they have now become the standard of care in chronic obstructive pulmonary disease (COPD) and asthma.

However, the choice of inhaler device prescribed in different subsets of patients is still not clear. Prescription of a device depends upon age, dexterity, hand–mouth coordination, and peak inspiratory flow rates (PIFR). Prescription of wrong inhaler and wrong technique is not uncommon. In our study, 52.6% cases had prescription of wrong inhaler device, as per their PIFR. Physicians often do not consider the PIFR and the respiratory effort of the patient, while advising inhaler device. Only 43% patients with asthma had an adequate asthma control [asthma control test (ACT) > 19].

One of the main causes of a general inability to use an inhaler device properly results from the generation of an inadequate PIFR. It is more pronounced in those using dry powder inhalers (DPI), as it requires a higher effort-dependent inspiratory flow rate. PIFR of patients was divided into four groups, ≤30, 31–60, 61–90, and >90 L/minute. The required PIFR was taken as 30–60 L/minute for metered dose inhaler (MDI) and >60 L/minute for DPI. A positive correlation was noted for PIFR and advice to change the device as per the readings ($p = 0.05$). A positive correlation was also noted with PIFR compared to smoking/biomass use ($p = 0.002$). Thus, clinicians should advise inhalers as per PIFR and also continue to monitor PIFR on subsequent visits.

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Introduction

The mainstay of treatment for obstructive airway diseases (OADs) is inhaler therapy. The two most commonly used devices are pressurized metered dose inhalers (pMDI) and dry powder inhalers (DPIs). pMDI works on the principle of aerosolization of drug particles on passing through an actuator. DPI works on the principle of disaggregation of drug particles with the generation of an adequate inspiratory force.[1] The pMDI usually requires a peak inspiratory flow rate (PIFR) of at least 30 L/minute for sufficient drug deposition in airways. Supra-optimal PIFR can increase oropharyngeal deposition. The PIFR advised for various DPI devices like Rotahaler and Revolizer is 60 L/minute and a lower cutoff of 50 L/minute for Breezhaler.

Materials and Methods

One hundred fifty patients with OADs of asthma and chronic obstructive pulmonary disease (COPD), diagnosed using spirometry and on treatment with inhaler devices of pMDI and DPI, were recruited from outpatient department (OPD) to inpatient department (IPD) of a tertiary care hospital in rural India (Table 1). The patients were diagnosed as per Global Initiative for Chronic Obstructive Lung Disease (GOLD) and Global Initiative for Asthma (GINA) criteria for COPD and asthma, respectively. PIFR categories were compared with patient demographics (Table 2), need for change in device as per PIFR (Tables 3 and 4), and smoking status (Table 5). Modified Medical Research Council (mMRC) grades were also compared pre- and posttreatment. PIFR was measured by Dial InCheck G16 (Clement Clarke International Limited, UK).[2] It is a handheld inspiratory flow device (Fig. 1).[2]

The data is tabulated and presented as mean ± standard deviation. Categorical variables were compared with Chi-square test and $p = 0.05$ is considered statistically significant (Tables 4 and 5). Data were analyzed with Statistical Package for the Social Sciences (SPSS) 26, MS Excel, and MS Word.

Results

The study was conducted on 150 patients undergoing treatment for COPD and asthma. The mean age of the study population was 53.35 years, with a male:female ratio of 3:2 (Table 2). The study had 101 cases of COPD, 44 of asthma, and 5 of asthma-COPD overlap (Table 6). The mean body mass index (BMI) of the population was 25.359. The mean mMRC score of the study population before starting treatment and after starting treatment was 2.93 and 1.61, respectively. 63.3% of the study population had smoking history/biomass exposure (Table 5). 36.7% were non- or

Table 1: Distribution of study population as per inhaler device being used

Initial device prescribed by clinicians	*Frequency*	*Percentage (%)*
DPI	81	54
DPI + MDI combination	2	1.33
MDI	50	33.34
MDI with spacer	2	1.33
Nebulization	15	10
Total	150	100

Table 2: Study population characteristics

Index	*Mean ± standard deviation/distribution*
Age	53.35 ± 14.532
Male:female	90:60 (60%:40%)
BMI	25.359 ± 3.5321
mMRC prior to start of therapy	2.93 ± 0.761
Asthma severity score	5.22 ± 0.465
Asthma control test	17.72 ± 4.853 Adequate control: 19 of 44 patients Uncontrolled: 25 of 44 patients
GINA asthma treatment stage	3.72 ± 0.454
CAT score	19.14 ± 3.569
COPD bode index	3.21 ± 0.895

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Table 3: Smoking and biomass users in study population

Frequency of smokers/biomass users vs nonsmokers/never-smokers in study population	*Smokers/biomass users*	*Nonsmokers/ never-smokers*	*Total*
Asthma	5 (11.36%)	39 (88.63%)	44
COPD	86 (85.14%)	15 (14.85%)	101
Asthma–COPD overlap	4 (80%)	1 (20%)	5
Total	95	55	150

Table 4: PIFR categories compared with need for change in inhalation device as per patient specific PIFR reading

PIFR	*Need for change in inhalation method*		*Total*	
	Yes	*No*		
≤30	9	2	11 (7.33%)	$X^2 = 7.5721$
>30 and ≤60	34	30	64 (42.67%)	$df = 3$
>60 and ≤90	28	36	64 (42.67%)	$p = 0.05$
>90	8	3	11 (7.33%)	
Total	79	71	150 (100%)	

Table 5: PIFR categories compared with smoking/biomass use

PIFR	*Smoking history/biomass use*		*Total*	
	Yes	*No*		
≤30	10	1	11 (7.33%)	$X^2 = 14.617$
>30 and ≤60	48	16	64 (42.67%)	$df = 3$
>60 and ≤90	33	31	64 (42.67%)	$p = 0.002$
>90	4	7	11 (7.33%)	
Total	95	55	150 (100%)	

Table 6: Gender distribution of study population as per disease

Sex distribution	*Males*	*Females*	*Total*
Asthma	16 (36.36%)	28 (63.64%)	44
COPD	70 (69.30%)	31 (30.70%)	101
Asthma-COPD overlap	4 (80%)	1 (20%)	5
Total	90	60	150

Fig. 1: Dial InCheck G16 peak inspiratory flow rate (PIFR) meter

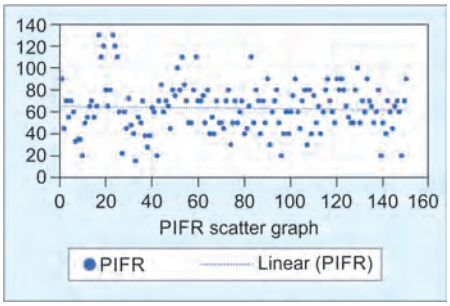

Fig. 2: Distribution of study population PIFR readings

never-smokers. The PIFR of patients was divided into four groups (with percentage of patients): ≤30 (7.33%, *n* = 11), 31–60 (42.67%, *n* = 64), 61–90 (42.67%, *n* = 64), and ≥90 (7.33%, *n* = 11) L/minute (Fig. 2). A total of 79 patients (52.67%) needed a change in their inhalation device or technique, as per their PIFR and device correlation (Table 4). However, out of 79 patients who needed a change in their inhalation device as per PIFR, about 54 patients (68%) had inadequate symptom control and 25 patients (32%) were happy with their symptom status in spite of using wrong device as PIFR. PIFR also found a significant correlation with smoking history and biomass exposure ($p = 0.002$) (Table 5).

Discussion

Inhaler devices are the mainstay of treatment in stable patients with asthma and COPD. Correct inhalation device and the correct technique are of paramount importance for optimal symptom control.[3] The use of inhaler devices is broadly dependent on the inspiratory effort generated for actuation of drug particles, along with inhalation technique. PIFR for the prescription of inhaler devices is seldom used by physicians when dealing with COPD and asthma.[1] Use of a handheld PIFR meter is researched in many countries like Korea, England, China, etc. However, there is very less data about India. The inspiratory effort required for pMDI is a minimum of 30 L/minute and upwards of 60 L/minute (up to 90 L/minute) for DPI.[2,4]

Pressurized metered dose inhaler is based on the use of carrier molecules along with drug particles. The drug is passed along an actuation chamber on pressing the canister. The patient is asked to do deep inspiration, starting with the pressing of canister. A low PIFR will cause oral deposition of the drug, resulting in lower bioavailability.[5] A supraoptimal PIFR will also increase pharyngeal deposition, also causing lower bioavailability.[6] It is important to maintain hand–mouth coordination in excess to maintaining an adequate inspiratory technique. Patients with improper hand–mouth coordination or improper inspiratory flow may be advised nebulization therapy or pMDI with spacer. However, these also require proper instruction for device use, to be informed to the patient.

Dry powder inhalers are based on the principle of an increased inspiratory flow, causing disaggregation of the capsule and its drug contents.[7] A higher PIFR is thus required to cause this extra activity. A suboptimal PIFR will result in partial drug remaining in the inhaler and oral deposition.[8] A supraoptimal PIFR will cause pharyngeal deposition and a lower drug delivery to the lungs.[9] Spacers in addition to pMDI also need added maintenance in terms of cleaning the device, are usually bulky, and difficult to carry around.

To check adequacy of inspiratory flow for a particular device use, we recommend the use of a handheld PIFR meter (like the Dial InCheck G16).[10]

Our study found a significant correlation of PIFR with current and previous history of smoking, along with biomass exposure (Table 5). We did not find a significant correlation of PIFR with alcohol use. PIFR values also did not correlate with symptom relief present even with wrong device as per PIFR readings (Fig. 2). This indicates that even though the device may be wrong for few patients as per PIFR, some may still have partial or complete symptom relief. This may be attributed to partial drug delivery or use of multiple drug therapies.

The PIFR can be determined at the first OPD visit and after stabilization of the patient after exacerbation and hospital stay. The device is also useful in subsequent patient visits for training of adequate and proper technique.

Patients should be subjected to PIFR on first visit, barring exacerbations. The PIFR should then be used as a guide for checking the effort and comfort of patients with various devices.[11,12] Proper technique should be taught. The inspiratory effort should also be checked upon subsequent visits and compared with clinical and spirometry improvement.

It is thus recommended that while dealing with cases of OAD, PIFR should be used for selection of inhaler. Patients should be taught about correct inhalation technique for the optimal control of their symptoms and disease.

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ORIGINAL ARTICLE

Conventional Synthetic Disease-modifying Drugs Remain the Mainstay of Therapy for Rheumatoid Arthritis in India

Varun Dhir[1*], Shung Ming Chiu[2], Rajiva Gupta[3], Shery Susan Phillip[4], Padmanabha Shenoy[5], Bharati Taksande[6], Dhiren Rawal[7], Kuldeep Kumar[8], Gargi Singh[9], Sandeep Kumar[10], Shahzeene Dhuria[11], Anuroopa Manovihar[12], Apoorva Bhagat[13], Chaitanya Soni[14], Sanjay Jain[15], Vineeta Shobha[16]

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Abstract

Background: There are limited data on the real-world utilization of disease-modifying antirheumatic drugs (DMARDs) in Indian patients with rheumatoid arthritis (RA).

Methods: This was a cross-sectional study of a multicentric observational cohort of RA patients across rheumatology clinics at six centers across India. Patients who met the American College of Rheumatology (ACR) 2010 criteria for RA were included. The demographics, disease-related parameters, and current therapy in terms of DMARDs were analyzed using a structured paper or electronic case record form.

Results: This study included 4,061 patients with RA across six centers in India. A majority were female (female-to-male ratio, 6:1), and their mean [standard deviation (SD)] age at the time of enrollment was 51 (12.2) years. Rheumatoid factor and/or anti-CCP were positive in 79 and 77%, respectively. Data on DMARDs were available for 3,550 RA patients. Conventional synthetic DMARDs alone were being used in 3,289 (93%), targeted synthetic DMARDs in 203 (6%), and biological DMARDs in 67 (2%). A total of at least 18 separate types or combinations of DMARDs were being prescribed, with the most common being a combination of methotrexate and hydroxychloroquine (22%), methotrexate monotherapy (17%), and a combination of methotrexate and leflunomide (16%). Overall, the most common DMARD prescribed (as monotherapy or in combination) was methotrexate (86%), followed by hydroxychloroquine (52%) and leflunomide (37%).

Conclusion: Cs-DMARDs remain the mainstay in the treatment of Indian patients with RA in this study, with the majority being treated with methotrexate alone or in combination with other DMARDs.

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Introduction

Rheumatoid arthritis (RA) is among the most common systemic autoimmune diseases, with a mean worldwide point prevalence of 0.5%, and an estimated prevalence in India varying from 0.3 to 0.7%. This systemic disease is characterized by inflammation of the synovial joints, with symmetrical involvement of both small and large joints.[1,2] Untreated RA leads to significant morbidity in the form of joint deformities and the need for joint replacements, and has a huge social impact in terms of absenteeism from work to job loss.[3]

The treatment of RA has undergone a major shift since the turn of the century. Prior to that time, therapy was restricted to the use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) methotrexate, sulfasalazine, and antimalarials (and gold). Afterward, there has been a revolution of sorts with the introduction of a new csDMARD, leflunomide, followed by newer classes, biologic disease-modifying antirheumatic drugs (DMARDs) and targeted synthetic DMARDs. Thus, there is scope for tremendous choice and diversity of therapy to suit the individual patient.[4]

The prescription of any therapy, including DMARDs, in RA depends on many factors, including but not limited to efficacy, availability, affordability, physician comfort, adverse effects of therapy, and coexisting comorbidities. There is little data on DMARD prescription patterns in India, particularly on bDMARDs and tsDMARDs, and the various combinations being used.[5] Thus, this study was planned as a cross-sectional, multicenter collaborative project to look at the pattern of DMARD use in RA patients in India.

Methods

This was a multicenter, prospective study under the BIRAC-funded Clinical Trial Network involving six sites across India (https://www.biracctnrheumatology.com/).

Participating centers included academic and nonacademic rheumatology clinics, government outpatient clinics, and private hospitals. Ethical approval was provided by the local institutional boards of all participating centers, and informed consent was obtained from all patients before their inclusion in the study.

The design of this prospective study includes two successive phases. During phase 1, a cross-sectional evaluation of patients with RA (as classified by ACR/EULAR 2010 criteria)[6] seen during a 2.5-year recruitment period at each center was performed (the whole recruitment period lasted from July 2020 to October 2022). All patients recruited during this phase formed the working cohort of the study. Data was collected through a face-to-face interview and a review of records of patients who attended the rheumatology clinics of these six centers. The participating physicians entered data either through a printed form or electronically *via* a specific web form through a designed portal—https://mier.hplug.co:4443/healthplug/#/login.

The results of phase 1 are reported here. The data were collected using the RA Baseline case report form, which included demographics, disease duration, treatment patterns, and comorbidities. Disease activity was assessed by the DAS28 (Disease Activity Score using 28 joints)–erythrocyte sedimentation rate (ESR) score, while function was assessed by the Health Assessment Questionnaire (HAQ). The serological status [presence or absence of rheumatoid factor (RF) and anticyclic citrullinated peptide antibodies

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(anti-CCP)] was recorded. All relevant extra-articular manifestations were documented. Comorbidities were recorded after reviewing the prescriptions for diseases such as hypertension, diabetes mellitus, hypothyroidism, hyperlipidemia, coronary artery disease, and tuberculosis (TB).

For each patient, the current use of medications was recorded, including nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids (CS), and disease-modifying drugs (DMARDs), either conventional synthetic (csDMARDs), targeted synthetic (tsDMARDs), or biologic (bDMARDs) and other immunomodulators/immunosuppressives. CsDMARDs included the four conventional drugs methotrexate, hydroxychloroquine, leflunomide, and sulfasalazine. Other immunomodulators/immunosuppressives included iguratimod and any other immunosuppressives, like azathioprine, etc.

Statistical Analysis

All analyses were performed using Microsoft Excel 2013 and IBM Statistical Package for the Social Sciences (SPSS) Statistics v. 20 software. Data were analyzed using descriptive statistics.

Demographic and descriptive continuous variables are expressed as mean [standard deviation (SD)] and median values. Categorical variables are expressed as percentages.

Results

We included 4,061 patients with RA across six centers in India. A majority were females (female-to-male ratio, 6:1), and their mean (SD) age at the time of enrollment was 51 (12.2) years. Rheumatoid factor and/or anti-CCP were positive in 79 and 77%, respectively. Baseline data are given in Table 1.

Use of Disease-modifying Antirheumatic Drugs

Data on drugs being used were available for 3,550 patients. Conventional synthetic DMARDs (csDMARDs) alone were being used in 3,289 (93%) patients, and biological and/or targeted synthetic DMARDs (b or tsDMARDs) were used in 270 (8%) patients. A total of at least 18 separate types of DMARDs or their combinations were being used by patients, with the most common being a combination of MTX and HCQ (22%), followed by MTX monotherapy (17%) and a combination of MTX and LEF (16%) (Fig. 1). Overall, the most common DMARD prescribed (as monotherapy or part of a combination) was MTX, followed by HCQ and LEF. CS was prescribed in 1,255 (35%) patients, and other immunomodulators/immunosuppressives were prescribed in 150 (4%) patients (Table 2).

Table 1: Baseline demographic and disease related parameters in study cohort (*n* = 4061)

Variables	*Values*
Age, years, mean ± SD	51.0 ± 12.2
Disease duration, mean ± SD	9.0 ± 7.3
Gender (F:M)	6:1
Age of onset, mean ± SD	42.0 ± 12.3
Rheumatoid factor, *n* (%)[1]	2620 (79)
Anti-CCP, *n* (%)[2]	1982 (77)
Antinuclear antibody, *n* (%)[3]	696 (46)
Disease activity (DAS28)[4]	
Remission	669 (31)
Low disease activity	496 (23)
Moderate disease activity	716 (33)
High disease activity	300 (14)
Extra-articular manifestations	
Rheumatoid nodules	334 (8)
Interstitial lung disease	212 (5)
Sicca symptoms	1019 (25)
Vasculitis	41 (1)
Comorbidities	
Diabetes mellitus, *n* (%)	453 (11)
Hypertension, *n* (%)	867 (21)
Hypothyroidism, *n* (%)	616 (15)
Coronary artery disease, *n* (%)	104 (3)
Asthma, *n* (%)	54 (1)
Tuberculosis (ever), *n* (%)	67 (2)

[1]Data available in 3315; [2]Data available in 2578; [3]Data available in 1525; [4]Data available in 2181

Table 2: Overall use of DMARD and glucocorticoids (as mono or combination therapy) in this study

DMARD	*n (%)*
Methotrexate	3044 (86)
Hydroxychloroquine	1871 (52)
Leflunomide	1321 (37)
Sulfasalazine	490 (14)
JAKi	203 (6)
Biologics	67 (2)
Corticosteroids	1255 (35)
NSAIDS	1364 (38)
Others	150 (4)

Others included iguratimod in 125, azathioprine in 9, tacrolimus in 8, cyclosporine in 2, cyclophosphamide in 3, mycophenolate mofetil in 3

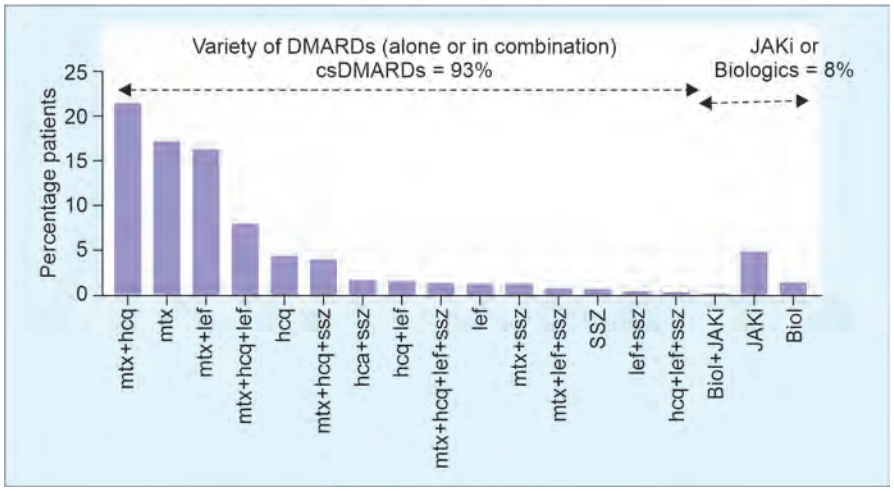

Fig. 1: Bar graph showing the various combinations/monotherapies of DMARDs prescribed to patients (*n* = 3550); biol, biologic; DMARD, disease-modifying antirheumatic drugs; hcq, hydroxychloroquine; JAKi, Janus kinase inhibitor; lef, leflunomide; Mtx, methotrexate; ssz, sulfasalazine; total value is above 100 due to rounding off

Conventional Synthetic Disease-modifying Antirheumatic Drugs

Among the 3,289 patients being treated exclusively with csDMARDs, monotherapy was used in 957 patients (29%), whereas combination therapy was used in 2,332 (71%) patients. In monotherapy, MTX was the most common, followed by HCQ. In combination therapy, the use of the dual combination of MTX and HCQ was most common, while in triple therapy, the combination of MTX, LEF, and HCQ was most common (Table 3).

Targeted Synthetic or Biological Disease-modifying Antirheumatic Drugs

These were used in 270 patients (8%), with tsDMARDs used in 203 (6%) and bDMARDs in 67 (2%) patients (both being used in 9 patients). Among patients receiving tsDMARDs and bDMARDs, 188 (94%) and 62 (95%), respectively, received them in combination with csDMARDs.

Discussion

Real-world data regarding the therapy of RA patients is limited in India. In the first phase of this 3-year-long prospective study, a cross-sectional evaluation of ongoing therapy from 4,061 RA patients is analyzed.

The most striking results from this study are that conventional synthetic DMARDs (csDMARDs) remain the mainstay of treatment for RA in India. We found that methotrexate, described as the gold standard and benchmark csDMARD, is by far the most used, with almost 86% of patients receiving this drug. This is higher than the use reported in most other studies from different parts of the world, which report current use of methotrexate ranging from 62.5 to 80%[7–15] (Table 4). The data from smaller studies in India are consistent with our results, with studies from Lucknow and Dehradun reporting the use of methotrexate in 75–100% and limited use of biologics.[16,17]

Expectedly, a combination of csDMARDs was more commonly prescribed than monotherapy. Combinations of two csDMARDs were more common than triple-DMARD combination therapy. Interestingly, among the csDMARDs, after methotrexate and hydroxychloroquine, leflunomide was preferred over sulfasalazine, both as part of dual and triple combination therapy (along with methotrexate). This is consistent with a study from Karnataka, which found the dual combination of csDMARDs to be the most prescribed (68.1%).[18]

The low use of biologics in our study (2%) is likely due to their higher price compared to csDMARDs (even for biosimilars). Although it is difficult to compare different studies from other parts of the world due to their varying publication years, it seems that the use of biologics was much lower than in most other countries, where it varied from 15 to 49% (except for low usage in Korea and Poland) (Table 4). Obviously, the use of biologics also depends on the provision of these medications by a nationalized health system or a high rate of health insurance that covers biologics. In India, the majority of patients are self-funded for purchasing therapy, with few having health insurance. A similar low use of biologics has been found in most other publications on RA from India.[16–18]

Interestingly, in our cohort, the rate of tsDMARDs, although higher than biologics, was still low. Currently, tofacitinib and baricitinib are licensed in India; however, only tofacitinib is

Table 3: cDMARDs used as part of mono or combination therapy (*n* = 3289)

Type of use of cDMARDs	*n (%)*
Monotherapy	957 (29)
Methotrexate	699 (17)
Hydroxychloroquine	178 (4)
Leflunomide	52 (1)
Sulfasalazine	28 (0.5)
Dual therapy	1739 (53)
Methotrexate + hydroxychloroquine	875 (22)
Methotrexate + leflunomide	661 (16)
Hydroxychloroquine + leflunomide	63 (2)
Hydroxychloroquine + sulfasalazine	68 (2)
Methotrexate + sulfasalazine	52 (1)
Leflunomide + sulfasalazine	20 (1)
Triple therapy	536 (16)
Methotrexate + hydroxychloroquine + leflunomide	323 (8)
Methotrexate + hydroxychloroquine + sulfasalazine	161 (4)
Methotrexate + leflunomide + sulfasalazine	34 (1)
Hydroxychloroquine + leflunomide + sulfasalazine	18 (0.5)
Quadruple therapy (all four)	57 (1)

Table 4: Current use of DMARDS across different countries in recent publications compared to the current study

Site	*Current (%)*	*Quest RA 2007*[7]	*Ziegler 2010*	*Eriksson 2013*[10]	*Batko 2017*[11]	*Won 2018*[12]	*Thomas 2018*[13]	*Nakajima 2020*[8]	*Pombo-Suarez 2021*[14]	*Grellman 2021*[15]
	India N = 3550	*Worldwide N = 5499*	*Germany N = 3323*	*Sweden N = 10094*	*Poland N = 1957*	*Korea N = 14081*	*Greece N = 2491*	*Japan N = 825772*	*Spain N = 859*	*Germany N = 2171*
DMARD type										
CsDMARDS	93	>62.5	84.6	84		97.77	82	95	79.3	
Biologics	2	19	16.2	15	2.94	2.09	42	22.9	48.7	
tsDMARDS	6							0.9		
Corticosteroids	35	49	54.3	67	42.5	86.9	40	42.1	57.3	
csDMARD type										
Methotrexate	86	62.5	56.4	74	80.1	57.9	77	63.4		38.3
Hydroxychloroquine	52		7.3		4.14	73.04	18			
Leflunomide	37		12.2		7.03	13.53	17			10.1
Sulfasalazine	14		7.8		14.43	31.16	1	24.9		7.4

available as a generic medicine at a reasonably low cost since 2020. Their current low rates may be related to the recent introduction of generics at a reasonable price and perhaps the apprehension of physicians to prescribe a new drug. It is possible that the share of tsDMARD prescriptions may increase in the future.

This study has many limitations, the primary one being that it was cross-sectional, thus making an association between drug treatment and disease activity not attempted. Although this study was multicentric with the inclusion of large rheumatology centers in the north, south, and west of India, there were no centers in the east or northeast of India. Strengths of our study include a large cohort and a mix of private, charitable, and government-funded hospitals. In conclusion, csDMARDs remain the mainstay of therapy for patients with RA in India, with methotrexate being prescribed in the majority, either alone or in combination. Biologics and targeted synthetic DMARDs were found to be low in this study.

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ORIGINAL ARTICLE

Proposed Algorithm for the Diagnosis and Management of Functional Dyspepsia in India

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Abstract

Disorders of gut–brain interaction (DGBI), formerly known as functional bowel disorders, encompass a diverse array of conditions and symptoms that may manifest in different parts of the gastrointestinal tract. Some of the most prevalent DGBIs include functional dyspepsia, irritable bowel syndrome, functional constipation, functional diarrhea, and functional bloating and distension. Around 80% of patients with dyspepsia have no identifiable organic cause and are labeled as functional dyspepsia. Globally, functional dyspepsia prevalence ranges from 11 to 30%. In India, physicians encounter 20–40% of patients with functional dyspepsia, with variations attributed to diagnostic criteria and regions. However, Indian clinical guidelines for functional dyspepsia are currently lacking. Fifty gastroenterologists participated in focus group discussions to create an India-specific algorithm for the diagnosis and management of functional dyspepsia. After several national and regional discussions among groups of gastroenterologists across India, an algorithm was finalized for careful and thorough clinical evaluation of patients presenting with chronic dyspeptic symptoms. This guidance document highlights the role of endoscopic evaluation and *Helicobacter pylori* infection in the diagnosis of functional dyspepsia, along with the role of proton pump inhibitors (PPIs) and prokinetics in its treatment. The experts also reviewed the use of several prokinetics and provided their views on the choice of drugs for varied clinical presentations of functional dyspepsia. Among prokinetics, the experts believed that itopride was the preferred and relatively safer option for the treatment of functional dyspepsia.

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Introduction

Disorders of gut–brain interaction (DGBI), formerly known as functional bowel disorders, encompass a diverse array of conditions and symptoms that may manifest in different parts of the gastrointestinal tract. Some of the most prevalent DGBIs include functional dyspepsia, irritable bowel syndrome, functional constipation, functional diarrhea, and functional bloating and distension.[1] Dyspepsia is characterized by a collection of symptoms affecting the gastroduodenal region of the gastrointestinal tract, including epigastric pain, epigastric burning, postprandial fullness, or early satiety for 6 months or more. It is noteworthy that around 80% of individuals diagnosed with dyspepsia exhibit no identifiable structural cause for their symptoms, indicating the presence of functional dyspepsia.[2] Globally, the prevalence of functional dyspepsia has been reported to fall within the range of 11–30%. Similarly, a survey conducted in India indicated that approximately two-thirds of the participating physicians encountered 20–40% of patients with functional dyspepsia in a month, with 10–30% of these patients being newly diagnosed.[3] The observed differences in the reported prevalence of dyspepsia could be attributed to variations in the diagnostic criteria employed or to actual disparities in prevalence across different regions of the country.[4] Despite observing a significant prevalence of functional dyspepsia in Asian populations, most of the defining characteristics of functional dyspepsia have been derived primarily from data from Western regions.[5] In the clinical setting, symptoms experienced by patients with functional dyspepsia are influenced by multiple factors, including dietary constituents and body habitus. These factors are known to exhibit variations between Western and Asian populations. Additionally, cultural attitudes, healthcare-seeking behavior, and resource utilization differ between populations, and these factors are important indicators of the impact of functional dyspepsia.[6] These variations lead to notable differences in its global epidemiology and clinical characteristics. An Indian study on health-related quality of life (HRQOL) assessment in patients with functional dyspepsia showed poor HRQOL with severe dyspepsia and longer duration of symptoms.[7] Another study on various functional gastrointestinal disorders (FGIDs) among students at a north Indian college pursuing medical, nursing, and humanities courses observed that risk factors for occurrence of functional dyspepsia included female gender, enrollment in a medical course, consumption of junk food, a nonvegetarian diet, consumption of tea/coffee, and anxiety.[8] Emphasizing Indian clinical data becomes pivotal in understanding common pathogenetic factors specific to the country. Additionally, guidelines and recommendations catering to the Indian setup are currently missing. Recognizing the significance of addressing this extensively prevalent gastrointestinal disorder, a set of focus-group discussions among 50 gastroenterologists was conducted to reach consensus on an algorithmic approach for the diagnosis and management of functional dyspepsia, specifically tailored for primary care physicians in India.

Five group discussions were conducted to develop an algorithm for diagnosing and managing functional dyspepsia in India, starting at the primary healthcare level. A group of 10 gastroenterologists from across India first formulated an initial framework for the algorithm. Sections of the algorithm that exhibited ambiguity or lacked consensus were further discussed in subsequent regional meetings. Three regional meetings were conducted, each involving 12 experts from distinct regions of India: the South region, the North and West regions, and the East region. During these meetings, experts shared their opinions based on clinical experience and practices in their respective regions. Based on the inputs gathered during the regional meetings, the algorithm was modified to incorporate all views. Subsequently, some members from the first meeting and a few others further discussed and finalized the algorithm. A consensus was successfully

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achieved for all components within the algorithm, including history and physical examination, alarm symptoms, laboratory investigations, endoscopy, *Helicobacter pylori* (*H. pylori*) test, and the management strategy for the disease.

Diagnosis of Functional Dyspepsia

The diagnosis of functional dyspepsia relies on identifying characteristic dyspeptic symptoms, reviewing the patient's medical history, and excluding other upper gastrointestinal tract and upper abdominal conditions that may manifest similar dyspeptic symptoms.[5]

Patients experiencing chronic dyspepsia may present with bothersome symptoms categorized into two main subtypes: epigastric pain syndrome (EPS), characterized by epigastric pain and epigastric burning, and postprandial distress syndrome (PDS), characterized by early satiety, bloating, nausea, vomiting/retching, and decreased appetite. The Rome IV criteria require the absence of any evidence suggesting a structural disease leading to these symptoms and that they have persisted for the last 3 months, with an onset at least 6 months prior to diagnosing functional dyspepsia.[9]

History-taking and Clinical Examination

A variety of organic, systemic, or metabolic conditions are known to cause symptoms resembling those observed in functional dyspepsia, including peptic ulcer disease, gastrointestinal and hepatobiliary tract cancers, parasitic infestations, chronic pancreatic diseases, hyperthyroidism, hypothyroidism, chronic renal failure, electrolyte imbalances, and the potential influence of medications.[5] The experts believed that thoroughly evaluating and ruling out such potential causes of the above-mentioned gastrointestinal symptoms is of utmost importance (Fig. 1). It is also crucial to help identify the presence of any alarm symptoms (Fig. 2) by conducting detailed and careful history-taking.[5,10–13]

The presence of alarm symptoms warrants prompt investigations, wherein an upper gastrointestinal tract endoscopy would be required.[5,11] The experts believed that in patients aged over 45 years, various organic impairments, including malignancy, may cause chronic dyspeptic symptoms; and in areas with a high prevalence of gastric malignancy, an age over 37 years may indicate the need to screen for malignancy.[5,11] Similarly, the causes for recurrent vomiting, weight loss, dysphagia, evidence of gastrointestinal bleeding, hematemesis, or melena should be investigated promptly.[5] Immediate screening is recommended for patients with a family history of malignancy to rule out malignancy as a potential cause of chronic dyspeptic symptoms.[5] In addition to the abovementioned factors, new-onset dyspepsia can also be considered an alarm sign in patients above 40 years of age in areas with a high prevalence of upper gastrointestinal tract malignancy, and in patients over 45 and 50 years in areas with intermediate and low prevalence, respectively.[5]

The experts recommended checking for signs of anemia, abdominal lump, and lymphadenopathy during the physical examination of patients. Additionally, a positive Carnett's sign would indicate that the pain originates from the abdominal wall.

- Systemic illnesses like cardiac diseases*
- Metabolic diseases like diabetes and thyroid, and calcium-related metabolic diseases*
- Small intestinal bacterial overgrowth, giardiasis
- Medication and drug interactions related symptoms
- Fatty liver*, gallstones, chronic pancreatitis
- Parietal etiology of abdominal pain*
- If postprandial symptoms, rule out gastroparesis by looking for diabetes and neuropathic complications
- Lactose intolerance
- Connective tissue disorders

Fig. 1: Conditions to rule out before diagnosing functional dyspepsia[5,10–13]; *Opinion of the Indian expert gastroenterologists

- Age >45 years (in areas with a high prevalence of gastric cancer: >37 years)*
- Recurrent vomiting
- Weight loss
- Dysphagia
- Evidence of bleeding
- Family history of cancer
- Hematemesis*
- New onset dyspepsia in subjects
  - >40 years of age in a population with a high prevalence of upper gastrointestinal malignancy and
  - >45 and >50 years in populations with intermediate and low prevalence of upper gastrointestinal malignancy, respectively

Fig. 2: Alarm symptoms to investigate in patients with dyspepsia[5,11]; *Opinion of the Indian expert gastroenterologists

Investigations

The Asian consensus report states that most patients with dyspeptic symptoms can be diagnosed with functional dyspepsia based on their clinical symptoms and results of upper gastrointestinal tract endoscopy. Besides routine laboratory tests, some cases may require additional investigations, such as upper abdominal ultrasonography (particularly in regions with a high incidence of liver cancers) and stool examination for parasites and occult blood if needed.[5] The experts recommended conducting basic laboratory tests, such as complete blood count (CBC), serum electrolytes, fasting blood glucose (FBG), renal function tests, thyroid function tests, liver function tests, stool tests, and an ultrasonography examination to help detect or rule out the underlying cause of dyspeptic symptoms to reach a closer diagnosis of functional dyspepsia.[5]

Depending on the presence or absence of alarm symptoms, patients presenting with dyspeptic symptoms can undergo investigations to identify the probable source of their symptoms or be managed with empirical treatment based on their predominant symptoms.[11,14] Diagnosing functional dyspepsia according to the definition by the Rome IV criteria implies that potential underlying organic disorders have been excluded with an endoscopy.[11] The consensus reached on endoscopy is similar to various other guidelines that have universally recommended timely upper gastrointestinal tract endoscopy for patients aged over 45–60 years with dyspeptic symptoms to rule out neoplasia and determine *H. pylori* status through biopsies. Additionally, endoscopy is necessary for younger patients who present

with alarm features.[11] The experts believed that endoscopy should be the first choice of investigation in patients who elicit any of the alarm signs.[10] They also recommended endoscopy for patients without alarm symptoms who have not responded to previous treatment with proton pump inhibitors (PPIs).[15] Abnormal findings during endoscopy may indicate the organic cause of the dyspeptic symptoms, whereas a normal endoscopy can lead to the diagnosis of functional dyspepsia after ruling out *H. pylori* etiology.[5]

In an Asian consensus report, *H. pylori* eradication was strongly advised even in the absence of dyspeptic symptoms, particularly in certain Asian countries with a high prevalence of gastric cancer.[5] Similarly, a European consensus report also recommended testing for *H. pylori* in all patients with dyspeptic symptoms, either through noninvasive methods or gastroscopy. The report mentioned that patients with dyspepsia who test positive for *H. pylori* gastritis should be classified as having functional dyspepsia only if their symptoms persist for 6–12 months after *H. pylori* eradication. On the other hand, patients with dyspepsia and *H. pylori*-negative gastritis should be considered to have functional dyspepsia. A subset of patients with dyspepsia who exhibit a normal endoscopy and are *H. pylori* positive may show improvement in symptoms after eradication therapy, and this is referred to as *H. pylori*-associated dyspepsia.[11] The experts mentioned that rapid urease test (RUT) or gastric biopsies can determine the presence of *H. pylori* infection. However, the experts noted that with limited data to validate results of the RUT, it may be difficult to reliably reassess the presence of *H. pylori* or its eradication. Among the other *H. pylori* tests, the C13 urea breath test is expensive and not available in India, while the C14 breath test was banned due to radiation hazards. When results from C13 to C14 urea breath tests were compared, there were discrepancies, with no validation available.

The experts believed that *H. pylori* tests can be performed during endoscopy, and if the results are positive, *H. pylori* eradication therapy should be initiated.[11] The response to the eradication therapy should be assessed by retesting for *H. pylori* after 30 days of treatment.[16] If the dyspeptic symptoms persist despite a negative retest for *H. pylori*, a diagnosis of functional dyspepsia is more likely.[11] Patients who show improvement of symptoms along with a negative retest are referred to as having *H. pylori*-associated dyspepsia.[11] In some patients, the *H. pylori* retest may be positive posteradication therapy, indicating a resistant *H. pylori* infection. The experts advised prescribing a modified regimen of eradication therapy to such patients and a further re-test after 30 days to confirm the diagnosis of *H. pylori*-associated dyspepsia.[16,17] The experts were of the opinion that additional investigations, such as plain X-ray abdomen, gastric scintigraphy, electrogastrography (EGG), computed tomography scan, celiac serology (only in areas with a high prevalence of celiac disease), or endoscopic deep duodenal biopsies for histopathology to rule out eosinophilic enteritis, can also aid in supporting the diagnosis of functional dyspepsia or ruling out other causes of chronic dyspeptic symptoms.[5,18,19]

Management of Functional Dyspepsia

Managing symptoms of functional dyspepsia can pose difficulties due to the presence of overlapping disorders and the involvement of various mechanisms, including gastric acid hypersecretion, visceral hypersensitivity, or gastroduodenal dysmotility.[20]

Acid Suppressing and Neutralizing Therapies

Treatment with PPIs has shown significant benefits in patients with functional dyspepsia. Their effect, however, may be limited to patients with symptoms of EPS, while those with symptoms of PDS may not respond to PPIs.[11,21] The role of H2 receptor antagonists (H2RAs) in functional dyspepsia remains controversial, despite evidence sometimes suggesting that they can be efficacious in a subset of patients with functional dyspepsia. H2RAs are not recommended as first-line treatment for functional dyspepsia; however, they are widely used in clinical practice, particularly when PPIs are ineffective.[20] Alginates with antacids may be useful in reducing dyspeptic symptoms such as epigastric pain.[22] The experts believed that acid-neutralizing/suppressing therapy in functional dyspepsia may include the use of PPIs, H2 receptor antagonists (H2RAs), alginates, and antacids. Dietary advice and medications that improve digestive function are more likely to be beneficial in patients with symptoms of PDS that show abnormal gastric function.[22] Tailoring dietary advice to the specific functional dyspepsia subtype, including a low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet for postprandial distress and bloating, could significantly improve symptoms and quality of life.[23]

Prokinetics

A review addressing prokinetic efficacy revealed that in PDS, dopamine receptor antagonists including metoclopramide, domperidone, levosulpiride, and itopride exhibited responder rates of approximately 59–81%, serotonin receptor agonists such as prucalopride from 32 to 91%, and muscarinic receptor antagonists such as acotiamide ranged from 31 to 80%.[24] The experts agreed that itopride improves gastrointestinal motility in functional dyspepsia and is reported to be efficacious and well-tolerated.[25] It was found comparable in efficacy to domperidone in relieving symptoms and was devoid of cardiac side effects.[26] For patients with nonulcer dyspepsia, a study reported higher complete symptomatic relief rates with itopride (81%) compared to domperidone (70%). Another study demonstrated significantly greater moderate to complete symptomatic relief with itopride (90%) in comparison to levosulpiride (83.3%) for patients with nonulcer dyspepsia ($p = 0.0146$).[24] Among various prokinetics used for functional dyspepsia, itopride may be the favorable choice for vulnerable groups, including the elderly and patients with diabetes.[24] It produces no undesirable cardiac effects due to its lack of affinity for the 5-HT4 receptors in the heart and no extrapyramidal side effects or hyperprolactinemia.[27] Acotiamide is useful for the relaxation of the fundus in PDS.[28] However, a clinical study reported that acotiamide has limited efficacy in patients with EPS and gastric acid hypersecretion.[29] Baclofen is known to act by inhibiting the postprandial increase in TLESRs.[30]

For patients with the EPS subtype of functional dyspepsia, the experts suggested first-line treatment typically with a PPI, while a prokinetic agent is considered as a second-line therapy.[10,11] Neuromodulators can be added if both the first-line and the second-line treatments are inadequate or fail to improve symptoms.[14] The PDS subtype of functional dyspepsia can be treated with prokinetics as first-line therapy, with the addition of a PPI and neuromodulators as second-line and third-line treatment, respectively.[10] The EPS-PDS overlapping subtype of functional dyspepsia can be treated using a combination of PPI and prokinetics, with the option of neuromodulators if required. Treatment response should be assessed in 4–6 weeks and modified if needed.

The experts concluded that prokinetics including itopride, cinitapride, acotiamide, baclofen, domperidone, levosulpiride, prucalopride, and metoclopramide may be used in patients with functional dyspepsia. For

delayed gastric emptying, experts preferred prokinetics such as itopride, levosulpiride, and domperidone and believed that levosulpiride may not be the prokinetic of choice for the elderly and should not be used in those with a family history of extrapyramidal disorders like Parkinson's disease. Caution should be exercised with the use of levosulpiride. Patients should be counseled and checked for extrapyramidal side effects in follow-up, especially in the older age groups. Immediate discontinuation of levosulpiride is advised if any warning signs are noted.[31] Domperidone and levosulpiride can potentially cause galactorrhea as a side effect, and patients must be informed about it.[32] Therefore, the experts considered itopride as a relatively safer option.

The experts considered acotiamide as the preferred choice only for impaired fundic accommodation. A water load test performed before an EGG can help identify fundic accommodation defect, indicated by a patient's inability to drink more than 300 mL of water at a time. Experts, however, believed that acotiamide is slower in action, as compared to other prokinetics, and relief is usually seen after 1 or 2 weeks. Overall, among all the prokinetic options, itopride was the preferred option as agreed upon by the experts.

Neuromodulators and Psychotherapy

Neuromodulators, including antidepressants for the relief of pain, may be useful in patients with EPS.[14] Amitriptyline, mirtazapine, selective serotonin reuptake inhibitors (SSRIs), and serotonin–norepinephrine reuptake inhibitors (SNRIs) may be beneficial, according to experts, as third-line therapy for functional dyspepsia. Psychotherapy in the form of hypnotherapy and lifestyle modifications, such as incorporating yoga and exercise into the daily routine, may benefit patients with functional dyspepsia. The various treatment options are listed in Figure 3.

Proposed Algorithm for the Diagnosis and Management of Functional Dyspepsia

Based on the focus-group discussions, the experts developed the algorithm shown in Figure 4 to help physicians in India in the diagnosis and management of functional dyspepsia. The algorithm features key steps that include a thorough initial evaluation of the patient, identification and ruling out of alarm symptoms, followed by endoscopy and *H. pylori* testing as the two key investigations that can help reach the diagnosis of functional dyspepsia. Considering the high prevalence of *H. pylori* infection in the Indian population, *H. pylori*-positive patients and their management with eradication therapy are also part of the algorithm. Patients can be managed with empirical pharmacological treatments based on their predominant dyspeptic symptom or by classifying the type of functional dyspepsia into either EPS, PDS, or EPS-PDS overlap. Treatment options include PPIs, prokinetics, and neuromodulators, among others listed in Figure 3.

Conclusion

Functional dyspepsia exhibits variations in Western and Eastern populations concerning sociodemography, lifestyle habits, dietary preferences, response to *H. pylori* eradication, and economic implications. Thus, despite being prevalent worldwide, its epidemiology and clinical characteristics differ significantly between these populations. Emphasizing data from the Indian clinical setting is important, as the Indian perspective will be useful for understanding the common pathogenetic factors here. To provide relevant guidance for primary care physicians in India, this consensus statement aims to articulate the experience and views of Indian experts. We anticipate that this statement will facilitate prompt and accurate management of functional dyspepsia, thereby alleviating its socioeconomic burden in the country.

Author Contributions

All the authors contributed to the acquisition and summarizing of literature, conduct of the focus-group discussions, development of consensus and the proposed algorithm, and review of all drafts of the manuscript, including the draft approved for submission.

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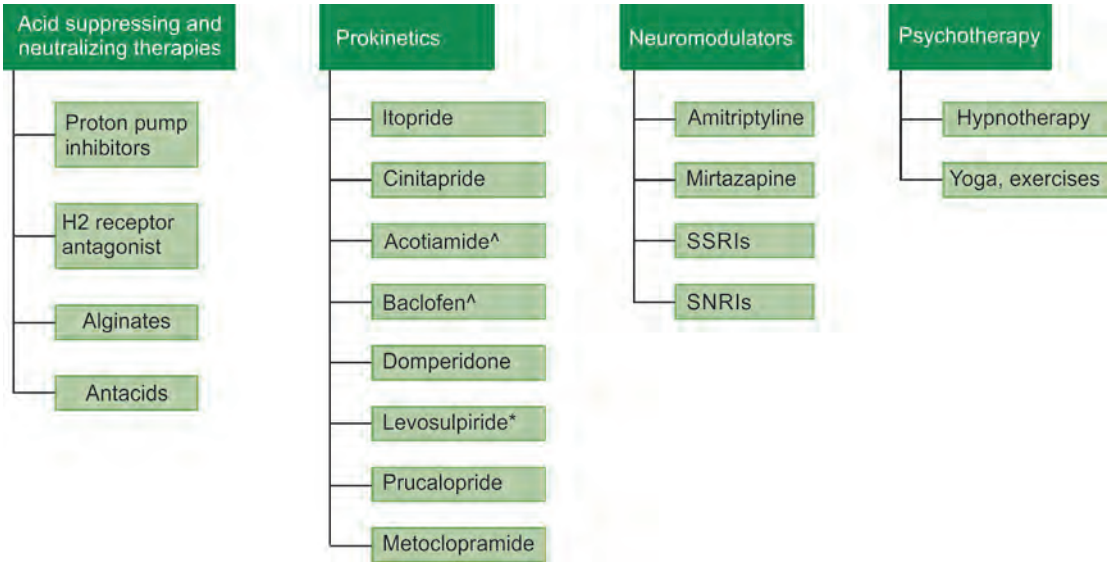

Fig. 3: Treatment options for patients with functional dyspepsia; ^Useful for fundus relaxation/PDS type of FD only. *Caution is advised with the use of levosulpiride. Counsel patients and follow up to check for extrapyramidal side effects, especially in older populations; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin and norepinephrine reuptake inhibitors

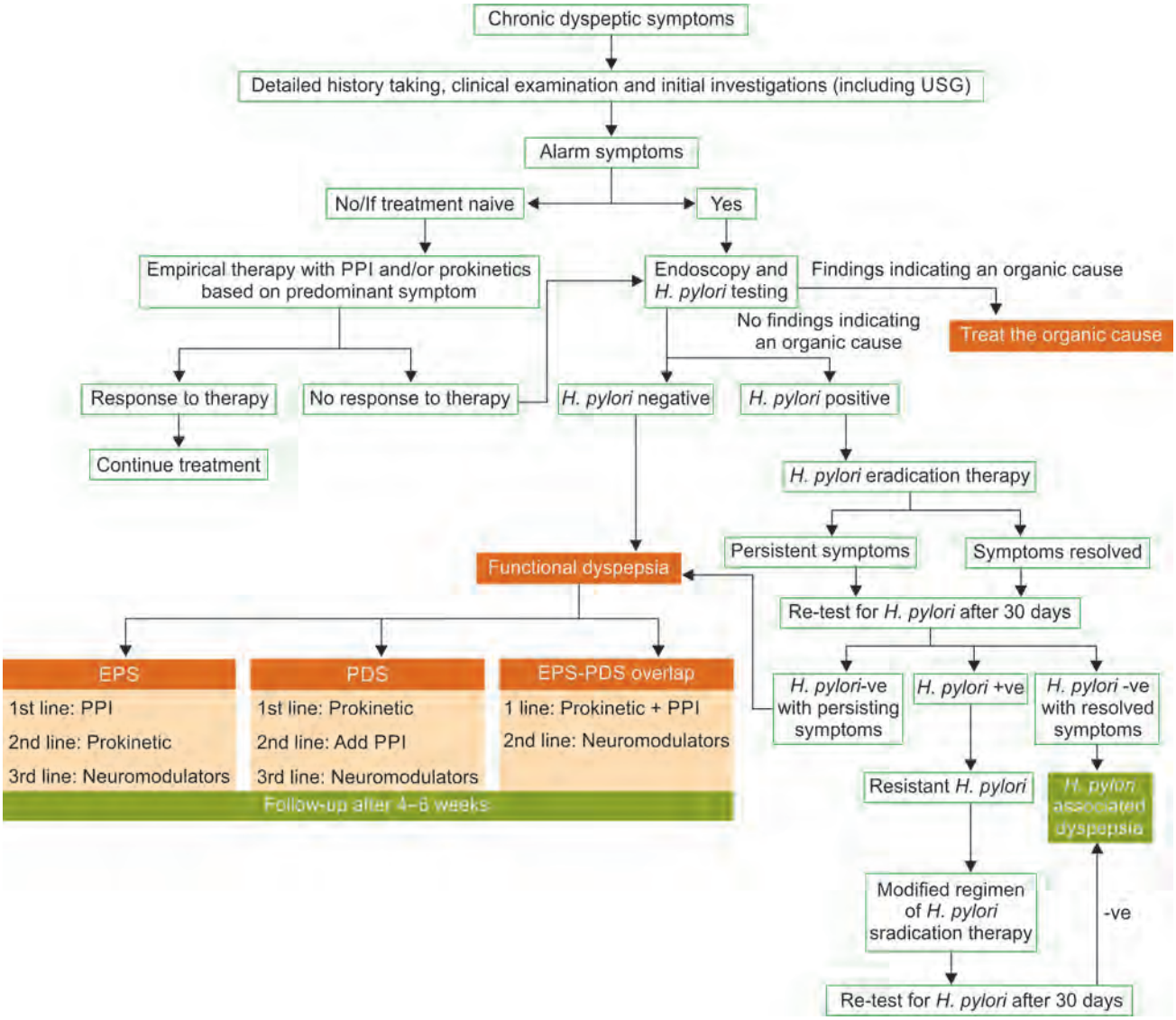

Fig. 4: Algorithm developed for the diagnosis and management of functional dyspepsia; EPS, epigastric pain syndrome; *H. pylori*, *Helicobacter pylori*; PDS, postprandial distress syndrome; PPI, proton pump inhibitors

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ORIGINAL ARTICLE

To Establish the Utility of Neck Circumference as a Novel and Simple Risk Marker for Detection of Metabolic Syndrome and Cardiometabolic Risk Factors in Indians

Nikita Sahay[1], Raviraj V Acharya[2], Kritika Sahay[3], Manisha Sahay[4*]

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Abstract

Introduction: Waist circumference (WC) is used as a measure of metabolic syndrome (MeS); neck circumference (NC) can predict MeS. It is simpler to measure and may provide an indication of obstructive sleep apnea (OSA).

Materials and methods: NC was measured. The mean NC was correlated with the markers of MeS and sleep apnea.

Results: A total of 183 participants were recruited in the study. The average age was 48.13 ± 13.3 years in men and 48.09 ± 11.1 years in women. The mean body mass index (BMI) was 26.42 ± 4.69 kg/m^2 in men and 28.25 ± 4.92 kg/m^2 in women. The mean WC in men and women were 91.1 ± 12.92 cm and 90.86 ± 12.7 cm, respectively, while the NC was 38.4 ± 6.60 cm in men and 33.9 ± 2.40 cm in women. MeS was diagnosed in 17.6% of men and 12.7% of women. Sleep apnea was noted in 33.1% of males and 29.2% of females. There was a positive correlation between the NC and systolic blood pressure (SBP) (r = 0.316 in males), fasting blood glucose (FBG) (r = 0.522 in males and 0.263 in females), triglyceride (TG) (r = 0.172 in males; 0.320 in females), while high-density lipoprotein cholesterol (HDL-C) showed a negative correlation in males and females. There was a positive correlation of NC with sleep duration in both males and females (r = 0.346 in males and 0.344 in females). Those with a NC of <35 cm had a sleep score of 7, while those with a NC of >35 cm had a score of 15, showing poor sleep quality.

Conclusion: NC was comparable to WC and waist-hip ratio (WHR) for cardiometabolic risk factors and also showed a good association with sleep apnea.

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Introduction

Metabolic syndrome (MeS) encompasses various biochemical and physiological parameters. MeS is an important risk factor for heart disease and type 2 diabetes, as defined by the International Diabetes Federation.[1] MeS is an important cause of increased morbidity and mortality, especially in the Asian population. Data from various studies have also shown that the presence of MeS poses a greater cardiovascular risk in women compared to men.[2] MeS further highlights the importance of the distribution of fat; that is, heart disease is more likely to be associated with abdominal fat compared to fat in other places, such as the hips. Central obesity and insulin resistance play a pivotal role in the above pathogenesis.

Traditionally, markers like waist circumference (WC), waist-hip ratio (WHR), and hip circumference (HC), along with body mass index (BMI), were used as markers for obesity and MeS.[3] Some studies have also looked at triceps skinfold thickness as a marker of MeS.[4] All these clinical markers prove to be useful in screening patients at high risk for MeS, especially in low-income countries.

Obstructive sleep apnea (OSA) is also an important cardiometabolic risk factor. It occurs due to the deposition of fat in the neck region. However, this does not reflect in the WC, HC, or WHR. Hence, a novel concept of neck circumference (NC) has emerged, which also takes into account the fat deposition in the neck.

The present markers of MeS can have some fallacies and may be difficult to measure. In some cases, especially in obese patients, WC may not be reliable. Also, doing a lipid profile would be time-consuming. Keeping this in mind, various other markers have been described in various studies in adults as well as children.[5–9] The neck, from man's earliest days, is the most decorated part of the body. But it holds importance in the field of clinical medicine as well. It has been considered that the NC can be used as a marker in the detection of MeS and has the potential to replace the use of WC as a diagnostic marker.[10–14] Many studies on NC have been carried out in different ethnic groups. However, very few studies have been done in India focusing on this aspect. Also, there is a good correlation between OSA and NC, which is an advantage over other traditional anthropometric markers.[15]

Aims and Objectives

- To determine the utility of NC as a marker for MeS.
- To determine the relation of NC with lipid profile and blood sugar.
- To demonstrate the relation of NC to OSA in patients.
- To compare the utility of NC as a marker for MeS with other traditional anthropometric parameters like WC and WHR.

Materials and Methods

It is a cross-sectional study, conducted on the patients visiting the outpatient department of Kasturba Medical College.

Inclusion Criteria

- Age 30–60 years.
- Those willing to give informed consent.

Exclusion Criteria

- Patients with thyroid disorders.
- Patients with neck malignancy.
- Patients with any neck swellings such as goiter.
- Patients unwilling to give informed consent.

Written informed consent was taken from the study population. The patients were asked to observe an overnight fasting period of 8 hours. NC was measured in the Frankfurt horizontal plane. A single investigator asked the subjects

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to stand barefoot in an upright position, look ahead, and keep their shoulders relaxed. A plastic tape (calibrated weekly) was used to measure NC (measured to within 0.5 mm). The upper border of the tape was placed just below the Adam's apple and at right angles to the neck. Weight was measured using a digital scale to within 0.1 kg with loose clothing. A stadiometer (least count 0.1 cm) was used to measure height. WC was measured halfway between the lowest rib and the uppermost point of the iliac crest, and HC was measured at the level of the great trochanters.

The skin fold thickness (SFT) was measured over the triceps using a Harpenden caliper.

Body mass index was derived using the weight and height in kg/m^2 and WHR by dividing the WC by the HC.

Blood pressure (BP) was measured in the right arm in the sitting position after 5 minutes of rest using a calibrated sphygmomanometer. The subjects' various blood parameters were recorded from their files. Blood samples were taken, and processing was done in the biochemistry laboratory of the hospital. Blood sugar was determined by the glucokinase method. An enzymatic calorimetric method was used to measure the total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C). The selective inhibition method was used to measure high-density lipoprotein cholesterol (HDL-C). The diagnosis of MeS was as per IDF criteria, that is, WC >90 cm in males and >80 cm in females (South Asians) was used to define central obesity. This measure, along with any two of the below-mentioned parameters:

- Triglyceride level >150 mg/dL (or on treatment for hypertriglyceridemia).
- High-density lipoprotein cholesterol <40 mg/dL in males and <50 mg/dL in females (or on treatment).
- High BP >130/85 mm of mercury (or if on medication to treat high BP).
- High fasting blood sugar ≥100 mg/dL (or if on anti-diabetic drugs).

A detailed sleep history was taken to identify sleep apnea using the Epworth Sleepiness Scale.[15]

Statistical Methods

Mean and standard deviation were used to express continuous variables, while the discrete variables were expressed as frequencies (percentages). Continuous variables were analyzed using Student's *t*-test or ANOVA. The Kolmogorov–Smirnov test was used to test normality. Mann–Whitney *U* or Kruskal–Wallis tests were used to compare the nonparametric variables, while categorical variables were compared using the Pearson test or Fisher's exact test. Logistic regression analysis was used to evaluate the association of cardiometabolic risk factors with NC. $p < 0.05$ was considered statistically significant. Epi Info™ Version 7.1, Division of Health Informatics and Surveillance, Centers for Disease Control, Atlanta, USA, was used for statistical analysis.

Before starting the study, Ethics Committee approval was taken from the Institution's Committee.

Results

A total of 183 participants aged 30–60 years participated in the study, of which 101 were males and 82 were females. Table 1 shows the anthropometric and metabolic parameters of the study subjects. The mean age was 48.13 ± 13.3 years in men and 48.09 ± 11.1 years in women. The mean BMI was 26.42 ± 4.69 kg/m^2 in men and 28.25 ± 4.92 kg/m^2 in women. The mean WC in men was 91.1 ± 12.92 cm, and in women, WC was 90.86 ± 12.7 cm. The mean NC was 38.4 ± 6.60 cm in men and 33.97 ± 2.40 cm in women.

Table 1: Demographics and lab parameters

	Male (n = 101)	*Female (n = 82)*
Age (yrs)	48.13 ± 13.3	48.09 ± 11.1
Height (cm)	160.2 ± 7.2	153.07 ± 5.1
Weight (kg)	74.76 ± 13.7	66.12 ± 10.9
NC (cm)	38.4 ± 6.60	33.97 ± 2.40
WC (cm)	91.1 ± 12.92	90.86 ± 12.7
HC (cm)	96 ± 7.29	101.74 ± 9.18
BMI (kg/m^2)	26.42 ± 4.69	28.25 ± 4.92
WHR	0.94 ± 0.06	0.88 ± 0.55
SBP (mm Hg)	133.1 ± 14.68	121.83 ± 16.35
DBP (mm Hg)	70 ± 12.02	77.89 ± 10.82
TG mg/dL	173.22 ± 43.17	162.04 ± 19.97
TC mg/dL	191.71 ± 46.6	189.31 ± 51.84
HDL mg/dL	40.79 ± 11.85	41.97 ± 13.19
Glucose mg/dL	119.23 ± 22.3	120 ± 30.2

Metabolic syndrome was diagnosed in 17.6% of men and 12.7% of women. High BP was diagnosed in 38.48 and 25.34% of men and women, respectively. Hyperglycemia was found in 33.9% of men and 28.8% of women. Hypertriglyceridemia was found in 28.76% of men and 26.5% of women. Decreased HDL cholesterol was found in 22.6% of males and 23.2% of females. Increased LDL cholesterol was detected in 35.6% of males and 33.8% of females. Sleep apnea was noted in 33.1% of males and 29.2% of females.

Neck circumference correlated positively with systolic blood pressure (SBP) (r = 0.316 in males), FBS (r = 0.522 in males and 0.263 in females), and TG (r = 0.172 in males; 0.320 in females), while there was a negative correlation of NC with HDL-C in both sexes (Table 2). NC was positively correlated with sleep duration in both males and females (r = 0.346 in males and 0.344 in females). Those with a NC <35 cm had a sleep score of 7, while those with a NC >35 cm had a score of 15, showing poor sleep quality.

Neck circumference was comparable to WC and WHR for cardiometabolic risk factors and also showed a good association with sleep apnea.

Table 2: Correlation between anthropometry and cardiometabolic risks

	WC (cm)	*NC (cm)*	*BMI (kg/m^2)*	*HC (cm)*	*WHR*
Males					
SBP	0.372*	0.316*	0.319*	0.214	0.344*
DBP	0.220	0.104	0.183	0.142	0.203
Fasting blood glucose (FBG)	0.054	0.522*	0.085	0.036	0.568
TG	0.227	0.172	0.1229	0.0817	0.360*
HDL	0.197	–0.147	0.178	0.154	0.288
TC	0.024	0.085	0.092	0.078	0.075
LDL	0.238	0.041	0.272	0.133	–0.02
Females					
SBP	0.235	–0.05	0.091	0.143	0.187
DBP		0.035	–0.017	0.172	–0.04
FBG	–0.115	0.263	0.098	0.112	0.02
TG	0.131	0.32	0.194	0.181	0.216
HDL	0.070	–0.082	0.033	0.219	0.002
LDL	0.063	0.22	–0.016	0.185	0.319*

r >0.3 significant

Discussion

The aim of this study was to determine if there was any association of NC with cardiometabolic risks and also to compare NC with the traditional anthropometric indices as a predictor of MeS. It was a cross-sectional study involving 183 patients from India. The study demonstrated a significant association of NC with cardiometabolic risk factors and showed that NC can be used to predict cardiometabolic risks in both males and females.

Neck Circumference and Metabolic Syndrome

Obesity is widely associated with metabolic disorders and a high cardiovascular morbidity and mortality, as seen in a study by Nikolopoulou and Kadoglou.[2] Traditional anthropometric markers like BMI, WC, and WHC are used to define obesity, as shown in studies from WHO, Al-Odat et al. and Gharipour et al.[16–18] However, many studies have suggested NC as a novel marker that is more practical and convenient. Parameters like a person's nutrition status, respiratory movements, and clothing can affect the WC, but these variables do not affect the NC. In a study by LaBerge et al., NC was found to be a more reliable index of central obesity.[19] In the Framingham Heart Study, involving >2,000 subjects, Preis et al.[9,10] demonstrated a positive correlation of NC with type 2 diabetes, hypertension, decreased HDL-C, and increased TG. After excluding the effect of BMI and WC, an association was observed between NC and type 2 diabetes in Zhou's study.[20] Similar findings were seen in the study by Onat et al. from Turkey.[8]

Our study showed a positive association of NC with SBP, diastolic blood pressure (DBP), TC, LDL, and TG and an inverse correlation with HDL in both males and females. This was similar to other studies in the past by Zhou et al.,[20] Ben-Noun et al.,[11] and Stabe et al.[12] NC also correlated well with the deposition of fat in the liver, as observed by Ferrannini et al.[21] Therefore, a higher NC value predicts a higher risk of cardiometabolic syndrome.

Comparison of Neck Circumference with Other Anthropometric Markers as Predictors of Cardiometabolic Risk

Studies comparing NC with other anthropometric measures have shown inconsistent results. In the study by Zhou et al., a significant association was observed between the anthropometric indices and metabolic syndrome risk factors. The authors found that among all the indices, NC had a better correlation than the WC, WHR, and BMI. Similarly, other studies by Onat et al.[8] and Yanq et al.[13] showed a good correlation between NC and cardiometabolic risk factors. However, in other studies, a weaker association with metabolic abnormalities was observed for NC as compared to the BMI, WHR, and WC, respectively.[10–12] In their study of >4,000 Chinese subjects, Zhou et al.[20] did not find NC as a superior predictor of cardiometabolic risks as compared to WC, BMI, and WHR. Dahlén et al.[22] showed that visceral fat (or central obesity) had a greater effect on the development of metabolic abnormalities than subcutaneous fat (general obesity). In studies by Ashwell et al.,[3] Seo et al.,[23] Lee et al.,[24] and Mohammadreza et al.,[25] visceral fat was quantified by WC, WHR, abdominal diameter, and visceral adiposity index. A variety of studies by Ashwell et al.[3] and Vasheqhani et al.[4] have demonstrated that these indices of visceral fat have a stronger association with metabolic abnormalities or CVD risks than BMI.

Optimal Cutoff of Neck Circumference and Cardiometabolic Risk

Zhou et al.[20] demonstrated cutoff values of NC ≥37 and ≥33 cm in Chinese males and females, respectively, for predicting MeS. Men had a higher cutoff than women. Higher cutoffs were observed in the Brazil study by Yang et al. (>40 and >36 cm in men and women, respectively).[14] The Turkish population also showed higher cutoff values of NC for the prediction of MeS in a study by Onat et al.[8] Zimmet et al. in his study[26] explained that the varying optimal cutoffs for NC may be due to differences in body size. Thus, ethnicity-specific NC measurements are needed to predict cardiometabolic abnormalities. NC was significantly associated with snoring in a study ($p < 0.05$).[27] In this study, NC also showed a good association with OSA.

In our study, we found associations between NC and cardiometabolic risk factors in both sexes. In the Indian population, NC predicted cardiometabolic risk independent of other anthropometric indices, as shown in a study by Yang et al. in a diabetic population.[14] Thus, measurement of NC might yield additional information in terms of the identification of cardiometabolic syndrome.

Limitations

The study had a few limitations. Firstly, the interpretation of the study may be flawed due to its cross-sectional design. Laboratory tests were conducted at a single visit; hence, the variability in tests could not be captured. Despite these limitations, the study was useful in identifying a simple marker for MeS. Further studies with a greater sample size and in different ethnic groups may be needed to validate our findings.

Conclusion

A significant association of NC with cardiometabolic risk factors was observed in our study beyond the classical anthropometric indices. NC is easily measured in comparison to WC and WHR. In addition, NC is not affected by ascites. NC also takes into account the neck fat, which contributes to sleep apnea.

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ORIGINAL ARTICLE

A Study Correlating the Effects of Subclinical Hypothyroidism on the Known Modifiable Risk Factors of Coronary Artery Disease in Indian Adults

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Abstract

Background: Subclinical hypothyroidism (SCH) is synonymous with thyroid failure (a milder form). It is a condition characterized by normal laboratory ranges of serum FT4 and FT3 levels, but serum thyroid stimulating hormone (TSH) levels are slightly increased above the normal range.

Objective: The leading aims and objectives of the study were: (1) establishing a correlation between the presence of modifiable risk factors of ischemic heart disease in subjects with SCH. (2) Quantification of the economic markers of ischemic heart disease in patients with SCH.

Methods: This study was accomplished at the Department of Internal Medicine, Ramakrishna Mission Seva Pratishthan, Vivekananda Institute of Medical Sciences, Kolkata, for the duration of 1 year, from March 2020 to February 2021. The study variables included history, physical examination, clinical examination, and investigations. The individuals who met the inclusion criteria set for the study were included. All the participants were informed about the study, and their informed consent was obtained. Data were analyzed using Microsoft Excel spreadsheet, followed by Statistical Package for the Social Sciences (SPSS) (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5.

Results: Of the total 80 subjects enrolled in the study, 54 were females and 26 were males. In the study sample, the mean age was 47.8 (+9) years. Different variables were analyzed, and the values obtained were recorded for statistical analysis.

Conclusion: According to the study, there is a positive correlation between established coronary artery disease (CAD) risk factors, such as hypertension, abnormal lipid profiles, and elevated body mass index (BMI), and SCH. We also noted a strong correlation between SCH and elevated levels of uric acid, fasting blood sugar (FBS), postprandial glucose test (PPBS), and hemoglobin A1c (HbA1c). As a result, early detection and management of SCH may have cardiac preventive benefits.

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Introduction

Subclinical hypothyroidism (SCH) is synonymous with thyroid failure (a milder form). It is a condition characterized by normal laboratory ranges of serum FT4, FT3 levels, but serum thyroid stimulating hormone (TSH) levels are slightly increased above the normal range (>4.2 mIU/L to <10 mIU/L).

This health condition has a prevalence of 3–8% of the population.[1] It is less common in men than in women, and its prevalence is found to exhibit an age-dependent increase. At present, the recommendations to manage SCH are giving individualized therapy based on clinical or symptom or laboratory profile for those individuals with a TSH of <10.0 mIU/L and giving levothyroxine replacement therapy for individuals with a persistently raised serum TSH of >10.0 mIU/L.

Serum TSH exhibits a logarithmic correlation with circulating thyroid hormone concentrations (a small two-fold variation in FT4 leads to a dramatic hundred-fold change in TSH secretion).[2] So, assessment of serum TSH levels is the cornerstone diagnostic test to diagnose the milder form of thyroid failure, that is, SCH, as it provides a sensitive indicator of thyroid function, even when serum thyroid hormone levels (T3 and T4) fall within the normal reference range.[3]

Thyroid hormones modulate cardiovascular hemodynamics, impacting cardiac contractility, vascular compliance, and systemic vascular resistance. The cardiovascular impact of SCH has garnered substantial attention from researchers in recent times. SCH has been linked to elevated cholesterol levels and accelerated atherosclerosis, prompting recommendations for screening and treatment to mitigate cardiovascular risk.[4] Furthermore, emerging evidence suggests a link between SCH, metabolic syndrome, and heart failure.[5]

This study proposes that addressing SCH may mitigate the risk of cardiovascular disease and mortality.[6] The principal aims of this investigation were to identify affordable coronary artery disease (CAD) markers and examine the interplay between SCH and associated risk factors.

Method and Methodology

The research project was executed within the Department of Internal Medicine at Ramakrishna Mission Seva Pratishthan, Vivekananda Institute of Medical Sciences, Kolkata, during the period of March 2020 to February 2021. The study was an observational and cross-sectional descriptive study. Approval from the Institutional Ethics Committee was obtained for the study. Patients visiting the outpatient department and those hospitalized in the Department of Medicine were recruited for the study during the study period.

Inclusion Criteria

- Patients with increased TSH levels and normal FT4 levels.
- Age of the patient ≥35 years.

Exclusion Criteria

- Patients with past history or presently under treatment for cardiac disease/hypertension/diabetes/dyslipidemia/hyperuricemia.
- Patients with family history of premature deaths caused by cardiac diseases.
- History of neck (thyroid) surgery.
- Sick euthyroid syndrome.
- Patients with history of medication use for drugs causing hypothyroidism/antihypertensives/optimal oral hypoglycaemic agents (OHA's)/insulin/hypolipidemic drugs/drugs for treatment of hyperuricemia.
- Lactation.
- Smoking.

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The study variables included history, physical examination, clinical examination, and investigations. The history included age, sex, comorbidities like cardiovascular disease, hypertension, diabetes mellitus, hyperuricemia, and dyslipidemia, as well as a family history of premature deaths caused by cardiac diseases. Physical assessment comprised anthropometric measurements of height, weight, and body mass index (BMI). Clinical examination included blood pressure, and investigations were carried out for TSH (ECLIA), FT4 (ECLIA), anti-TPO antibodies (ECLIA) (thyroid peroxidase antibody test) to diagnose a case of SCH, lipid profile [low-density lipoprotein (LDL)], high-density lipoprotein (HDL) (direct measure, PTA MgCl2-Vitros), total cholesterol (CHOD-POD), triglyceride (enzymatic end point), sugar profile—fasting blood sugar (FBS) (hexokinase, GOD-POD), postprandial glucose test (PPBS) (hexokinase, GOD-POD), hemoglobin A1c (HbA1c) [high performance liquid chromatography (HPLC)—ion exchange chromatography], and uric acid.[7,8]

Patients fulfilling the predetermined inclusion criteria were enrolled in the study, and informed consent was obtained from each participant following a thorough explanation of the research.

A total of 80 subjects were included in the research.

Data Modeling

Microsoft Excel was employed for data analysis, which was then complemented by the Statistical Package for the Social Sciences (SPSS) (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5.

Results

Of the total 80 subjects enrolled in the study, 54 (67.5%) were female and 26 (32.5%) were male. Participants' mean age in the study was 47.8 (±9) years; classification according to age-group can be seen in Table 1. The study sample had a mean BMI of 25.3 (±3). The BMI analysis of the study population is presented in Table 2. Figures 1 and 2 illustrates the distribution of systolic and diastolic blood pressure (DBP) in cases of SCH.

Table 1: Distribution of age in groups

Age in group (years)	*Frequency (no. of cases)*	*Percentage (%)*
35–39	13	16.3
40–44	17	21.3
45–49	23	28.8
50–54	11	13.8
55–59	8	10.0
60–64	1	1.3
65–69	5	6.3
70–74	2	2.5
Total	80	100.0

Bio-chemical/Serum Tests

Of the 80 subjects, 28 (35.0%) reported normal anti-TPO levels, and 52 (65.0%) patients had deranged anti-TPO levels. Normal blood uric acid levels were found in 70 (87.5%) patients, while 10 (12.5%) patients had deranged values.

A total of 31 (38.75%) patients had normal, and 49 (61.25%) patients showed abnormal total cholesterol levels. This study also investigated the triglyceride levels in patients with SCH and showed normal levels in 22 (27.5%) patients and abnormal levels in 58 (72.5%) patients. The number of patients who had deranged HDL-C was 48 (60.0%), while normal values were seen in 32 (40.0%) patients.

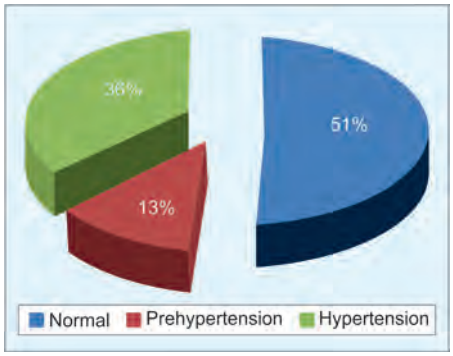

Fig. 1: Distribution of SBP in SCH cases

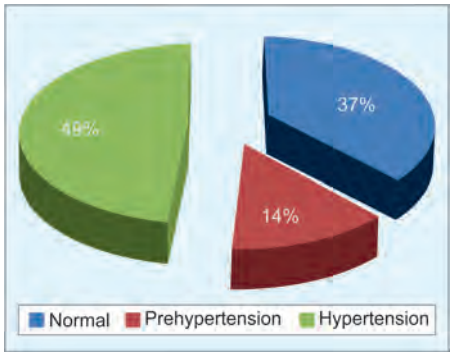

Fig. 2: Distribution of DBP in SCH cases

Table 2: Distribution of BMI in SCH cases

BMI	*Frequency (no. of cases)*	*Percentage (%)*
Normal (18.5–24.9)	41	51.3
Over weight (25.0–29.9)	31	38.8
Obese (30.0 and above)	8	10.0
Total	80	100.0

There were 67 (83.8%) patients who had normal postprandial blood glucose, while 13 (16.3%) patients had diabetes postprandial blood glucose. 67 (83.8%) patients reported normal HbA1c levels, whereas 13 (16.3%) patients had diabetes HbA1c levels.

Thyroid stimulating hormone levels showed a mean and a standard deviation of 6.4 (±1). The mean FT4 concentration in the patient population was 1.31 (±1), and the mean antithyroid peroxidase (anti-TPO) antibody level in patients was 45.1 (±33).

The mean systolic blood pressure (SBP) of patients was 127.8 (±20), while the mean DBP of patients was 86.4 (±11). The mean value of uric acid among the patients was found to be 5.5 (±2), the mean total cholesterol of patients was 210.1 (±41), the mean LDL-C of patients was 112.2 (±41), and the mean HDL-C of patients was 40.1 (±11). The mean triglycerides (TG) of patients was 171.3 (±38).

The mean FBS of patients was 99.4 (±25), the mean PPBS of patients was 135.4 (±39), and the mean HbA1c of patients was 5.4 (±1). Table 3 summarizes the mean and standard deviation values for the various study variables.

Risk of Ischemic Heart Disease

The association of different variables and the risk of CAD was analyzed for all study participants. Of the total 80 subjects in the study, 58 (72.5%) patients were at risk of CAD. In this study, any SCH subject with any one positive/deranged risk factor for CAD was considered to be a SCH subject with risk for CAD. The association of age-group vs risk of CAD was statistically significant ($p = 0.0292$). The association of age-groups and risk of CAD can be seen in Figure 3. The association of gender vs risk of CAD was not statistically significant ($p = 0.9360$). In SCH subjects with risk of CAD, 24 (41.4%) subjects had normal anti-TPO, and 34 (58.6%) subjects had deranged anti-TPO. The association of anti-TPO vs risk of CAD was not statistically significant ($p = 0.0520$).

The study also analyzed the association of BMI and the risk of CAD as seen in Table 4. The number of patients at risk of CAD was 22, who had normal SBP, 7 patients had prehypertension SBP, and 29 patients had hypertension SBP; the association of SBP vs risk of CAD was statistically significant ($p < 0.0001$). The number of patients at risk of CAD was 15 (25.9%) who had normal DBP, 4 (6.9%) patients had prehypertension DBP, and 39 (67.2%) patients had hypertension DBP; the association of DBP vs risk of CAD was statistically significant ($p < 0.0001$).

The number of patients at risk of CAD was 48 (82.8%) who had normal uric acid and 10 (17.2%) patients had deranged uric acid; the association of uric acid vs risk of CAD was statistically significant ($p = 0.0373$).

The number of patients at risk of CAD was 9 (15.5%) who had normal total cholesterol and 49 (84.5%) patients had deranged total cholesterol; the association of total cholesterol vs risk of CAD was statistically significant ($p < 0.0001$). Fifteen (25.9%) patients had normal LDL-C and 43 (74.1%) patients had deranged LDL-C; the association of LDL-C vs risk of CAD was statistically significant ($p < 0.0001$). The number of patients at risk of CAD was 58 (72.5%) who had deranged TG level in SCH; the association of TG vs risk of CAD was statistically significant ($p < 0.0001$). The number of patients at risk of CAD was 48 (82.8%) who had deranged HDL-C and 10 (17.2%) patients had normal HDL-C; the association of HDL-C vs risk of CAD was statistically significant ($p < 0.0001$).

The number of patients at risk of CAD was 42 (72.4%) who had normal FBS, 3 (5.2%) patients had prediabetes FBS, and 13 (22.4%) patients had diabetes FBS; the association of FBS vs risk of CAD was statistically significant ($p = 0.0324$). The number of patients at risk of CAD was 45 (77.6%) who had normal postprandial blood glucose and 13 (22.4%) patients had diabetes postprandial blood glucose; the association of PPBS vs risk of CAD was statistically significant ($p = 0.0152$). The number of patients at risk of CAD was 45 (77.6%) who had normal HbA1C levels and 13 (22.4%) patients had diabetes HbA1C levels; the association of HbA1C vs risk of CAD was statistically significant ($p = 0.0152$).

The difference in the mean of different variables and the risk of CAD was calculated. The mean age of patients at risk of CAD was 47.9 (±10), and the difference in mean age and the number of patients at risk of CAD was found to be not statistically significant ($p = 0.9649$). The mean BMI of patients at risk of CAD was 26.3 (±3), and the difference in mean BMI and the number of patients at risk of CAD was found to be statistically significant ($p < 0.0001$). The mean TSH of patients at risk of CAD was 6.3 (±1), and the difference in mean TSH and the number of patients at risk of CAD was found to be not statistically significant ($p = 0.4911$), as seen in Figure 4.

The mean FT4 of patients at risk of CAD was 1.3 (±1), and the difference in mean FT4 and the number of patients at risk of CAD was not statistically significant ($p = 0.3968$). The

Table 3: Distribution of mean

	Number	*Mean*	*SD*	*Minimum*	*Maximum*	*Median*
Age (in years)	80	47.80	9.01	35.00	73.00	46.50
BMI	80	25.29	3.41	19.69	33.50	24.70
TSH mIU/mL	80	6.43	1.09	4.51	9.10	6.31
FT4 ng/dL	80	1.31	0.16	0.98	1.67	1.29
Anti-TPO IU/mL	80	45.08	32.67	2.80	111.00	43.500
SBP	80	127.75	19.65	100.00	168.00	118.00
DBP	80	86.35	10.93	70.00	112.00	80.00
Uric acid mg/dL	80	5.46	1.54	2.80	10.00	5.05
Total cholesterol	80	210.10	41.40	122.00	288.00	220.00
LDL-C	80	112.22	41.25	36.00	173.00	139.00
HDL-C	80	40.10	11.31	21.00	59.00	37.00
TG	80	171.25	38.22	91.00	275.00	175.50
FBS	80	99.38	24.69	74.00	215.00	93.00
PPBS	80	135.36	39.17	95.00	259.00	121.00
HbA1c	80	5.41	0.88	4.30	8.70	5.20

Table 4: BMI vs risk of CAD

	Risk of CAD		
BMI	*No*	*Yes*	*Total*
Normal	22	19	41
Row%	53.7	46.3	100.0
Col%	100.0	32.8	51.3
Over weight	0	31	31
Row%	0.0	100.0	100.0
Col%	0.0	53.4	38.8
Obesity	0	8	8
Row%	0.0	100.0	100.0
Col%	0.0	13.8	10.0
Total	22	58	80
Row%	27.5	72.5	100.0
Col%	100.0	100.0	100.0

Chi-square value: 28.8646; *p*-value: <0.0001

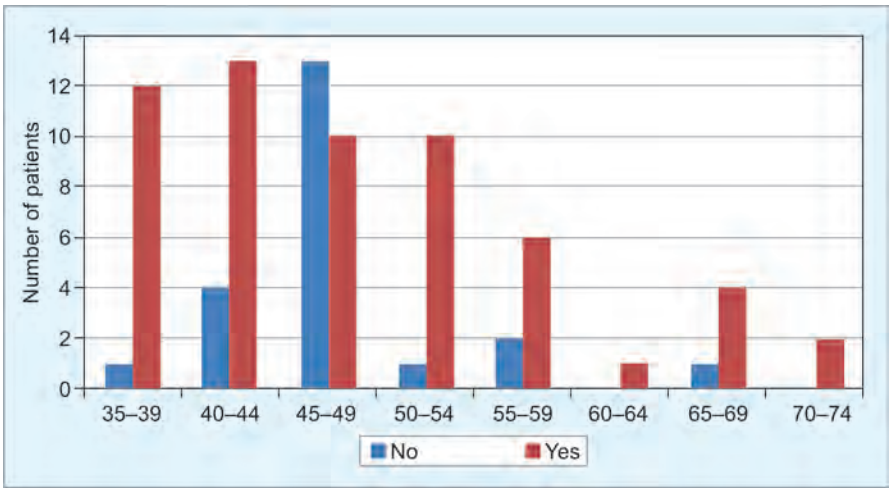

Fig. 3: Association between age in group: risk of CAD

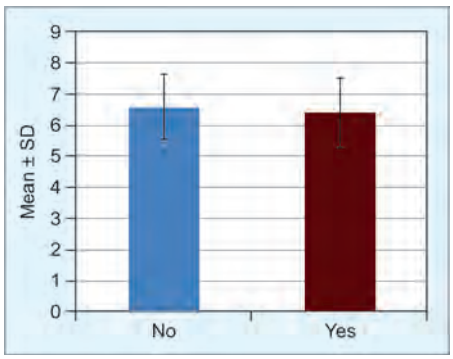

Fig. 4: TSH level in SCH cases: Risk of CAD

mean anti-TPO of patients at risk of CAD was 39.9 (±31), and the difference in mean anti-TPO and the number of patients at risk of CAD was statistically significant ($p = 0.0199$).

The mean SBP of patients at risk of CAD was 133.3 (±20), and the difference in mean SBP and the number of patients at risk of CAD was statistically significant ($p < 0.0001$). The mean DBP of patients at risk of CAD was 89.8 (±11), and the difference in mean DBP and the number of patients at risk of CAD was statistically significant ($p < 0.0001$).

The total mean cholesterol of patients at risk of CAD was 228.8 (±31), and the difference in total mean cholesterol and the number of patients at risk of CAD was statistically significant ($p < 0.0001$). The mean LDL-C of patients at risk of CAD was 128.0 (±37), and the difference in mean LDL-C and the number of patients at risk of CAD was statistically significant ($p < 0.0001$). The mean HDL-C of patients at risk of CAD was 35.3 (±9), and the difference in mean HDL-C and the number of patients at risk of CAD was statistically significant ($p < 0.0001$). The mean TG of patients at risk of CAD was 189.1 (±27), and the difference in mean TG and the number of patients at risk of CAD was statistically significant ($p < 0.0001$).

The mean FBS of patients at risk of CAD was 102.6 (±28), and the difference in mean FBS and the number of patients at risk of CAD was not statistically significant ($p = 0.0553$). The mean PPBS of patients at risk of CAD was 141.8 (±44), and the difference in mean PPBS and the number of patients at risk of CAD was statistically significant ($p = 0.0165$). The mean HbA1C of patients at risk of CAD was 5.5 (±1), and the difference in mean HbA1C and the number of patients at risk of CAD was statistically significant ($p = 0.0451$).

Discussion

Findings from the study of Dey et al. indicate a significant connection between SCH and established risk factors for CAD in the Indian adult population. Dey et al.'s research explored the cardiovascular implications of SCH, highlighting emerging cardiac risk factors. Our study population had a mean age of 47.8 (SD = 9.01), which is close to the mean age of 35.1 (SD = 10.26) in the research conducted by Dey et al.[9] The prevalence of SCH demonstrates a pronounced rise within the 35–54 age bracket, underscoring its association with advancing age. The most important implication observed in both studies is that SCH is likely to transition to clinical hypothyroidism, necessitating timely intervention.

Our study revealed that 67.5% of participants with SCH were female, contrasting with Mishra et al.[10] findings (90% female), yet both studies confirm a higher prevalence of SCH among females, escalating with age.

In our study, 28 (35.0%) participants reported normal anti-TPO levels, while 52 (65.0%) had deranged anti-TPO levels. In Kim et al.'s study, normal anti-TPO was observed in 68 (25.5%) participants, and 132 (9%) had deranged anti-TPO levels.[11] It was analyzed through this study that anti-TPO does not affect cardiovascular events.

The association of variables and the risk of CAD in SCH was seen in our study as well as reported by Soman et al. The angiographic pattern and severity of CAD in women were found to be the same in both studies.[12]

In our study, 41 (51.3%) patients reported normal BMI, 31 (38.8%) patients had overweight BMI, and 8 (10.0%) patients had obese BMI, while in the study of Solanki et al., the patients who reported normal BMI were 147, patients with overweight BMI were 100, and patients with obese BMI were 145. Solanki et al.'s study reported increased atherogenic indices, including TC/HDL-C and LDL-C/HDL-C ratios, in the study population relative to controls.[13]

Hence, CRP levels exhibited a significant positive association with BMI ($r = 0.29$, $p < 0.02$), and tHct levels showed a significant positive association with increasing age ($r = 0.24$, $p < 0.05$).[13] Our findings indicate that middle-aged women with SCH are more likely to develop hypertension.

Research by Luboshitzky and Herer revealed an increased prevalence of cardiovascular risk factors—hypertension, hypertriglyceridemia, hypercholesterolemia, and atherogenic indices (elevated TC/HDL-C and LDL-C/HDL-C ratios)—in SCH patients versus controls. In our study, 22 patients had normal SBP, 7 patients had prehypertension SBP, and 29 patients had hypertension SBP. The association of SBP with the risk of CAD was statistically significant ($p < 0.0001$). In the risk of CAD, 15 (25.9%) patients had normal DBP, 4 (6.9%) patients had prehypertension DBP, and 39 (67.2%) patients had hypertension DBP. The association of DBP with the risk of CAD was statistically significant ($p < 0.0001$), while Luboshitzky and Herer research reported mean SBP values of 121.36 (SD 17.16) and mean DBP of 79.76 (SD 8.84). Our results support and align with the current scientific consensus.[14]

In our study, 15.5% of patients had normal total cholesterol and 84.5% had deranged total cholesterol, 25.9% of patients had normal LDL-C, and 74.1% had deranged LDL-C, while the study conducted by Kishore Chander et al. showed that 16% of patients had normal total cholesterol and 84% had deranged total cholesterol, 27% of patients had normal LDL-C, and 76% had deranged LDL-C.[15]

We analyzed that 72.5% of patients had deranged TG levels in SCH. 82.8% of patients had deranged HDL-C, and 17.2% of patients had normal HDL-C. 58% of patients had deranged TG levels in SCH, while the research conducted by Kc et al. found that 76% of subjects had deranged HDL-C, and 24% of patients had normal HDL-C, which closely relates to our study.[16]

We found that 61 (76.3%) patients had normal FBS, 6 (7.5%) patients had prediabetes FBS, and 13 (16.3%) patients had diabetes FBS. 67 (83.8%) patients had normal postprandial blood glucose, and 13 (16.3%) patients had diabetes postprandial blood glucose. Normal HbA1c levels were seen in 67 (83.8%) patients, and 13 (16.3%) patients had HbA1c levels in the diabetic range. 58 (72.5%) patients in our study had a risk of CAD, and the same was reported by Tseng et al.[17]

Conclusion

This study aimed to investigate the cardiac risk factors that result from SCH. Notwithstanding the small sample size, our study revealed significant correlations between certain factors, including CAD. According to our statistical analysis, women in the age-group 35–54 are more likely than men to experience SCH. The study confirms that there is a strong association between SCH and known risk factors of CAD, like deranged lipid profile, hypertension, and increased BMI. We also observed that increased uric acid, FBS, PPBS, and HbA1c levels have a positive association with SCH.

Our investigation shows that SCH is frequently accompanied by several cardiovascular disease risk factors. By screening the vulnerable group, the cardiovascular risk in such people might be reduced (i.e., female subjects >35 years). Early detection and mitigation of the numerous related cardiac risk factors, as well as the prevention of the development of clinical hypothyroidism, are two potential benefits of the diagnosis and treatment of SCH.

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REVIEW ARTICLE

Current Update on Promising New Anti-Alzheimer's Drugs in Different Phases of Clinical Development: Where Exactly Are We Lacking?

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Abstract

The prevalence of Alzheimer's disease (AD) is rising with an aging population worldwide and is expected to surpass 130 million by 2050. India is no exception, but the true prevalence data on AD is not conclusive. By 2050, India will have almost 15% of the population aged 60 years or above. It is the need of the hour to have newer and more effective agents that can address various therapeutic needs of Alzheimer's viz., halt or delay disease progression, and offer better improvement in symptomatology. The most desirable would be to have an intervention that can prevent AD onset. The prime focus of the present review is to introduce to the readers the promising drug candidates across the world. We reviewed all the information available to us through a literature search. It is quite apparent that the developmental efforts are concentrated not only on disease-modifying therapies that can prevent the development but also on palliative therapies that improve the quality of life of AD patients. Several approaches including biological and small molecules are being explored to tap their potential in AD therapeutics using sound scientific research principles and execution. Besides conventional development approaches, the drug repurposing strategy has emerged as quick, cost-effective, and less risky and is being exploited to the fullest. The drugs in the pipeline and undergoing various phases of clinical trials for the past 5 years are taken from the ClinicalTrials.gov registry. It remains to be seen the advent of a successful disease-modifying agent for AD in future.

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Alzheimer's disease (AD) is an incapacitating neurodegenerative condition. It is associated with dementia and affects over 35 million people worldwide.[1] The characteristic diagnostic features of AD that are essential for diagnosis are amyloid plaques and neurofibrillary tangles.[2] Atrophic changes involving amygdala and hippocampus in association with temporal horn enlargement is hallmark of AD.[3–5] Some of the typical structural changes visible on magnetic resonance (MR) imaging have been shown in Figures 1 and 2. Data on the prevalence of AD in India is scant. Moreover, there could be a substantial regional difference in AD incidence within the heterogeneous population. In India, the number of individuals aged 60 years or older is projected to be 319 million by 2050 and that would account for almost 15.4% of the aged population (>60 years) worldwide.[6] A recent study from India reported dementia prevalence in individuals >60 years to be 7.4%, and it translates to nearly 9 million Indians >60 years suffering from dementia. However, the authors emphasized future research to better assess subtypes of dementia as the present study focuses on all-cause dementia in those who are aged 60 years or above.[7] Results of a meta-analysis conducted with 20 epidemiological studies reported the prevalence of dementia to be 20 per 1,000 population (95% CI: 0.02–0.03). However, there was no difference in prevalence rates between gender, rural, and urban. Individuals aged 75 years and above showed a higher prevalence than those below 75 years of age. Unfortunately, the study could not estimate dementia prevalence specific to AD.[8] The incidence rate can only be measured accurately in prospective incidence studies. A study[9] showed that the age-adjusted prevalence of AD varied from 1.91% in people over 55 years of age and 3.56% in those over 65 years. AD is a major public health problem with a global healthcare cost of $305 billion as estimated by the World Alzheimer's Association. Incidence rates of AD in people between 65 and 85 years of age are 5 to >30%, respectively. It is predicted that the prevalence of the disease will reach almost 131.5 million worldwide by 2050.[10] Not surprisingly, it would result in substantial global healthcare costs and impact on individuals, caregivers, and society.

Currently, available drugs for AD are primarily used to improve cognitive deficits.[11–13] None of the available treatments either reduce or halt the disease progression.

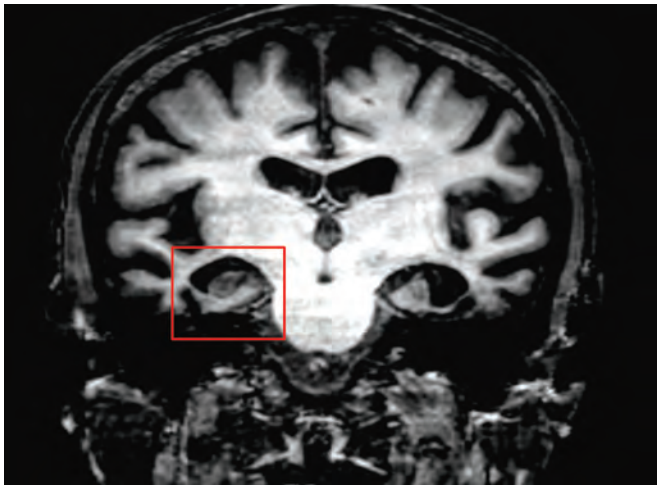

Fig. 1: MR image (T1 sequence) shows widening of choroid fissure and temporal horn of lateral ventricles and loss of hippocampal volume (red box)

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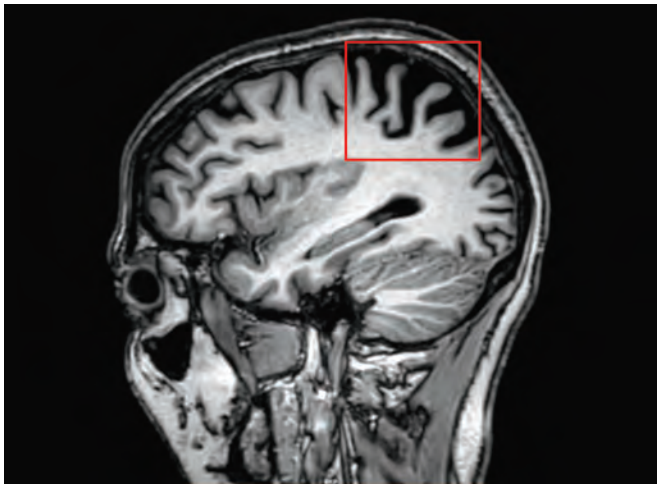

Fig. 2: MR image (T1 sequence) showing knife blade atrophy (red box) of cortical sulci in parietal lobe

None can afford a cure[14] and are largely used as palliative therapy.

There is an urgent need for novel agents that have promising disease-modifying potential. Further, drugs that have clinically meaningful effects on behavioral and psychological symptoms of dementia (BPSD) need to be developed using novel or repurposed (systematic "omics" data mining) development programs. There is a lot of skepticism about the shortcomings of the available therapies and the paucity of an effective and safe therapy that offers clinical benefits beyond symptomatic improvement. Today, research and development strategies are more focused on disease-modifying therapies and many such molecules are in the pipeline.

It takes 10–15 years to run a new molecular entity (NME) development program and is associated with a meager average success rate.[14–16] The inappropriate preclinical animal models and lack of validated, precise diagnosis criteria add up to greater failures. The driving force to initiate and develop new drugs is the big opportunity for industries to address unmet clinical needs. The plausible explanation for a tardy pace of development is unarguably due to inadequate information and understanding of complex pathologic mechanisms underlying neurodegeneration in AD resulting in a failure rate as high as 99%.[17] The improper selection of representative clinical trial patients resulted in the introduction of heterogeneity and confounding together distorted efficacy results. Overreliance and failure to precisely understand preclinical data and implement this information into the clinical phase led to many failures.[18–20]

We searched the site ClinicalTrials.gov for clinical trials in AD in the past 5 years. The search criteria were any interventional phase III trial that is recruiting patients or is active with no further recruitment worldwide. After applying all the relevant filters, the site yielded 44 relevant studies as per our search criteria. The review has tried to classify the drugs as per the target they are acting on. The review's focus is to provide the reader with a glimpse of drugs in the pipeline with relevant clinical information as necessary. It has discussed all agents that are either disease-specific or meant to address side symptoms of AD.

Tyrosine Kinase Inhibitors

Masitinib

It is an orally active agent that inhibits tyrosine kinase activity, particularly of activated mast cells and microglia in the neuroimmune system. The drug was evaluated in combination with memantine or any cholinesterase inhibitor in mild to moderate AD. The study results were not that robust, and the authors concluded that it may benefit patients with mild to moderate AD.[21] However, a confirmatory trial is underway to substantiate these claims.

Antiamyloid Therapies

Lecanemab and Aducanumab

Aducanumab disassembles and degrades Aβ fibrils whereas lecanemab removes aggregated forms of Aβ. Both have been granted accelerated approval to address unmet clinical needs.[22,23] However, both drugs have to prove continued improvement in further confirmatory clinical trials to stay in the market. Recently, the US Food and Drug Administration (US FDA) granted full approval to lecanemab and enjoys the status of being the first Alzheimer's treatment that specifically targets the disease process. Aducanumab's continued approval status will be decided based on the verification of the results showing consistent clinical benefit in confirmatory trials. Surrogate endpoint-based approval, associated safety concerns, and high cost led to the rejection of marketing authorization of these antibodies by the European Medicines Agency (EMEA) and the Pharmaceuticals and Medical Devices Agency (PMDA) (Japan).[22]

Remternetug (LY3372993)

Developed by Eli Lilly also designated as N3pG-Aβ mAb. This antibody specifically identifies and targets a pyroglutamate form of Aβ that aggregates abundantly in amyloid plaques. In 2018, Lilly started a phase I trial to enroll patients with mild cognitive impairment (MCI) and healthy volunteers. The study was prematurely closed after enrolling and testing only 36 healthy adults, with no enrolment of patients. The results of the study were never revealed in the public domain. TRAILRUNNER-ALZ1, a phase III clinical trial aims to randomize 400 participants with early symptomatic AD to remternetug or placebo for 1 year to assess the percentage of patients whose amyloid plaques are cleared.[24]

Valiltramiprosate

Valiltramiprosate gets converted to homotaurine *in vivo* as it is a prodrug. 3-sulfopranpanoic acid, a metabolite prevents Aβ42 from forming oligomers and thus inhibits Aβ42 aggregation in the brain.[25] On *post hoc* analysis of tramiprosate indicated its potential favorable effect in participants who carried two copies of ApoE4.[26,27] Alzheon Inc. is evaluating the efficacy, safety and biomarker effects of ALZ-801 in early AD and APOE4/4 genotype in a randomized, double-blind, placebo-controlled phase III study.

Donanemab

Donanemab removes the pyroglutamate form of Aβ that is aggregated in amyloid plaques. The major advantage of donanemab is that it not only reduces existing amyloid burden but also prohibits new plaque formation or growth of existing plaques. It could revolutionize AD treatment if it succeeds in halting the disease progression and leading to the reversal of existing plaques at the same time. TRAILBLAZER-ALZ 2, initially started as a phase II safety and efficacy trial by Lilly in 500 people with early AD but was later registered as a phase III study with a larger number of (n = 1,800) subjects. Results of this phase III study are expected any time soon (probably in the fall of 2023). The US FDA granted breakthrough designation to this antibody to facilitate and accelerate its development.

Gantenerumab

This breakthrough therapy disassembles and degrades Aβ fibrils developed by Swiss Pharmaceutical firm Roche®. The antibody also suppressed the neurotoxicity of Aβ42 oligomers.[28] The company intended to file a new drug application (NDA) as it had high hopes from ongoing trials and favorable procedure responses from the FDA. However, the company announced that the drug failed to show any clear benefit in twin trials that explored its impact on memory, problem-solving, and other cognitive skills in people with early AD.[29]

Semaglutide

A GLP-1 analog capable of entering the brain wherein it can enhance insulin signaling pathways.[30] It accelerates autophagy of Ab25-35 by acting on GLP-1 receptors and prevents apoptosis by downregulating Bax and upregulating Bcl2 expression.[31] Two phase III clinical trials (EVOKE and EVOKE Plus) are underway to evaluate whether the drug is safe and efficacious enough in patients with early AD.

Simufilam

Simufilam binds to a scaffolding protein called filamin known to regulate the interaction of α7nAChR (a type of nicotinic acetylcholine receptor) and Aβ42. This interaction facilitates tau phosphorylation and synaptic dysfunction.[32] The sponsor of the molecule began two phase III trials concurrently. One of the phase III studies will dose 1,083 patients either to placebo or simufilam twice a day for 18 months.[33]

Antitau Therapies

For almost the past 30 years, the amyloid hypothesis has been centric to AD research. Experience gleaned from past studies antiamyloid agents failed in advanced stages of development or some of them could offer some benefits but are less than desirable. This resulted in a faded conviction for the amyloid hypothesis in disease causation. It appeared later from available data that the tau protein is more closely related to the severity of cognitive decline than amyloid β. Therefore, the antitau strategy is now considered pivotal to explore an effective therapy. Although the antitau strategy emerged with a little pause but is one of the most promising targets to offer much-awaited desirable therapeutic benefits. Tau is a protein that has diverse physiological functions but primarily mediates the assembly and stability of axonal microtubules.

TRx0237

TauRx Therapeutics Ltd. evaluated TRx0237 for its safety and efficacy in patients of AD up to 90 years of age including children in a phase III trial. The study was started in 2018 and completed in April 2023 as per data available on ClinicalTrials.gov. Despite a thorough literature search, we could not find any information on the study outcome.

E2814

This is a monoclonal antibody[34] that binds specifically to that region of tau which is an important component of tau tangles and thus prevents the genesis of harmful tau aggregates. It also promotes the clearance of tau aggregates by microglia. The sponsor enrolled the first patient in 2022 in a phase III clinical study.

ACI 35

Aberrant folding results in protein aggregation and formation of proteinaceous deposits that have a β-sheet structure known as amyloid characteristically observed in AD.[35] ACI-35 is a vaccine formulated as a liposomal preparation. The rationale behind using the vaccine is that it will treat tauopathy in Alzheimer's disease by eliciting a B- or T-cell-mediated immune response targeted specifically against pathologically phosphorylated tau.

Bepranemab

A monoclonal antibody that binds to a site near tau's microtubule-binding domain which is located in the central region of tau. This particular antibody has a remarkable ability to block tau seeding in cell-based assays.[36] A randomized, phase II trial with placebo as control is already active in 450 patients who reported MCI or mild AD dementia.

BIIB080

Structurally, it is an antisense oligonucleotide (ASO). This agent is the first ASO that is being tested in a clinical trial. In the phase I trial, tau antisense therapy was not only found to be acceptably safe but also reduced CSF tau levels by 30–50%.[37] Based on encouraging results of a phase I study, a placebo-controlled phase II trial for subjects with MCI or mild dementia.

JNJ-63733657

Microtubule binding region (MTBR) of tau protein to which this monoclonal antibody recognizes and binds. It has a specifically high affinity for tau protein exhibiting phosphorylation of residue 217. A placebo-controlled phase II study has been ongoing since 2022 with >400 participants who have demonstrated PET scans positive for tau and also experiencing early AD symptoms.

LY3372689

This is an inhibitor of the *O*-GlcNAcase (OGA) enzyme and thus preventing *N*-GlcNAcylation of tau reduces its ability to form toxic aggregates[38] and keeps tau in a more soluble form. After positive and encouraging results from four phase I studies Eli Lilly and Co. decided to go ahead with a phase II trial in 2021 in 330 people with early AD with completion expected in June 2024.[39]

Semorinemab

This is an antitau IgG4 antibody that has completed two phase II clinical trials and the decision to undertake a phase III study is pending. In the first phase II study, the semorinemab not only missed the primary efficacy endpoint but also did not have a favorable effect on the two secondary endpoints.

APNmAb005

A monoclonal antitau IgG antibody packaged in an artificial lipid vesicle to elicit antibodies that would enhance tau oligomer clearance from synapses.

ASN51

An inhibitor of *O*-GlycNA case that fosters glycosylation and thus prevents aggregation and keeps tau protein in a more soluble, nonpathogenic state. It not only reduced the formation of tau tangles but also improved tau glycosylation in the brain.[40] The drug was capable of penetrating the blood-brain barrier. Further, increased tau glycosylation was demonstrated in peripheral blood cells.

MK-2214

Cellular inclusions of hyperphosphorylated tau are a hallmark of tauopathies. It is an antibody against hyperphosphorylated tau protein. The antibody recognized pathological tau in the brain of a mouse model of AD but not normal tau in controls as expected.[41] As of date, two phase I clinical trials are ongoing.

Stem Cell Therapies

Please refer to Table 1.

Miscellaneous Agents

Piromelatine (Neu-P11)

An agonist of serotonin (5-HT_{1A} and 5-HT_{1D}) and melatonin receptors. Data from both human and animal studies indicate that poor sleep quality is implicated in the pathogenesis of AD. Piromelatine is a sleep-inducing substance that acts by various mechanisms.

Table 1: Stem cell therapy in Alzheimer's disease[42]

Agent	*Phase*	*NCT**	*Completion date*
Human mesenchymal stem cells	II	NCT02833792	31st December 2024
Allogeneic human mesenchymal stem cells	I	NCT04040348	1st August 2023
Autologous adipose tissue-derived mesenchymal stem cells	II	NCT04482413	20th December 2024
Autologous adipose-derived stem cells	I	NCT05667649	November 2024

*National Clinical Trial number; three studies were shown as withdrawn and for five studies status "unknown"

In a first phase II trial, patients without polymorphisms in chromosome 2q12 showed significant improvement in the ADAS-Cog14 and Pittsburg Sleep Quality Index (PSQI).[42]

Buntanetap

This agent inhibits the translation of several neurotoxic proteins involved in the pathogenesis of neurodegenerative disorders only under conditions where their translation is elevated. The agent lowered neurotoxic and inflammatory biomarkers as well as improved axonal integrity, synaptic function, and psychometric test results.[43] The drug has progressed into a phase III trial.

Blarcamesine

The compound is a mixed ligand for Sigma1 (high affinity) and muscarinic receptors (lower affinity). In animals, the agent has shown neuroprotective activity[44] and may also block tau protein hyperphosphorylation.[45] In a phase IIb/III study in patients with MCI or early dementia, the drug slowed the decline of the ADAS-Cog by 45% and of the secondary CDR-SB by 27%.

Hydralazine

The drug has an antioxidant hydrazide group in its structure that has the potential to reduce Aβ production and prevent oxidative damage[46] thus possessing antineurodegenerative properties through manipulating several molecular pathways.

Caffeine

Dietary components are also being explored that may have potential salutary effects in AD. The main dietary source of caffeine is coffee, tea, and yerba mate[47] but it is also present in soft and energy drinks. Several experimental studies using caffeine in animal models of AD have offered some benefits to cognition.[48,49] Caffeine has psychostimulant properties that enable it to be used as a symptomatic treatment. At higher doses, it may result in anxiety and insomnia which Alzheimer's patients are more vulnerable to.

AR1001

A selective inhibitor of phosphodiesterase-5 (PDE5). The logic behind using PDE5 inhibitors in AD emerged when numerous PDE5 inhibitors in mouse models of AD reported reduced amyloid production and neuroinflammation. At the same time, they improved learning and memory deficits as well.[50]

KarXT

It is xanomeline combined with trospium. M1 agonists (AF710B) attenuated Aβ and tau pathology in experimental studies with rats and female mice.[51] KarXT development has progressed to phase III and is being evaluated for safety and efficacy in the treatment of psychosis associated with AD dementia.

Guanfacine (Extended Release)

A phase III trial [(noradrenergic add-on therapy with extended-release guanfacine in Alzheimer's disease (NorAD)], funded by the UK National Institute of Health Research. The trial commenced in January 2019, with 48 patients randomized by March 2020. The trial was suspended due to the UK-wide lockdown consequent to the COVID-19 pandemic. Further patient recruitment and subsequent planned follow-up visits were stopped at the trial site.[52] The study was restarted with relevant modifications in the protocol in August 2020 and as per information available the study was concluded on 31 December 2022. The results of the study are still not available in the public domain.

AXS-05

This investigational compound is a fixed-dose combination of D-methorphan and bupropion. The drug was granted breakthrough therapy designation for agitation in AD by the US FDA in 2020. A phase III study named ADVANCE-2 (Addressing Dementia *Via* Agitation-Centered Evaluation 2) is planned to assess the safety and efficacy of the compound given for 5 weeks in agitation associated with AD.

AVP-786

It is deudextromethorphan hydrobromide plus quinidine sulfate which is being compared to a placebo in a phase III trial for the treatment of agitation of AD.

Fosgonimeton

It activates signaling through hepatocyte growth factor (HGF)[53] that supports the proliferation and survival of neurons. It has a positive impact on learning and memory through the enhancement of hippocampal synaptic plasticity.

Masupirdine

An oral agent, a centrally acting selective antagonist of the 5-HT_6 receptor. Its beneficial effects on learning and memory are probably through the modulation of cholinergic and/or glutamatergic neurotransmission in certain brain areas.[54]

Metformin-XR

The effects of metformin on AD and its plausible mechanisms of action remain elusive and equivocal. Several recent studies have shown it to be antiinflammatory, antiapoptotic, and antioxidative. It has easy and rapid access to the brain and accumulates in different areas.[55] Metformin in Alzheimer's Dementia Prevention (MAP) is a phase III study that is underway.

Nabilone

Nabilone in a previous study with 39 patients was found to be an effective treatment for agitation but was associated with higher sedation compared to a placebo. There was also a small improvement on the standardized mini-mental state examination (sMMSE), unlikely to be clinically relevant.[56]

Drug Repositioning

Discovering a new molecule and taking it to the stage of marketing is a tough, labor-intensive, expensive, and time-consuming task with an enormous risk of failure. Drug repositioning, on the other hand, is a more fascinating, time- and cost-effective strategy to identify drugs for AD within available approved drugs for other ailments. The rationality of this approach emanates from the fact that many such drugs are capable of targeting and manipulating important brain receptors that are intricately involved in the formation of memory, learning, and cognition. Adoption of this approach has accelerated novel drug discoveries for AD.[57] Although there are several instances of failures that have also been encountered. They may probably account for a poor understanding of

the complexity involved in its pathogenesis and the paucity of information on the natural history of the disease. Chyr et al.[1] developed an alternative technique called drug repositioning approach using optimal transport for Alzheimer's disease (DOTA) to effectively repurpose FDA-approved drugs. This approach is more cost-effective and recognizes several promising drugs such as quetiapine, aripiprazole, risperidone, brimonidine, betaxolol, and suvorexant.

Conclusion

Research on Alzheimer's in the past few years has witnessed a complete overhaul. The present review provides comprehensive information on the likely future therapies for AD. Many of them have disease-modifying potential, and few would address side symptoms of AD, for example, agitation, etc. It is expected that by 2050, there will be >130 million AD patients worldwide. The major focus in recent years has been on compounds that could have the potential to modify disease processes. A plethora of new and existing compounds are being explored with the hope of finding a truly effective agent. This will significantly add to the scarce therapeutic armamentarium available for the treatment of AD. The whole scientific community is desperately looking forward with high hopes for the arrival of a new successful therapy. Such an agent may be viewed as a boon to the entire AD community. As per prediction by 2050, India will have the largest number of individuals above 60 years of age. In India, the true prevalence of AD-associated dementia is not convincingly known and is yet to be estimated. We should be aware of the fact that AD affects not only the Western developed population but the Asian population as well. It is time to wake up to strengthen and develop strategies to tackle this public health problem more effectively and well in time. We can face this disabling disease that poses mammoth treatment challenges more effectively if a few disease-modifying drugs in the pipeline make it to the market. However, in a resource-constrained country, it would be quite challenging. The advent of new but affordable, successful disease-modifying therapies would be a win–win situation for all. New palliative therapies are also being reconsidered for the effective management of disease consequent to the setbacks that have been reported while developing disease-modifying therapies. The lessons learned from past experiences have made pharma industries a little wiser and more cautious in their developmental approach. These agents will supplement the shortages of effective drugs and can also be used as alternatives for the treatment of one of the several symptoms of AD. For example, agitation, a disabling and difficult-to-treat symptom of AD is responsible for the poor quality of life of both the patient and caregiver plus a higher institutionalization rate. The available options are modest in efficacy and associated with a heightened risk of side effects. Brexpiprazole has been a valuable addition to the treatment available for agitation. Identifying safer and more effective treatments for agitation should be a much-needed and desirable research preference. Considerable efforts have been made in the past few years evidenced by a healthy pipeline of new drugs for the treatment of AD pathology and symptomatology (cognitive deficit, dementia, agitation, and psychosis). There is a dire need for drugs with improved efficacy and safety that can effectively address need of the AD patients.

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Abridged Prescribing Information
Active Ingredients: Metformin hydrochloride (as sustained release) and glimepiride tablets **Indication:** For the management of patients with type 2 diabetes mellitus when diet, exercise and single agent (glimepiride or metformin alone) do not result in adequate glycaemic control. **Dosage and Administration:** The recommended dose is one tablet daily during breakfast or the first main meal. Each tablet contains a fixed dose of glimepiride and Metformin Hydrochloride. The highest recommended dose per day should be 8 mg of glimepiride and 2000mg of metformin. Due to prolonged release formulation, the tablet must be swallowed whole and not crushed or chewed. **Adverse Reactions:** For Glimepiride: hypoglycaemia may occur, which may sometimes be prolonged. Occasionally, gastrointestinal (GI) symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhea may occur. Hepatitis, elevation of liver enzymes, cholestasis and jaundice may occur; allergic reactions or pseudo allergic reactions may occur occasionally. For Metformin: GI symptoms such as nausea, vomiting, diarrhea, abdominal pain, and loss of appetite are common during initiation of therapy and may resolve spontaneously in most cases. Metallic taste, mild erythema, decrease in Vit B12 absorption, very rarely lactic acidosis, Hemolytic anemia, Reduction of thyrotropin level in patients with hypothyroidism, Hypomagnesemia in the context of diarrhea, Encephalopathy, Photosensitivity, hepatobiliary disorders. **Warnings and Precautions:** For Glimepiride: Patient should be advised to report promptly exceptional stress situations (e.g., trauma, surgery, febrile infections), blood glucose regulation may deteriorate, and a temporary change to insulin may be necessary to maintain good metabolic control. Metformin Hydrochloride may lead to Lactic acidosis; in such cases metformin should be temporarily discontinued and contact with a healthcare professional is recommended. Sulfonylureas have an increased risk of hypoglycaemia. Long-term treatment with metformin may lead to peripheral neuropathy because of decrease in vitamin B12 serum levels. Monitoring of the vitamin B12 level is recommended. Overweight patients should continue their energy-restricted diet, usual laboratory tests for diabetes monitoring should be performed regularly. **Contraindications:** Hypersensitivity to the active substance of glimepiride & Metformin or to any of the excipients listed. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis, diabetic pre-coma). Severe renal failure (GFR<30ml/min). In pregnant women. In lactating women.Acute conditions with the potential to alter renal function (dehydration, severe infection, shock, intravascular administration of iodinated contrast agents); acute or chronic disease which may cause tissue hypoxia (cardiac or respiratory failure, recent myocardial infarction, shock); hepatic insufficiency; acute alcohol intoxication; alcoholism. **Use in a special population:** Pregnant Women: Due to a lack of human data, drugs should not be used during pregnancy. Lactating Women: It should not be used during breastfeeding. Pediatric Patients: The safety and efficacy of drugs has not yet been established. Renal impairment: A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.
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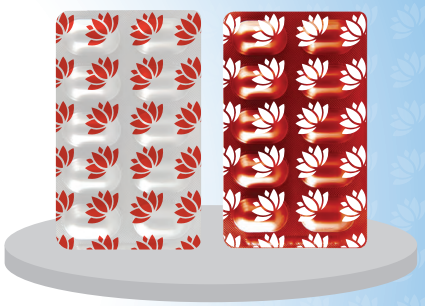

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UDAPA-TRIO Forte UDAPA-TRIO Dapagliflozin, Sitagliptin & Metformin Hydrochloride Extended Release Tablets Composition: Dapagliflozin 10 mg, Sitagliptin 100 mg & Metformin Hydrochloride Extended Release 1000 mg tablets Dapagliflozin propanediol monohydrate eq. To Dapagliflozin 10 mg Sitagliptin Phosphate Monohydrate IP Eq. Sitagliptin 100 mg Metformin Hydrochloride IP (as Extended Release) 1000 mg Dapagliflozin10 mg, Sitagliptin 100 mg & Metformin Hydrochloride Extended Release 1000 mg tablets Dapagliflozin propanediol monohydrate eq. To Dapagliflozin 10 mg Sitagliptin Phosphate Monohydrate IP Eq. Sitagliptin 100 mg Metformin Hydrochloride IP (as Extended Release) 500 mg Indication: It is indicated as an adjunct to diet and exercise to improve Glycemic Control adults with type 2 diabetes mellitus Recommended Dosage: As directed by the physician. Method of Administration: Oral Adverse Reactions: Most common adverse reactions reported are: Dapagliflozin - Female genital mycotic infections, Nasopharyngitis, Urinary tract infections. Sitagliptin - Upper respiratory tract infection, nasopharyngitis and headache. Metformin - Diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache. Warnings and Precautions: Dapagliflozin: Volume depletion; Ketoacidosis in patients with Diabetes Mellitus; Urosepsis and Pyelonephritis; Hypoglycemia; Genital mycotic infections Sitagliptin: General: Sitagliptin should not be used in patients with type 1 diabetes or for the treatment of Diabetic Ketoacidosis. Acute pancreatitis: Hypoglycemia is used in combinations when combined with other anti-hyperglycemic medicinal product; Renal impairment: Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions - Steven johnson syndrome; Bullous pemphigoid Metformin Hydrochloride: Lactic acidosis; In case of dehydration (severe diarrhea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a healthcare professional is recommended. Contraindications: Hypersensitivity to the active substance of Dapagliflozin, Sitagliptin & Metformin or to any of the excipients listed. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis). Diabetic pre-coma; Severe renal failure (eGFR < 30ml/min); Acute conditions with the potential to alter renal function such as: Dehydration, Severe infection, Shock; Acute or chronic disease which may cause tissue hypoxia such as: Cardiac or respiratory failure. Recent myocardial infarction, Shock, Renal Impairment, Acute intoxication, Alcoholism. Use in special population: Pregnant women: Due to lack of human data, drugs should not be used during pregnancy. Lactating women: It should not be used during breastfeeding. Pediatric patients: The safety and efficacy of drugs has not yet been established. No data is available. Geriatric Patients: In patients >65 years, it should be used with caution as age increases. For Additional Information/full prescribing information, please write to us: USV Private Limited, Arvind Vithal Gandhi Chowk, B.S.D Marg, Govandi, Mumbai - 400088
Last updated on 02/04/2024.

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Dapagliflozin Tablets 10 mg & 5 mg. Composition: Each film-coated tablet contains: Dapagliflozin 10 mg or 5 mg. Indications: 1) In adults aged 18 years and older with type II diabetic mellitus to improve glycemic control. 2) In adults for the treatment of heart failure. 3) In adults for the treatment of patients of Chronic Kidney Disease (CKD) up to eGFR of greater than or equal to 25 ml/min/1.73m2. **Recommended Dosage:** As directed by the Physician. Method of **Administration**: Oral. **Adverse Reactions:** The common adverse reactions in patients treated with Dapagliflozin 10 mg in clinical trials and post-marketing are Genital infection, Urinary tract infection, Diabetic ketoacidosis, Back pain and polyuria. **Warnings and Precautions:** Renal Impairment There is a limited experience with initiating treatment with Dapagliflozin in patients with eGFR<25mL/min/1.73m2. The glucose lowering efficacy of Dapagliflozin is dependent on renal function and is reduced in patients where eGFR is <45mL/min/1.73m2.Ketoacidosis in patients with diabetes mellitus Patients treated with Dapagliflozin who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dl). **If ketoacidosis is suspected,** discontinuation or temporary interruption of Dapagliflozin should be considered and the patient should be promptly evaluated. Use with **medications known to cause hypoglycemia Insulin and insulin** secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with Dapagliflozin in patients with type 2 diabetes mellitus. **Contraindications:** Dapagliflozin is contraindicated in patients with a history of any serious hypersensitivity reaction to the active substance or to any of the excipients. **For Additional Information/full prescribing information,** please write to us: USV Private Limited, Arvind Vithal Gandhi Chowk, B.S.D Marg, Govandi, Mumbai - 400088. Updated on 01st October'24, Expiry by 01st October'25, **In case of any query related to product contact us on pv@usv.in**

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REVIEW ARTICLE

Olmesartan: 360-degree Perspectives Befitting an Angiotensin Receptor Blocker

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Abstract

India has a high burden of hypertension (HTN), which is often poorly controlled, leading to hypertension-mediated organ damage (HMOD). In the management of HTN, angiotensin receptor blockers (ARBs) assume prime importance, being first-line agents for most patient subgroups. Olmesartan is a highly efficacious ARB that demonstrates sustained blood pressure (BP) reduction over 24 hours. Moreover, it also assumes a protective role by reducing microvascular inflammation, left ventricular hypertrophy, proteinuria, vascular stiffness, central aortic BP, cardiocerebrovascular events and atrial fibrillation. To enhance therapeutic compliance and achieve BP goals, single-pill combinations with other antihypertensive agents are also available. This review holistically summarizes the evidence of olmesartan for HTN management for not only BP reduction but also organoprotective effects.

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India has a high prevalence of hypertension (HTN), with 315 million cases, that is, 35.5% of the general population.[1] The global burden of disease (GBD) Study estimated that in India, HTN resulted in 1.6 million deaths and was the most important cause of disease burden.[2] Between 40 and 69 years of age, every 20 mm Hg rise in systolic blood pressure (SBP) or 10 mm Hg rise in diastolic blood pressure (DBP) is associated with a doubling of mortality risk from stroke or ischemic heart disease (IHD).[3] Undiagnosed or poorly controlled HTN often leads to hypertension-mediated organ damage (HMOD), which primarily affects the brain, kidneys, heart, retina, and arteries.[4,5] As HMOD sets in the initial phase, patients usually do not have (or) experience minimal symptoms. In this oligosymptomatic phase, the kidneys exhibit changes of nephrosclerosis with proteinuria, the myocardium undergoes compensatory left ventricular hypertrophy (LVH), early signs of retinopathy may occur, or the brain may show Binswanger lesions (small-vessel ischemic changes). As HMOD progresses, it can cause chronic kidney disease (CKD), coronary artery disease (CAD), arrhythmias, myocardial infarction (MI), left ventricular dysfunction, heart failure (HF), dementia, or stroke.[5] Notably, clustering of different HMOD types in the same individual has also been observed.[6] In the Framingham Heart Study cohort, half of the patients with high BP had one type of HMOD, while one-third had at least two types of HMOD.[7] Effective BP control can reduce the risk of MI by 25%, stroke by 40%, and HF by 50%, and can prevent up to 0.5 million deaths in India per year.[2,6]

Therapeutic Landscape of Angiotensin Receptor Blockers for Hypertension and Beyond

Angiotensin receptor blockers (ARBs) play a pivotal role in HTN management and are first-line agents for most patients according to global and Indian guidelines.[8–11] Not only are they effective in reducing BP, but they are also associated with significant reductions in HF (10%), major cardiovascular (CV) events (9%), and stroke (9%).[12] In patients with CKD, ARBs reduce albuminuria, delay progression to end-stage kidney disease (ESKD), and reduce CV risk.[13] ARBs have also demonstrated beneficial effects in HF (specifically candesartan, losartan, and valsartan) and post-MI (valsartan) settings.[14] In contrast to ACE inhibitors (ACEis), ARBs prevent the 'renin escape' phenomenon whereby renin and angiotensin II (A-II) return to pretreatment levels by irreversibly binding to AT_1 receptors to exert their pharmacodynamic effects. Moreover, unlike ACEis, ARBs do not affect bradykinin metabolism, thereby avoiding the dry cough associated with ACEis.[15] The placement of ARBs and their combinations across notable HTN guidelines is summarized in Table 1.

Olmesartan–Key Pharmacological Takeaways

Olmesartan medoxomil is a prodrug that is rapidly activated by ester hydrolysis to olmesartan during absorption.[16] Olmesartan exhibits a 12,500-fold greater affinity for AT_1 receptors than AT_2 receptors, that is, a four times greater AT_1/AT_2 receptor affinity than telmisartan (3,000-fold AT_1/AT_2 affinity).[17] This translates to greater inhibition of A-II's pressor (vasoconstrictor) effect with olmesartan compared to telmisartan (61 vs 40%).[17] Importantly, olmesartan does not interact with cytochrome P450 enzymes, which reduces its potential for pharmacological interactions with drugs such as warfarin, digoxin, and aluminum magnesium hydroxide.[18] The pharmacology and pharmacokinetics of commonly prescribed ARBs in Indian settings are shown in Table 2. Given once daily, olmesartan effectively maintains 24-hour BP control.[19–22]

Olmesartan: Clinical Efficacy in Hypertension

Olmesartan is an effective ARB for HTN control, exhibiting greater BP reduction than other ARBs such as losartan, candesartan, valsartan, and telmisartan. Ambulatory BP monitoring (ABPM) studies further attest to the 24-hour BP control provided by olmesartan.[19–23] Relevant studies, ranging

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Table 1: Key hypertension guidelines with recommendations on ARBs

Guidelines	*Recommendations*
2023 European Society of Hypertension Guidelines[8]	Monotherapy • Grade 1 HTN and low risk if BP is only marginally elevated (<150 mm Hg systolic blood pressure and <95 mm Hg diastolic blood pressure) • High-normal BP and very high cardiovascular risk • Frailty ± advanced age Combination therapy • Uncomplicated HTN – initiation of therapy with a two-drug combination is recommended for most patients with HTN. Preferred combinations should comprise a RAAS blocker with a CCB or thiazide/thiazide-like diuretic • HTN with HFpEF • HTN with CAD: ARB + BB is the combination of choice • HTN with HFrEF – ARNi can be substituted • HTN with AF • CKD stage 1–5 (stage 4 and 5 not on dialysis) Triple combination • If BP is uncontrolled with two drugs, treatment should be increased to a three-drug combination, usually a RAAS blocker + CCB + thiazide/thiazide-like diuretic
2020 International Society of Hypertension Guidelines[9]	As monotherapy • In low-risk grade 1 HTN • In very old (≥80 years) or frailer patientsAs dual-drug single-pill combination (ARB + CCB) in step 1 (low dose) and step 2 (full dose) Consider (ARB + CCB + thiazide-like diuretic) as a triple-drug combination in step 3 In combination with thiazide-like diuretic in: • Post-stroke patients • Very elderly • Incipient HF • Beta-blocker intolerance Also recommended in: • HTN + CAD • HTN + HFrEF; ARNi can be used as an alternative • HTN + CKD • HTN + COPD • HTN + DM • HTN + dyslipidemia • HTN + inflammatory rheumatic disease • HTN + psychiatric disorder
2019 Indian Guidelines on Hypertension-IV[10]	• As monotherapy in younger patients (step 1) • In combination with CCB/diuretic (step 2) • As triple combination (ARB + CCB + diuretic; step 3)
2017 AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guidelines[11]	• For initiation of antihypertensive therapy • HTN and stable ischemic heart disease (with other drugs) • HFpEF and persistent HTN • HTN and CKD (stage ≥3/stage 1 or 2 with albuminuria) • HTN and DM (especially those with albuminuria) • Prevention of AF recurrence

AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor/neprilysin inhibitor; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; CV, cardiovascular; DBP, diastolic blood pressure; DM, diabetes mellitus; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HTN, hypertension; RAAS, renin-angiotensin system; SBP, systolic blood pressure

Table 2: Comparative clinically relevant pharmacological profile of key ARBs prescribed for HTN in India

	Losartan	*Telmisartan*	*Olmesartan*
AT1 vs AT2 affinity	1,000-fold	3,000-fold	12,500-fold
Time to BP effect (weeks)	3–6 weeks	4 weeks	1–2 weeks
% inhibition of A-II's pressor effect	25–40%	40%	61%
Food interaction	10% ↓ bioavailability	6–20% ↓ bioavailability	No
Common drug interactions	Rifampin, fluconazole	Digoxin	No interaction with these agents

A-II, angiotensin-II; ARBs, angiotensin receptor blockers; AT1, type 1 angiotensin II receptors; AT2, type 2 angiotensin IIreceptors; BP, blood pressure; HTN, hypertension

from randomized controlled trials (RCTs) to real-world evidence (RWE), are summarized below in Table 3.

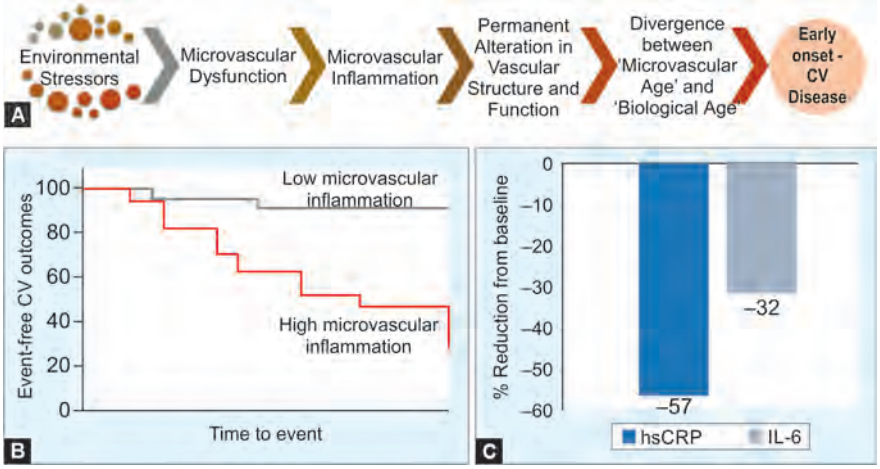
Effects of Olmesartan beyond Blood Pressure Control

Anti-inflammatory Effects

In addition to being a potent vasoconstrictor and activating the renin-angiotensin-aldosterone system (RAAS), A-II also has a proinflammatory effect on the vascular tree.[31,32] Microvascular inflammation is associated with increased CV events (Figs 1A and B).[33] Vascular hsCRP (production of which is stimulated by IL-6 and IL-1) inhibits endothelial NO synthase (eNOS), increases the expression of adhesion molecules in endothelial cells, and increases free radical production in the vascular tree.[34] Hence, the net effects are vasoconstriction, vascular smooth muscle cell (VSMC) proliferation, platelet activation, and increased vascular stiffness.[34] Therefore, agents that reduce vascular inflammation play a holistic role in HTN management. Olmesartan has consistently been shown to reduce surrogate markers of microvascular inflammation, namely hsCRP, IL-6, hsTNF-α, and MCP-1, in various studies as summarized in Table 4.

Effect on Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH) in hypertensive patients develops as a compensatory response to myocardial



Figs 1A to C: (A) Microvascular inflammation is initiated by environmental stressors and triggers a cascade of changes, leading to permanent alterations in vascular structure and function. This results in a divergence between "high microvascular age" relative to biological age, contributing to early CV disease[33]; (B) High microvascular dysfunction is associated with an increased risk of CV events[33]; (C) In the OLIVUS trial, olmesartan reduced hsCRP and IL-6 by 57 and 32%, respectively, from baseline[35]

Table 3: Clinical efficacy of olmesartan in management of HTN

Author (year)	*Patients (n) and stratification*	*Study details and relevant endpoints*	*Results*	*Takeaways*
Sirenko et al. (2022)[24]	Mild-to-moderate HTN *N* = 40 Per 4–8 mg/day (*n* = 20) Olm 20–40 mg/day (*n* = 20)	Investigational study Duration: 6 months Outcomes: Central BP 6 months (vs baseline)	Central SBP reduced significantly (*p*, 0.05) in both groups • Olm group = –20.13 ± 5.89 mm Hg • Per group = –16.15 ± 4.59 mm Hg • Intergroup diff. = –4 mm Hg	Central aortic BP in both groups decreased significantly
Khan et al. (2020)[25]	Patients with essential HTN *N* = 459 • Olm (*n* = 302) • Olm + 1 AHD (*n* = 119) • Olm + 2 AHDs (*n* = 30) • Olm + 3 AHDs (*n* = 8)	Retrospective, observational study Duration: 1 month Primary outcomes: Change in SBP and DBP from baseline Secondary outcome: Patients who achieved individualized BP goals as per ESC/ESH 2018 guidelines	Olm monotherapy and Olm + 1 AHD • Change in SBP ($p < 0.001$) = –13.4 mm Hg and –11.7 mm Hg • Change in DBP ($p < 0.001$) = –8.3 mm Hg and –6.6 mm Hg In patients with HTN+ DM: Olm (*n* = 174) vs Olm + 1 AHD (*n* = 63) • Change in SBP ($p < 0.001$) = –15.5 mm Hg and –13.5 mm Hg • Change in DBP ($p < 0.001$) = –8.7 mm Hg vs –7.6 mm Hg BP goals achieved (HTN + DM) as per ESC/ESH 2018 guidelines: Olm alone and Olm + 1 AHD • SBP: 38.5 and 31.7% • DBP: 49.4 and 42.9%	Olm prescribed as mono/add-on therapy significantly reduced BP in Indian patients with essential HTN as well as in patients with comorbid diabetes
Kalikar et al. (2017)[26]	Stage 1 HTN patients Total *N* = 60 divided in three groups • Olm 20 mg OD (*n* = 20) • Tel 40 mg OD (*n* = 19) • Los 50 mg OD (*n* = 28)	Randomized, open-label, parallel group, comparative study Duration: 3 months Primary outcome—change in SeDBP at 12 weeks Secondary^ outcome—change in SeSBP at 12 weeks	Reduction in SeDBP at 12 weeks: Olm = –13.8 mm Hg Tel = –12 mm Hg Los = –7.3 mm Hg Reduction in SeSBP at 12 weeks: Olm = –17.3 mm Hg Tel = –11.7 mm Hg Los = –11.2 mm Hg	Olm group showed statistically significant reduction in SeSBP vs both Tel & Los. Olm had numerically greater reduction in SeDBP vs Tel and statistically significant reduction vs Los

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Author (year)	*Patients (n) and stratification*	*Study details and relevant endpoints*	*Results*	*Takeaways*
Daikuhara et al. COTO Study (2014)[27]	Patients with HTN and T2DM *N* = 317 Study 1: CO group (*n* = 165)—Pts. on Can (8 mg OD) switched to Olm (20 mg OD) for 16 weeks, and switched back to Can (8 mg OD) for 16 weeks Study 2: TO group (*n* = 152)—Pts. on Tel (40 mg OD) switched to Olm (20 mg OD) for 16 weeks, and switched back to Tel (40 mg OD) for 16 weeks	Open-label controlled study—two studies done concurrently to investigate the effects of switching from two different ARBs to olmesartan Duration: 8 months Outcomes: Primary: Morning home BP Secondary: Clinic BP	Study 1 (CO group): Morning home SBP and DBP • SBP: ↓ by –5.8 mm Hg when switched from Can to Olm and ↑ by +5.2 mm Hg when switched back to Can • DBP: ↓ by –2.3 mm Hg when switched from Can to Olm and ↑ by +2 mm Hg when switched back to Can Clinic-measured SBP and DBP • SBP: ↓ by –3.9 mm Hg when switched from Can to Olm and ↑ by +3.3 mm Hg when switched back to Can • DBP: ↓ by –1.8 mm Hg when switched from Can to Olm and ↑ by +1.5 mm Hg when switched back to CanStudy 2 (TO group): Morning home SBP and DBP • SBP: ↓ by –6.1 mm Hg when switched from Tel to Olm and ↑ by +5 mm Hg when switched back to Tel • DBP: ↓ by –2.1 mm Hg when switched from Tel to Olm and ↑ by +1.9 mm Hg when switched back to Tel Clinic-measured SBP and DBP • SBP: ↓ by –3.6 mm Hg when switched from Tel to Olm and ↑ by +3.1 mm Hg when switched back to Tel • DBP: ↓ by –1.6 mm Hg when switched from Tel to Olm and ↑ by +1.4 mm Hg when switched back to Tel	Treatment with Olm for 16 weeks after switching from candesartan or telmisartan shows an added significant reduction in the morning home BP and clinic BP The reversal of the BP when reswitched over from Olm to either Tel or Can attests that the incremental reduction in BP is purely due to Olm
Kumbla et al. WINOVER Study (2014)[28]	Newly diagnosed HTN *N* = 8940 Treated with Olm 20 mg/40 mg OD for 6 months	Open label, noncomparative, multicentric, observational study Duration: 6 months Outcome: Reduction of SBP <140 mm Hg & DBP <90 mm Hg at 3 and 6 months of Olm initiation	in SBP and DBP (mm Hg) at 1, 3 and 6 months ($p < 0.0001$): • SBP: –19, –29.8, and –34.5 mm Hg • DBP: –11, –16.3, and –18 mm Hg% responders for both SBP and DBP increased consistently from day 15 to month 6 Only 0.08% patients reported AEs	In Indian HTN patients, Olm 20 mg/40 mg is effective and well tolerated
Ono et al. (2013)[29]	Patients with nondiabetic CKD *N* = 44 Olm (*n* = 10), Can (*n* = 9), Val (*n* = 9), Los (*n* = 13)	Retrospective investigational study Duration: 24 months Outcome: Reduction of SBP and DBP	In SBP and DBP after 1 month ($p < 0.05$) & 24 months ($p < 0.05$) • Greatest with Olm vs other ARBs	In patients with nondiabetic CKD, Olm showed the highest BP reduction in BP vs other ARBs
Nakayama et al. (2008)[23]	Early stage T2DM with HTN (*N* = 20) Patients on Val 80 mg OD switched to Olm 20 mg OD or Tel 40 mg OD for 8 weeks then crossover	Open-label crossover study Duration: 4 months Measure: 24-hour ABPM at 0, 8, and 16 weeks	in 24-hour BP: Olm vs Tel ($p < 0.05$) • Δ Systolic: –3.3 mm Hg • Δ Diastolic: –2.7 mm Hg • Δ Mean: –3.1 mm Hg In daytime BP: Olm vs Tel ($p < 0.02$) • Δ Diastolic: –3.2 mm Hg • Δ Mean: –3.1 mm Hg In nighttime BP: Olm vs Tel ($p < 0.05$) • Δ Systolic: –5.4 mm Hg • Δ Diastolic: –3.3 mm Hg • Δ Mean: –4 mm Hg	Olm showed more potent BP lowering effects than Tel with Olm having significantly greater reduction in SBP, DBP and mean BP
Garcia et al. (2007)[30]	Mild-to-moderate essential HTN *N* = 71 Pts. put on Olm 10–40 mg/day	Investigational, single-arm study Duration: 16 weeks Outcomes: Change in 24-hour BP, diurnal BP and nocturnal BP	Significant decrease in 24-hour BP ($p < 0.0001$), diurnal BP ($p < 0.0001$) and nocturnal BP ($p < 0.0001$) also occurred	Olm effectively reduces 24-hour BP and also effectively reduces nocturnal BP

^, only outcomes relevant to summary section are considered; ABPM, ambulatory blood pressure monitoring; AHD, antihypertensive drugs; Can, candesartan; CKD, chronic kidney disease; DBP, diastolic blood pressure; HTN, hypertension; Los, losartan; OD, once daily; Olm, Olmesartan; Per, perindopril; SBP, systolic blood pressure; SeDBP, seated DBP; SeSBP, seated SBP; T2DM, type 2 diabetes mellitus; Tel, telmisartan; Val, valsartan

Table 4: Clinical studies of olmesartan on vascular inflammation

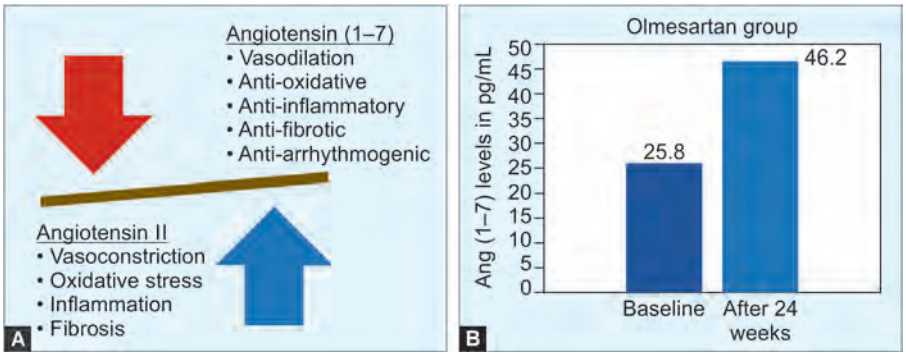
Author (year)	*Patients (n) & stratification*	*Study details and relevant endpoints*	*Results*	*Takeaways*
Miyoshi et al. OLIVUS substudy (2013)[35]	Patients with stable CAD undergoing PCI *N* = 135 Olm (*n*): 70 Placebo (*n*): 65	Prospective, multicentre RCT Duration: 14 months Outcome: Change in hsCRP and IL-6 levels from baseline to at 14 months	Greater reduction in hsCRP and IL-6 with Olm vs baseline ($p < 0.05$ for both): For hsCRP (baseline vs 14 months) (Fig. 1C) • Olm: 2.1 ± 1.6 vs 0.9 ± 0.9 (diff.: –1.2); (↓57%) • Placebo: 1.9 ± 1.4 vs 1.4 ± 1.2 (diff.: –0.5); (↓26%) • Intergroup diff.: $p < 0.01$ For IL-6 (baseline vs 14 months) • Olm: 3.1 ± 2.1 vs 2.1 ± 1.3; (Diff.: –1.0) (↓32%) • Placebo: 3.3 ± 2.4 vs 2.4 ± 1.5 • Intergroup diff.: $p = 0.55$	Olm showed significant reduction in hsCRP with at 14 months vs baseline as well as vs placebo arm There was greater numerical reduction of IL-6 in Olm arm but it did not reach statistical significance in this study
Miyoshi et al. (2011)[36]	Uncomplicated essential HTN *N* = 30 patients treated with Olm 20 mg daily	Prospective, open-label study Duration: 6 months Outcomes: change in hsCRP	hsCRP (baseline vs 6 months) Decreased from 0.94 mg/L to 0.82 mg/L ($p < 0.01$)	Olm reduced hsCRP in patients with essential HTN
Nakayama et al. (2008)[23]	Early-stage T2DM with HTN, *N* = 20 Val (80 mg OD) for at least 8 weeks; switched to Olm 20 mg OD (or) Tel 40 mg OD for 8 weeks, then crossover	Open-label crossover study Duration: 4 months Outcomes: hsCRP and IL-6	Compared to Tel, significant reduction of hsCRP ($p = 0.004$) andIL-6 ($p = 0.001$) occurred with Olm	Significant reduction in hsCRP and IL-6 was observed with Olm compared to Tel
Fliser et al. EUTOPIA study (2004)[37]	Patients with HTN + microinflammation Total *N* = 199 • Olm = 100 • Placebo = 99	Phase IIIb, placebo-controlled, double-blind, parallel-group RCT Duration: 3 months Outcomes: Effect of Olmesartan on hsCRP, hsTNF-α, IL-6, ICAM-1, MCP-1	At 6 weeks vs baseline: • hsCRP: –15.1% ($p < 0.05$) • hsTNF-α: –8.9% ($p < 0.02$) • IL-6: –14.0% ($p < 0.05$) • MCP-1: –6.5% ($p < 0.01$) At 12 weeks vs baseline: • hsCRP: –21.1% ($p < 0.02$) • hsTNF-α: –15.1% ($p < 0.05$) • IL-6: –18% ($p < 0.01$)	Olm showed consistent reduction in inflammatory markers associated with microinflammation up to 12 weeks

CAD, coronary artery disease; hsCRP, high sensitivity C-reactive protein; hsTNFα, high sensitivity tumor necrosis factor—α; ICAM-1, intercellular adhesion molecule 1; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; OD, once daily; Olm, Olmesartan; PCI, percutaneous coronary intervention; T2DM, type 2 diabetes mellitus; Tel, telmisartan; Val, valsartan

contraction against a chronically elevated afterload.[38] LVH is a known risk factor for heart failure (HF), arrhythmias, and sudden cardiac death (SCD).[38] In a large echocardiographic review of 37,700 patients, 19%–48% of untreated hypertensive patients had LVH.[39] An Indian study conducted in a smaller cohort of 86 hypertensive patients also noted that LVH was present in nearly one-fourth (24.4%) of the study population.[40] A recent meta-analysis of 46 studies compared the effects of ACE inhibitors (ACEis), ARBs, β-blockers, calcium channel blockers (CCBs), and diuretics, demonstrating that ARBs were the most effective antihypertensive agents for LVH regression.[41] Studies showing the effect of olmesartan on LVH regression are summarized in Table 5 below.

Effect on Angiotensin (1–7)

Angiotensin (1–7) [Ang-(1–7)], a vasoactive peptide of the RAAS, is mainly generated by angiotensin-converting enzyme 2 (ACE2).[45] Although the classical RAAS has been known for >125 years, this protective arm of the system was only recently discovered.[45,46] Over the past 2 decades, numerous studies have noted the key beneficial actions of Ang-(1–7), which are generally opposite to those of A-II.[45–49] The protective action of Ang-(1–7) (Fig. 2A) warrants consideration, since agents that increase Ang-(1–7) have shown clinical benefits in hypertensive patients.[42,50] Clinical studies that have



Figs 2A and B: (A) Key beneficial actions of Ang-(1–7), which oppose the deleterious effects of Ang II[4549]; (B) Kim and colleagues demonstrated that in patients with hypertension and type 2 diabetes, olmesartan increased Ang-(1–7) levels by 79% compared to baseline levels at 24 weeks[50]

Table 5: Clinical studies of olmesartan on LVH regression

Author (year)	*Patients (n) & stratification*	*Study details and relevant endpoints*	*Results*	*Takeaways*
Yushko et al. (2020)[42]	Patients with T2DM and grade 2–3 HTN aged 43–70 years N = 76 Olm (*n* = 38) Rmi (*n* = 38)	Investigational study Duration: 12 months Outcomes: Change in LVMi	In LVMi after 12 months: Olm vs Rmi • 6.5 vs 6.3% ($p < 0.01$) Reduction of LVMi in patients with basal levels of Ang-(1–7) < 105.51 ng/L • Only in the Olm group was there a significant reduction by 6.8% ($p < 0.01$ vs baseline) • In the Rmi group, changes in LVMi were not significant ($p > 0.5$)	Olm (but not Rmi) significantly increased Ang-(1–7) levels in T2DM patients with HTN. In patients with low levels of Ang-(1–7), Olm (but not Rmi) reduced LVMi significantly led to improvement in LVH
Tsutamoto et al. (2010)[43]	Essential HTN on Can for >1 year Total *n* = 50 • Control group, that is, Can continued (*n* = 25) • Olm group (*n* = 25)	Investigational study Duration: 1 year Outcomes: Change in LVMi Change in A-II	LVMi was significantly decreased from baseline to 12 months in Olm group (135 ± 36 vs 123 ± 29 gm^{-2}) ($p < 0.01$). Serum A-II also decreased in Olm group without significant change in BP	When switched from Can to Olm, patients had decrease in LVMi and A-II without significant change in BP
Albayrak et al. (2009)[44]	HTN with LVH *N* = 44 Olm 20 mg OD	Investigational study Duration: 6 months Outcomes: Effect of Olm on LVH	Improvement in LVH and LVMi after 6 months of Olm • LVMi reduced by 16.6% from 180 ± 37.2 to 150.6 ± 43 ($p < 0.001$) • Left atrial diameter reduced from 3.8 ± 0.4 cm to 3.61 ± 0.39 cm ($p < 0.001$)	Olm reduces LVMi and left atrial diameter. The effect on LVMI proves the effect of Olm on LVH regression

A-II, angiotensin II; BP, blood pressure; Can, candesartan; HTN, hypertension; LVH, left ventricular hypertrophy; LVMi, left ventricular mass index; Olm, olmesartan; Rmi, ramipril; T2DM, type 2 diabetes mellitus

Table 6: Clinical studies of olmesartan on increasing Ang (1–7) levels

Author (year)	*Patients (n) and stratification*	*Study details and relevant endpoints*	*Results*	*Takeaways*
Kim et al. (2023)[50]	Patients with T2DM and HTN (Total *n* = 80) Randomized to Olm 20mg OD (*n* = 40) Aml 5 mg OD (*n* = 40)	Prospective, active comparator, RCT Primary endpoint: changes of serum Ang-(1–7) from baseline to week 24	From baseline levels, serum Ang-(1–7) levels were more significantly increased by Olm (25.8 ± 34.5 pg/mL to 46.2 ± 59.4 pg/mL) than by Aml (29.2 ± 38.9 pg/ mL to 31.7 ± 26.0 pg/mL) (intergroup diff. $p = 0.01$) (Fig. 2B)	Olm increased serum Ang-(1–7) levels by 79% from baseline vs Aml which increased it by 8.5% from baseline
Yushko et al. (2020)[42]	Patients with T2DM and grade 2–3 HTN aged 43–70 years *N* = 76 Olm (*n* =38) Rmi (*n* = 38)	Investigational study Duration: 12 months Outcomes: levels of Ang-(1–7)	Levels of Ang-(1–7): Olm vs Rmi • 20.3% ↑ with Olm ($p < 0.01$)	Olm (but not Rmi) significantly increased Ang-(1–7) levels in T2DM patients with HTN

Aml, amlodipine; Ang-(1–7), angiotensin-(1–7); HTN, hypertension; Olm, olmesartan; Rmi, ramipril; T2DM, type 2 diabetes mellitus

documented the effect of olmesartan on increasing Ang-(1–7) are summarized in Table 6.

Effect on Proteinuria

Microalbuminuria is an independent and strong risk factor for cardiovascular (CV) disease and an early marker of chronic kidney disease (CKD).[51–53] It is also associated with an increased risk of heart failure (HF), arrhythmias, and stroke.[52] In patients with albuminuria, RAAS blockade is prudent for both BP control and albuminuria reduction.[54] Studies with ARBs in patients with HTN and diabetes mellitus (DM) with microalbuminuria have demonstrated a reduction in albuminuria irrespective of pretreatment levels.[55] Additionally, RAAS inhibitors have been proven to decrease proteinuria and slow CKD progression independent of their effects on BP.[56,57] Studies demonstrating reduction in proteinuria with Olmesartan are summarised in Table 7.

Effects on Vascular Stiffness and Reduced Plaque Progression

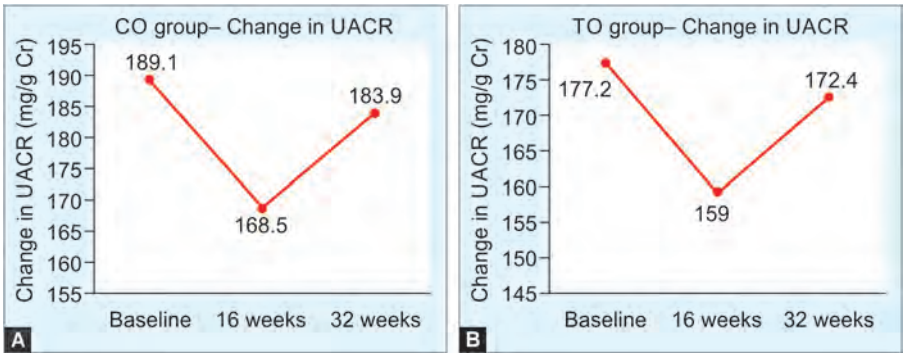
Arterial stiffness is an independent predictor of cardiovascular (CV) disease and contributes to the progression of end-organ damage.[58,59] According to recent research, A-II promotes arterial remodeling and atherosclerotic plaque progression, thereby contributing to atherosclerotic cardiovascular disease (ASCVD), as illustrated in Figure 4.[60]

Validated research methods exist to test arterial stiffness and intravascular plaque progression. The gold standard test to measure arterial stiffness is carotid-femoral pulse wave velocity (PWV).[61] Another indirect measure of arterial stiffness is the augmentation index (AIx).[62] Recently, the cardio-ankle vascular index (CAVI) has emerged as a novel modality for measuring arterial stiffness.[58] CAVI is operator-

Table 7: Clinical studies of olmesartan on proteinuria reduction

Author (year)	*Patients (n) and stratification*	*Study details and relevant endpoints*	*Results*	*Takeaways*
Daikuhara et al. COTO Study (2014)[27]	Patients with HTN and T2DM *N* = 317 Study 1: CO group (*n* = 165)-Pts. on Can (8 mg OD) switched to Olm (20 mg OD) for 16 weeks, switched back to Can (8 mg OD) for 16 weeks Study 2: TO group (*n* = 152)—Pts. on Tel (40 mg OD) switched to Olm (20 mg OD) for 16 weeks and switched back to Tel (40 mg OD) for 16 weeks	Open-label controlled study—Two studies done concurrently to investigate the effects of switching from two different ARBs to Olm Duration: 8 months Secondary Outcome: • Change in UACR	UACR change in CO group: ↓ by –20.6 mg/gm when switched from Can to Olm ($p < 0.05$) and ↑ by +15.4 mg/gm when switched back to Can ($p < 0.05$) (Fig. 3A) UACR change in TO group: ↓ by –18.2 mg/gm when switched from Tel to Olm ($p < 0.05$) and ↑ by +13.4 mg/gm when switched back to Tel. ($p < 0.05$) (Fig. 3B)	Olm led to greater reduction in proteinuria compared to Can or Tel. The rebound increase in proteinuria when reswitching back to Can or Tel proves that the greater proteinuria reduction was due to Olm alone
Ono et al (2013)[29]	Patients with nondiabetic CKD *N* = 44 Olm (*n* = 10), Can (*n* = 9), Val (*n* = 9), Los (*n* = 13)	Retrospective investigational study Duration: 24 months Outcome: Reduction of proteinuria at 1, 3, 6, 12, and 24 months	Olm significantly decreased proteinuria vs other ARBs At 1 month—Proteinuria reduction with Olm greater than Los ($p < 0.01$), Val ($p < 0.01$) and Can ($p < 0.05$) After 2 years—Proteinuria reduction with Olm greater than that of Los ($p < 0.01$), Val ($p < 0.01$) and Can ($p < 0.05$)	Olm significantly decreased proteinuria greater than Los, Val, and Can at 1 month with this effect consistently shown even after 2 years. This suggests that renoprotective effects of Olm may be better than other ARBs
Haller et al. ROADMAP Trial (2011)[57]	T2DM with no albuminuria *N* = 4447 • Olm group (*n* = 2232) • Plb group (*n* = 2215) Olm group received Olm 40 mg/day	Multicentric, double-blind, placebo-controlled RCT Duration: 3.2 years (median) Outcome: Time to the onset of microalbuminuria	Microalbuminuria developed in • Olm group = 8.2% • Plb group = 9.8%Time to onset of microalbuminuria was increased by 23% with Olm (HR = 0.77; 95% CI = 0.63–0.94) ($p = 0.01$).	In patients with DM without albuminuria, Olm was associated with a delayed onset of microalbuminuria significantly

ARB, angiotensin receptor blocker; Can, candesartan; CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension; Los, losartan; Olm, olmesartan; Plb, placebo; T2DM, type 2 DM; Tel, telmisartan; UACR, urinary–albumin–creatinine ratio; Val, valsartan



Figs 3A and B: (A) UACR decreased by –20.6 mg/gm when switched from candesartan (189.1 mg/gm Cr) to olmesartan (168.5 mg/gm Cr) ($p < 0.05$) and increased back by +15.4 mg/gm when switched back to candesartan (183.9 mg/gm Cr) ($p < 0.05$)[27]; (B) UACR decreased by –18.2 mg/gm when switched from telmisartan (177.2 mg/gm Cr) to olmesartan (159 mg/gm Cr) ($p < 0.05$) and increased back by +13.4 mg/gm when switched back to telmisartan (172.4 mg/gm Cr) ($p < 0.05$)[27]; Can, candesartan; Olm, Olmesartan; Tel, telmisartan; UACR, urine–albumin–creatinine ratio

independent, measures arterial stiffness from end diastole to end systole, reflects stiffness across the entire arterial tree (from the aorta to the tibial arteries), and is less BP-dependent than other modalities.[58,59] CAVI values are categorized as normal (<8), borderline (8–9), or abnormal (≥9).[59] Intravascular ultrasound (IVUS) is effective for evaluating coronary plaque in its vascular surroundings. Clinical studies have utilized IVUS to study the effect of pharmacological agents on plaque progression/regression by measuring total atheroma volume (TAV) and percentage atheroma volume (PAV).[60] Olmesartan has numerous studies that attest to its effect on reducing vascular stiffness and its favorable effects on plaque regression. Key studies are summarized in Table 8.

Other Effects of Olmesartan

ARBs likely prevent atrial fibrillation (AF) by reversing changes in cardiac structure and function.[70] Left ventricular hypertrophy (LVH) and left atrial enlargement (both of which are strongly associated with the development of AF) are complications of hypertensive cardiac remodeling.[70] A meta-analysis of 42,892 hypertensive patients showed that ACE inhibitors (ACEi)/ARBs reduced the risk of AF recurrence by 52% compared to calcium channel blockers (CCBs) and by 61% compared to β-blockers.[71] Another meta-analysis of 25,075 hypertensive patients showed that ARB usage reduced the risk of AF by 49% compared to nonusers (HR = 0.51, 95% CI = 0.44–0.58) ($p < 0.001$).[72] ARBs also prevented new-onset AF better than ACEi in patients with a history of stroke or transient ischemic attack (TIA).[72] ARBs have also demonstrated a beneficial effect on stroke prevention in hypertensive patients and in the prevention of diabetic retinopathy.[73,74]

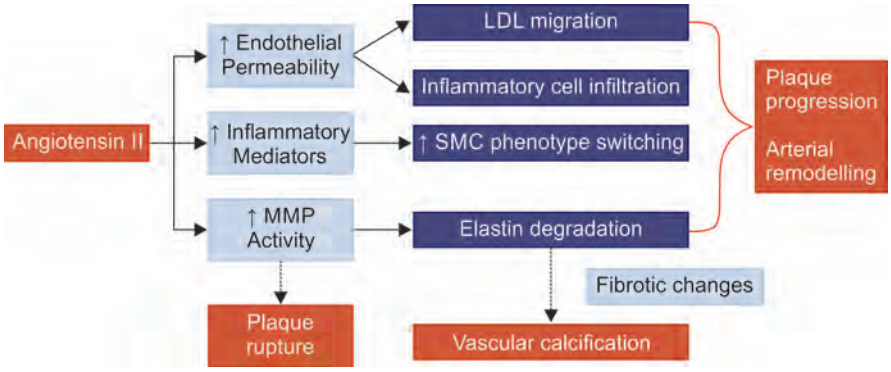


Fig. 4: Angiotensin II role in atheromatous plaque modulation; LDL, low-density lipoprotein; MMP, matrix metalloproteinase; SMC, smooth muscle cell; Adapted from Alkatiri et al.[60]

Studies with olmesartan on the above aspects are summarized in Table 9. Overall effects of olmesartan are illustrated in Figure 5.

Synergistic Strategies: Single Pill Combinations with Olmesartan

A 2021 global study by the NCD-RISC group involving 104 million participants showed that only 17% of the hypertensive population in South Asia achieved BP control.[77] From the Indian perspective, Koya and

Table 8: Clinical studies of effects on arterial tree, for example, vascular stiffness, plaque regression, central aortic BP

Author (year)	*Patients (n) and stratification*	*Study details and relevant endpoints*	*Results*	*Takeaways*
Sirenko et al. (2022)[24]	Mild-to-moderate HTN *N* = 40 • Per 4–8 mg/day (*n* = 20) • Olm 20–40 mg/day (*n* = 20)	Investigational Study Duration: 6 months Outcomes: AIx and PWV at 6 months (vs baseline)	AIx decreased by: • Olm group (–8.13%) • Per group (–2.6%) (intergroup $p < 0.05$) PWV decreased by: • Olm group = –2.72 m/second • Per group = –0.88 m/second (intergroup $p < 0.05$)	AIx and PWV both decreased significantly in Olm group compared to per group
Raff et al. (2015)[63]	HTN with metabolic syndrome *N* = 69 Aim: to analyze effect of Olm 80 mg vs Olm 20 mg vs Aml 5 mg	Double-blind, three-phase crossover study Each of the three treatment phases had a duration of 6 weeks Outcomes: Central SBP, PWV	Central SBP reduction was highest with Olm 80 (14.1 mm Hg) and was greater than Aml 5 (9.7 mm Hg) ($p = 0.0117$) PWV was significantly reduced by Olm 80 (0.58 m/second, $p = 0.0088$) and by Olm 20 (0.48 m/second, $p = 0.0362$) but not by Aml 5 (0.28 m/second, $p = 0.2$).	Olm significantly improves arterial stiffness as demonstrated by reduction in PWV and central SBP
Laurent et al. Vascular Mechanism Study (2014)[64]	HTN with metabolic syndrome *N* = 133 assigned to • Olm 20 mg (*n* = 44) • Olm 40 mg (*n* = 42) • Olm 80 mg (*n* = 47)	Phase III, multicentric, randomized, double-blind, parallel-group study Duration: 1 year Outcomes: Aortic stiffness (carotid-femoral PWV) and carotid parameters at baseline, 24 weeks, 52 weeks	PWV significantly decreased ($p < 0.001$) with time in each group, with no significant time-dose interaction Patients receiving Olm 40 and 80 mg had inward carotid remodeling	Olm 40 and 80 mg were able to significantly remodel and destiffen the arterial during long-term treatment (partly independently of BP) compared to 20 mg
Hirohata et al. OLIVUS-Ex Study (2012)[65]	Extension study of patients of OLIVUS Trial[63] HTN with stable CAD scheduled for PCI (total *N* = 247)	4-year clinical outcomes and annual progression rate of atherosclerosis, (assessed by serial IVUS) were compared with MACCE	Cumulative event-free survival was significantly higher in the Olm group than in control group ($p = 0.04$)	Olm therapy confers benefits in long-term clinical outcomes in patients with HTN and stable CAD
Miyoshi et al. (2011)[36]	Uncomplicated essential HTN *N* = 30 patients treated with Olm 20 mg daily	Prospective, open-label study Duration: 6 months Outcomes: change in CAVI	CAVI (baseline vs 6 months)—Decreased from 8.70 ± 0.98 to 8.37 ± 0.97 ($p < 0.01$)	Olm reduced arterial stiffness in patients with essential HTN
Hirohata et al. OLIVUS Study (2010)[66]	HTN with stable CAD scheduled for PCI (total *N* = 247)—Olm: 10–40 mg (*n* = 126) Control (*n* = 121) IVUS performed on nonculprit vessels at baseline and end of study to determine TAV and PAV	Prospective, randomized, multicentric trial Duration: 14 months Outcomes: Impact of Olm on coronary atherosclerotic changes evaluated by volumetric IVUS	% change in TAV: Olm vs control • +0.6 vs +3.1% ($p < 0.03$) % change in PAV: Olm vs control • –0.7 vs +3.1% ($p < 0.01$) Olm had decreased odds ratio for increased atheroma volume during follow-up periods OR = 0.41 (95% CI = 0.23–0.75)	Plaque regression and lower rate of coronary atheroma progression and was noted with Olm for patients of HTN with stable CAD

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Author (year)	*Patients (n) and stratification*	*Study details and relevant endpoints*	*Results*	*Takeaways*
Miyashita et al. (2009)[67]	T2DM patients with HTN *N* = 70 Olm 20 mg OD (*n* = 35) Aml 5 mg OD (*n* = 35)	Randomized, open study Duration: 12 months Outcome: Reduction in CAVI	CAVI reduction after 12 months • Olm: From 9.4 ± 0.72 to 9.0 ± 0.81 (CAVI ↓ by 4%) ($p < 0.05$) • Aml: From 9.7 ± 0.78 to 9.6 ± 0.79 (CAVI ↓ by 1%) (NS)Changes in BP were almost the same	Olm reduced CAVI (measure of arterial stiffness) significantly while Aml did not (effect was independent of BP reduction)
Stumpe et al. MORE Study (2007)[68]	Patients with SBP/DBP 140–180/90–105 mm Hg *N* = 165 Olm 20–40 mg/day; (*n* = 78) or Aten 50–100 mg/day (*n* = 77)	Multicenter, double-blind trial Duration: 104 weeks Outcomes: Primary: Δ CC-IMT at week 28, 56 and 104 Secondary: Δ PV at week 28, 56 and 104	Mean CC-IMT (SEM) mm: Olm vs Aten Olm: –0.090 (0.015) mm Aten: –0.082 (0.014) mm Mean PV (SEM) mm: Olm vs Aten • At 28 weeks: –3.4 (1.9) vs –0.4 (1.2); difference: –6.9 • At 56 weeks: –3.8 (1.9) vs –0.5 (1.6); difference: –9.5 • At 104 weeks: –4.4 (1.9) vs –0.1 (1.5); difference: –9.0 In the patient subgroup with baseline PV >33.7 µL, significant between-treatment differences existed in ΔPV ($p = 0.023$), because PV regressed significantly with Olm [ΔPV: –11.5 (4.4) µL] but not with Aten [ΔPV: 0.6 (2.5) µL]	Carotid IMT and BP decreased similarly with Olm and Aten, but only Olm reduced the volume of larger atherosclerotic plaques
Smith et al. VIOS Study (2008)[69]	Stage 1 HTN *N* = 60 • Olm (*n* = 27) • Aten (*n* = 22) • Control (*n* = 11)	Randomized, controlled, open-label study Duration: 1-year Outcome: Change in% wall:lumen ratio of small resistance vessels assessed by pressurized myography	Arterial wall:lumen ratio Significantly reduced with Olm: from 14.9 to 11.1%; ($p < 0.01$) No significant change from baseline with Aten	Olm was effective in causing reversal of vascular hypertrophy
Garcia et al. (2007)[30]	Mild-to-moderate Essential HTN *N* = 71 Patients put on Olm 10–40 mg/day	Investigational, single-arm study Duration: 16 weeks Outcomes: Change in PWV between carotid and femoral arteries at baseline vs 16 weeks	PWV decreased from 10.50 m/second (baseline) to 9.26 m/second (after 16 weeks) ($p < 0.0001$). The reduction degree was higher in the youngest patients, where BP decrease was less evident	Olm effectively decreases arterial stiffness, mainly in young patients irrespective of decrease in SBP

Aix, augmentation index; Aml, amlodipine; Aten, atenolol; CAD, coronary artery disease; CAVI, cardio-ankle vascular index; CC-IMT, common carotid intima media thickness; HTN, hypertension; IVUS, intravascular ultrasonography; MACCE, major adverse cardiac and cerebrovascular events; Olm, olmesartan; PAV, percentage atheroma volume; PCI, percutaneous coronary intervention; Per, perindopril; PV, plaque volume; PWV, pulse wave velocity; SBP, systolic blood pressure; TAV, total atheroma volume

colleagues demonstrated that only 22.5% of Indian hypertensive patients achieved BP control.[78] To achieve BP control and improve compliance, olmesartan is available as dual and triple SPCs. Olmesartan-based SPCs (Olm-SPCs) induce smoother, well-sustained, 24-hour BP control compared to monotherapy and also improve therapeutic adherence.[79] In addition to synergistic effects, ARBs offer beneficial effects when combined with CCBs or diuretics to enhance the tolerability of the agents. Combining ARBs with a CCB can reduce peripheral edema, whereas combining them with diuretics may mitigate diuretic-induced metabolic/electrolyte-related adverse effects (AEs).[80,81] The key studies on Olm-SPCs are summarized below in Table 10.

Settling the Controversy: from Trials and Tribulations to Solutions

A controversy arose when the ROADMAP and ORIENT studies revealed a surprising, unexpected finding of increased risk of cardiovascular (CV) death in the olmesartan group.[57,91] This raised concerns, and the US-FDA conducted an independent drug safety review to investigate the matter. The US-FDA noted that the risk of nonfatal heart attacks was, in fact, lower in olmesartan-treated patients and published this finding in the 2014 drug safety communication.[92] Notably, *post hoc* analysis of secondary endpoints of the ROADMAP trial showed that for patients without a history of coronary artery disease (CAD), there was a 52% reduced risk of combined cardiac morbidity (defined as a composite of acute coronary syndrome, silent myocardial infarction (MI), coronary revascularization, and hospitalization due to congestive heart failure) for patients in the olmesartan group compared to the control group (HR = 0.48, 95% CI = 0.28–0.83; $p < 0.01$).[57] Observational follow-up of the ROADMAP trial showed that patients in the olmesartan group had a trend toward reduced cardiocerebrovascular mortality and morbidity (Olm 8.3% vs control 9.8%; $p = 0.325$).[76] Also, the olmesartan group had a reduced risk of congestive heart failure (HF) requiring hospitalization (0.3% vs comparator 1.4%) (OR = 0.23, 95% CI = 0.06–0.85; $p = 0.027$).[76] As noted by the US-FDA

from the ORIENT trial, when deaths occurring 30 days after the last drug dose were excluded from the analysis, there was no difference in mortality between the olmesartan and control groups.[93] A large, well-powered, retrospective cohort study (conducted as per US-FDA guidance) involving more than 57,000 olmesartan users showed that olmesartan did not increase the risk of either sudden cardiac death (SCD) or all-cause mortality compared to users of other ARBs or ACE inhibitors.[94] Based on the overall safety assessment, the US-FDA concluded that there is no clear evidence of increased CV risk with olmesartan. Hence, it continues to be licensed in the US (and EU) for the management of hypertension.[92] A recently published large, multicentric, retrospective study involving 24,806 hypertensive patients showed that olmesartan users did not have any increased risk of CV outcomes (composite

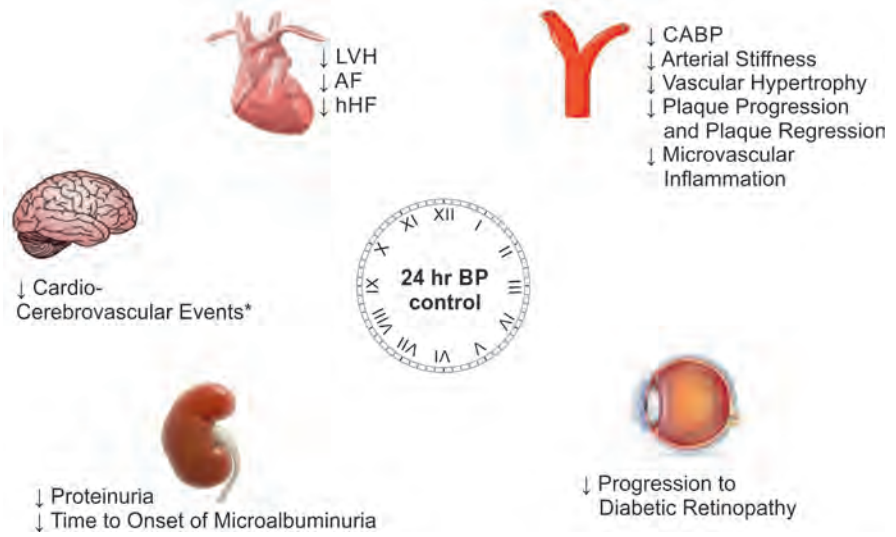

Fig. 5: Effects of Olmesartan—BP control and beyond; AF, atrial fibrillation; CABP, central aortic blood pressure; hHF, hospitalization for heart failure; LVH, left ventricular hypertrophy

Table 9: Clinical studies of other beneficial effects

Author (year)	*Patients (n) and stratification*	*Study details and relevant endpoints*	*Results*	*Takeaways*
Zhang et al. (2016)[75]	AV-B patients with DDD pacemaker implantation Total *N* = 116 • Olm 20 mg (*n* = 57) • Control (*n* = 59)	Single-center, prospective, single-blind, RCT Duration: 24 months Outcomes: • Prevention of new-onset AF • AF burden	• Fewer patients, that is, 17.5% (*n* = 10) in the Olm group had new-onset AF vs 40.7% (*n* = 24) in the control group (*p* = 0.04) • AF burden was lower in the Olm group (8.02 ± 3.10%) vs the control group (13.66 ± 6.14%) (*p* = 0.04)	24-month of Olm therapy could reduce new-onset AF and AF burden in patients with DDD pacemakers
Menne et al. ROADMAP Observational Follow-up Study (2015)[76]	T2DM without microalbuminuria *N* = 1,758	Observational Follow-up Study Duration: 3.3 years (avg.)	• DR significantly reduced in the Olm group (0.9%) vs control (2.6%), OR = 0.34 (95% CI = 0.15–0.78) (*p* = 0.011) • hHF significantly reduced in the Olm group (0.3%) vs control (1.4%), OR = 0.23 (95% CI = 0.06–0.85] (*p* = 0.027) • Trend of reduced cardio-/cerebrovascular events: Olm (8.3%) vs control (9.8%) (*p* = 0.325, NS)	RAAS blockade with Olm in real world settings confers microvascular and macrovascular benefits *via* "legacy effect"

AF, atrial fibrillation; AV-B, atrio-ventricular block; DDD, dual-chamber pacemakers; DR, diabetic retinopathy; hHF, hospitalisation for heart failure; Olm, olmesartan; RAAS, renin–angiotensin–aldosterone axis; T2DM, type 2 diabetes mellitus

Table 10: Key studies of olmesartan based combinations

Author (year)	*Patients (n) and stratification*	*Study details and relevant endpoints*	*Results*
Olmesartan-based dual combination therapy			
Cui et al. SVK Study (2023)[82]	Patients with essential HTN from 36 medical centers *n* = 1341 Olm-Aml 20/5 mg	Prospective, single-arm, multicenter, real-world study Duration: 8 weeks Key outcomes: • Mean change in SeDBP and SeSBP from week 0 to week 8 • Proportion of patients achieving China BP targets, that is, SeSBP/SeDBP <140/90 mm Hg • Proportion of patients achieving BP response • Changes in home—measured BP from week 0 to week 8 • Change in physician and patient satisfaction with HTN T/t (VAS) from week 0 to week 8	Change of SeSBP/SeDBP (mean ± SE): • Week 4: –10.8 ± 0.4/–6.6 ± 0.3 mm Hg • Week 8: –12.7 ± 0.5/–7.6 ± 0.3 mm Hg BP targets achieved by China criteria (Target SeSBP/SeDBP <140/90 mm Hg) • Week 4: 78.8% patients achieved BP target • Week 8: 84.7% patients reached BP target BP response achieved at week 4 and week 8: 80.2% and 86.4% • Home-measured SeSBP and SeDBP decreased from week 1 to week 8 (both *p* < 0.001) • Physicians' satisfaction was elevated at week 8 vs baseline (both *p* < 0.001)

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Author (year)	*Patients (n) and stratification*	*Study details and relevant endpoints*	*Results*
Cui et al. SEVIKAR Subgroup Analysis (2023)[83]	Patients aged ≥65 years with essential HTN *N* = 463 Olm/Aml 20/5 mg	Prospective, single-arm, multicenter, real-world study Duration: 8 weeks Key outcomes: • Mean change in SeDBP and SeSBP from week 0 to week 8 • Proportion of patients achieving China BP targets • Proportion of patients achieving BP response • Changes in home—measured BP from week 0 to week 8 • Change in physician and patient satisfaction with HTN treatment (VAS) from week 0 to week 8	Change of SeSBP/SeDBP (mean ± SE) • Week 4: –10.3 ± 0.8/–4.6 ± 0.5 mm Hg • Week 8: –12.5 ± 0.8/–5.6 ± 0.5 mm Hg Proportion of patients achieving AHA and China BP targets • Week 4: 74.1 and 26.8% of patients achieved BP target • Week 8: 78 and 38.7% of patients reached these BP targets Proportion of patients achieving BP response • Week 4: 76.5% • Week 8: 80.5% Changes in home-measured SeSBP and SeDBP: Decreased significantly from week 1 to week 8 (both $p < 0.001$) • Satisfaction of both patients and physicians was elevated at week 8 vs week 0 (both $p < 0.001$)
Ruilope et al. SEVITENSION Study (2013)[84]	Patients with HTN and ≥3 CV risk factors *N* = 486 Olm/Aml 40/10 mg (*n* = 244) Per/Aml 8/10 mg (*n* = 242)	Multicenteric, double-blind, parallel-group, noninferiority Duration: 24 weeks Outcomes: Primary: Change in CSBP from baseline to week 24 Secondary: BP normalization at 24 weeks	Change in CSBP with Olm/Aml vs Per/Aml: 14.5 ± 0.83 mm Hg vs 10.4 ± 0.84 mm Hg Difference: –4.2 ± 1.18 mm Hg ($p = 0.0001$) BP normalization with Olm/Aml vs Per/Aml at 24 weeks: 75.6 vs 57.5% ($p = 0.0001$)
Sellin et al. (2005)[85]	Patients with essential HTN *N* = 535 Placebo vs • Olm (*n* = 174) • Olm 20 mg + HCTZ 12.5 mg (*n* = 184) • Olm 20 mg + HCTZ 25 mg (*n* = 177) Followed in nonresponders by 8 weeks of double-blind treatment	Partially randomized, multicentric, double-blind, placebo-controlled, phase III study Duration: 12 weeks Outcomes: Primary: Change in mean daytime DBP from baseline to 12 weeks Secondary: Change in mean 24-hour daytime and nighttime DBP and SBP	Change in mean daytime DBP from 0 to 12 weeks (95% CI) vs placebo: • Olm: –9.5 vs 2.8 • Olm + Hctz 12.5 mg: –11.1 vs –5.0 • Olm + Hctz 25 mg: –13.6 vs –6.7 Change in mean 24-hour daytime DBP from 0 to 12 weeks vs placebo: • Olm: –10.2 vs –2.9 • Olm + HCTZ 12.5 mg: –11.5 vs –4.8 • Olm + HCTZ 25 mg: –13.6 vs –6.6 Change in mean 24-hour daytime SBP (mm Hg) from 0 to 12 weeks vs placebo: • Olm: –13.2 vs –4 • Olm + HCTZ 12.5 mg: –17.3 vs –7.8 • Olm + HCTZ 25 mg: –19.9 vs –11.4
Olmesartan-based triple combination therapy			
Oh et al. RESOLVE INT study (2023)[86]	*N* = 2401/3145 completed study Dosing: Olm/Aml/Hctz • 20/5/12.5 mg • 40/5/12.5 mg • 40/10/12.5 mg	Prospective, multicentric, observational study Duration: 24 weeks Primary outcome: • Intensive BP control rate, that is, proportion of patients with SBP <130 mm Hg and DBP <80 mm Hg at week 24 Secondary outcome: • Standard BP control rate, that is, proportion of patients with SBP <140 mm Hg and DBP <90 mm Hg at week 24 • Changes in BP at week 24 from baseline	At 24 weeks: • Intensive BP control rate: 41.4% • Standard BP control rate: 73.3% • SBP/DBP reduction (mean) = –17.8 mm Hg/–9.3 mm Hg in ($p < 0.05$)

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Author (year)	*Patients (n) and stratification*	*Study details and relevant endpoints*	*Results*
Sohn et al. RESOLVE PRO study (2021)[87]	Essential HTN *N* = 3052 Olm/Aml/Hctz SPC (20/5/12.5 mg, 40/5/12.5 mg and 40/10/12.5 mg)	Prospective, multicenter, noncomparative real-world observational study Duration: 12 months Outcomes: Change in the mean SBP/DBP and BP control rate (%) at different time points	Olm/Aml/Hctz led to significant ($p < 0.0001$) in mean SBP/DBP by • 3 months: 11.5/6.6 mm Hg • 6 months: 12.3/7.0 mm Hg • 9 months: 12.3/7.2 mm Hg • 12 months: 12.8/7.4 mm Hg BP control rate of <140/90 mm Hg ($p < 0.0001$): • 3 months: 65.9% • 6 months: 67.9% • 9 months: 68.9% • 12 months: 70.6%
Volpe et al. (2012)[88]	Patients with moderate-to-severe HTN *N* = 1679 Olm/Aml/Hctz: Five doses • 20/5/12.5 (*n* = 335) • 40/5/12.5 (*n* = 336) • 40/5/25 (*n* = 336) • 40/10/12.5 (*n* = 336) • 40/5/25 (*n* = 336)	Multicenter, multinational, phase III, randomized, double-blind, parallel-group study Duration: 10 weeks Outcomes: • SeDBP and SeSBP (mean) from baseline to week 10 • Patients (%) achieving SeBP thresholds (<140/90) from baseline to week 10	Reduction in SBP/DBP at 12 weeks vs baseline (mm Hg): Triple vs dual Olm combination • 20/5/12.5: –33.2*/– 22.5‡ • 40/5/12.5: –33.7*/– 22.5‡ • 40/5/25: 35.3**/– 23‡ • 40/10/12.5: –35.5‡/– 23.9‡ • 40/5/25: –36.2*/– 23.8‡ *$p < 0.001$; **$p < 0.0001$; ‡$p < 0.01$; Ɨ $p < 0.05$ Patients achieving target (%) • 20/5/12.5: 66.2% • 40/5/12.5: 66.4% • 40/5/25: 72.8% • 40/10/12.5: 71.7% • 40/10/25: 72.6%
Weir et al. (2011)[89]	Patients with HTN uncontrolled on monotherapy 40/10/12.5 (*n* = 671) 40/10/25 (*n* = 484)	Phase 4, prospective, open-label, multicenter, single-arm, dose-titration study Duration: 12 weeks Outcomes: • SeDBP and seSBP (mean) from baseline to week 10 • Patients (%) achieving SeBP thresholds (<140/90) from baseline to week 10	Reduction in SBP/DBP at 12 weeks vs baseline (mm Hg) ($p < 0.0001$) • 40/10/12.5: –23.8/– 13.3 • 40/10/25: –25.1/– 13.7 Patients achieving target (%) at 12 weeks • 40/10/12.5: 86.7% • 40/10/25: 90.3%
Oparil et al. TRINITY study (2010)[90]	Moderate-to-severe HTN *N* = 2492 • Olm/Aml 40/10 mg (*n* = 628) • Olm/Hctz 40/25 mg (*n* = 637) • Aml/Hctz 10/25 mg (*n* = 600) • Olm/Aml/Hctz 40/10/25 mg (*n* = 627)	Multicenter, randomized, double-blind, 12-week, parallel-group study Duration: 12 weeks (prior 3-week washout period with no medication) Outcomes (baseline to week 12) • Change in SeDBP • Change in SeSBP • Patients (%) achieving BP targets of <140/90 mm Hg, <120/80 mm Hg, SeSBP <140 mm Hg, and SeDBP <90 mm Hg at week 12	Mean change in SeDBP (mm Hg; $p < 0.001$) • Olm/Aml/Hctz: –21.8 • Olm/Aml: –18 • Olm/Hctz: –16.9 • Aml/HCTZ: –15.1 Mean change in SeSBP (mm Hg, $p < 0.001$) • Olm/Aml/Hctz: –37.1 • Olm/Aml: –30 • Olm/Hctz: –29.7 • Aml/Hctz: –27.5 Proportions of patients reaching the BP target of <140/90 mm Hg at week 12: • Olm/Aml/Hctz: 69.9% • Olm/Aml: 52.9% • Olm/Hctz: 53.4% • Aml/Hctz: 41.1%

Aml, amlodipine; CSBP, central systolic blood pressure; HCTZ, hydrochlorothiazide; HTN, hypertension; Olm, olmesartan; Per, perindopril; SeDBP, seated systolic diastolic blood pressure; SeSBP, seated systolic blood pressure

of all-cause mortality, MI, stroke, and HF) vs comparators.[95]

Conclusion

Olmesartan is an effective ARB with greater pharmacodynamic and clinical efficacy than telmisartan or losartan. Olmesartan confers effective and sustained 24-hour BP reduction, as shown by ABPM studies. Notably, studies also attest to the reduction of central aortic BP, which is of greater importance than just peripheral BP reduction. In hypertensives, the benefits conferred by olmesartan go beyond BP control and target an organoprotective approach toward preventing/reversing HMOD and reducing microvascular inflammation. These multi-faceted effects of olmesartan make it a valuable armamentarium in the clinical management of HTN.

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UPDATE ARTICLE

A Comprehensive Review on Allergic Disorders, Their Epidemiological Trend and Barriers in Management

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Abstract

Allergy is an important public health disorder. Common allergic disorders include asthma, rhinitis, conjunctivitis, atopic eczema, contact dermatitis, and food and drug allergies. In this article, allergic disorders are discussed comprehensively, along with their epidemiological trends, quality of care, and barriers in management. Allergic disorders have increased in prevalence throughout the world, except for a few foci (e.g., Spain) where asthma is decreasing. Prevention of allergen exposure, pharmacotherapy, and immunotherapy are different modes of controlling allergy. Extensive training, research, and awareness can improve the quality of allergy care.

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Introduction

As allergy is an important public health disorder and its prevalence has increased worldwide, awareness among physicians is essential regarding different allergic disorders, as well as their management and prevention strategies. Despite tremendous advancements in the medical field, a knowledge gap still exists in the pathogenesis and management of allergic disorders. Without proper awareness among physicians and further advancements in the field of allergy, allergic disorders will remain underdiagnosed, underinvestigated, and undertreated.

Allergy Types and Pathogenesis

Allergy is an immune-mediated exaggerated reaction of the body to foreign antigens or triggers that are harmless to most people. It includes type I to IV hypersensitivity reactions (HR).[1]

Type I is an immediate HR mediated by immunoglobulin E (IgE) antibodies against soluble antigen. It may be systemic (anaphylaxis or urticaria) or localized, such as in respiratory conditions (asthma). During the sensitization phase, antigen-presenting cells present allergens (antigens) to T cells. T cells then signal B cells to produce antigen-specific IgE antibodies, which bind to FcεR1 receptors on mast cells (MC) and basophils. Subsequently, similar allergen exposure cross-links bound IgE antibodies on sensitized MCs, resulting in degranulation of stored mediators and synthesis of new mediators. Mediators released include histamine, proteolytic enzymes, prostaglandins, platelet-activating factors (PAF), sphingosine-1-phosphate (S1P), tryptase, and others. Cytokines released are of the Th2 type and include IL-4, IL-5, and IL-13. IL-5 helps in the maturation, mobilization (from the bone marrow), recruitment, and activation of eosinophils at allergic sites. IL-4, IL-13, histamine, and TNF-α cause the induction of eotaxins.[2] Eotaxin-1 acts on C-C chemokine receptor (CCR3) and is a potent chemoattractant for eosinophils, basophils, and Th2 lymphocytes.

Mediators released cause peripheral vasodilation, smooth muscle contraction, and increased permeability of vessels. Patients experience profuse mucus secretion, cramps in the abdomen, urticaria, angioedema, runny nose, bronchospasm, hypoxia, and hypotension. Fluid shifting into the interstitial space causes pulmonary and generalized edema. After 4–12 hours, a late-phase response can be seen in type I HR, which can last for 1–3 days. The early phase is due to preformed mediators, while in the late phase, cytokines released in the early phase activate basophils, eosinophils, and neutrophils, causing a late reaction that can occur even in the absence of an antigen.

Complement activation synergizes with classical IgE-mediated responses. Allergen proteases (exogenous or endogenous) can cleave complement proteins and generate anaphylatoxins C3a and C5a, which act as potential effectors in type I HR. For example, C3a-mediated PAF release can cause peanut-induced anaphylaxis.[3]

Type II HRs are cytotoxic and involve IgG or IgM antibody-mediated (along with complement activation) destruction of antigens, e.g., mismatched blood-transfusion reactions. Drug-induced immune hemolytic anemia or thrombocytopenia are other examples of type II HR.[4] Type III HR is immune complex-mediated. Examples include vasculitis, drug-induced lupus, serum sickness reaction, and others. Type II HR can be differentiated from type III by the location of antigens. In type II, antigens are cell-bound, but in type III, antigens are soluble. Type IV delayed-type HR is mediated by a cellular response of T cells against antigens. Th1 response is common in type IV HR, with the release of cytokines like interferon-γ, IL-2, and TNF-β. Type IV HR occurs 48–72 hours after exposure to soluble antigens. Examples of type IV HR include allergic contact dermatitis (ACD), allergic phytodermatitis (APD), delayed drug reactions such as morbilliform drug reactions, drug reaction with eosinophilia and systemic symptoms (DRESS) [new name: drug-induced hypersensitivity syndrome (DIHS)], Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).

IgE-mediated sensitization and allergic reactions are known as atopy. In atopy, a genetic predisposition is found for allergic disorders, especially atopic asthma, hay fever (rhinitis), and atopic dermatitis. In contrast to allergy, autoimmunity is against one's own antigens and includes type II, III, or occasionally type IV HRs. The term "autoallergy" refers to a type I, IgE-mediated HR against self-antigens. Autoallergy is seen in chronic spontaneous urticaria, pemphigus, and others. Idiosyncrasy is an abnormal reactivity to a chemical that is peculiar to a given individual. Although its mechanism is still poorly understood, it is thought to be immune-mediated. Pseudo-allergy mimics allergy but is not mediated by an immunological mechanism, e.g., inhibition of angiotensin-converting enzyme leading

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to an excess of tissue bradykinin, triggering angioedema.

Allergy Triggers and Presentations

Common triggers of allergy include airborne allergens, such as pollen, house dust mites (HDMs), molds, and animal dander; foods, particularly peanuts, tree nuts (e.g., walnuts, almonds, pine nuts), grains with gluten (e.g., wheat, barley, oats, rye), soy, crustacean shellfish (e.g., shrimp, lobster, crab), eggs, milk, and sesame; insect stings, like bee or wasp; medications, like penicillin, β-lactams, sulfonamides, nonsteroidal anti-inflammatory drugs (NSAIDs), radiocontrast materials; and latex.

Respiratory allergy: Respiratory allergies have a wide spectrum of disorders. Allergic asthma is due to IgE-mediated type I HR. It causes type 2 inflammation that leads to the generation of cytokines IL-4, IL-5, and IL-13. Type 2 inflammation in asthma may also be nonallergic. In India, dust and air pollution are the main asthma triggers (49% each) in asthmatics, and in only a small proportion of asthmatics, triggers are pollen grains (5%) and pets (9%). In contrast to the Western world, allergy exacerbations are more common in winter (more dust and air pollution) than in spring (pollen season) in India.[5] Allergic bronchopulmonary aspergillosis is a type I HR to the fungus *Aspergillus fumigatus*, which colonizes the mucosa in the airways of patients with asthma or cystic fibrosis and causes recurrent allergic inflammation in the lung. Hypersensitivity pneumonitis (HSP) is an allergic reaction of the lung to inhaled microorganisms, plant and animal proteins, or chemicals, e.g., bird feathers or droppings, household mold, and animal dander. Acute HSP occurs primarily *via* type III HR. Subacute and chronic forms of HSP are thought to be a transition to type IV HR with granuloma formation. Allergic rhinitis is the most prevalent allergic disorder and usually precedes allergic asthma. It may also be associated with allergic sinusitis or conjunctivitis.

Eye allergy: Eye allergies are due to airborne allergens (e.g., pollen, cat hair, HDM) or contact allergens (e.g., creams, cosmetics, detergents, eye drops). They involve the conjunctiva, cornea, or eyelids. Symptoms include swelling, redness, itching, and watering. Children and adolescents are more commonly affected, and symptoms tend to diminish with age. Seasonal and perennial allergic conjunctivitis are common forms (type I HR). Nasal and eye allergy may present simultaneously as allergic rhino-conjunctivitis. Type III HRs of the eye include SJS, corneal immune ring (Wessely), phaco-allergic endophthalmitis, and others. Type IV HR of the eye includes phlyctenular keratoconjunctivitis, corneal allograft rejection, ACD of the eyelids, and others.

Skin allergy: Skin allergies are due to airborne allergens or direct contact. Skin allergies include atopic eczema, ACD, photoallergic dermatitis, and others. In contact dermatitis, small fluid-filled blisters or vesicles are formed, while weeping plaques (broad, raised areas) are common in atopic dermatitis. Both are itchy, but contact dermatitis is more likely to cause pain and burning. In contrast to ACD, irritant contact dermatitis damages the skin directly following single or multiple exposures to a chemical, along with the release of inflammatory mediators. ACD is a type IV delayed HR due to the interaction of T cells and cytokines, which appears as a rash a day or two after exposure of the skin to an allergen, e.g., hair dye or nickel in jewelry. Irritant contact dermatitis is limited to the area of contact, but in ACD, the rash can spread to other parts of the body. Textile contact dermatitis is a type of ACD, commonly due to chemicals used in processing clothing or fabric.

Occupational ACD among construction workers is prevalent in India. A study from West Bengal showed a high prevalence of ACD among construction workers of bridges, flyovers, and roads.[6] Dichromate is the major allergic component in cement. Hexavalent chromate has the highest allergenic potential. Hand dermatitis is commonly seen, but other areas such as the forearm, legs, thighs, trunk, face, and neck are also involved.

Allergic phytodermatitis (APD) occurs due to exposure to different families of plants, especially *Anacardiaceae* (e.g., cashew, mango) and *Compositae* or *Asteraceae* (e.g., aster, daisy, or sunflower family).[7] Mango fruit causes facial and perioral dermatitis when a sensitized individual bites an unpeeled mango and gets exposure to urushiol in the exocarp. Eating raw cashew fruit causes dermatitis on the face, but boiling and processing it destroys catechols and reduces the risk of dermatitis. *Ginkgo biloba* tree is also a source of urushiol-like catechols and can cause APD. Chrysanthemum-induced APD is seen worldwide. *Parthenium hysterophorus* causes APD due to parthenin. Sensitization to *parthenium* occurs through direct and airborne skin exposure. Dermatitis is commonly seen on exposed parts of the body. Lichenification on the face causes leonine facies. Laundrymen (dhobis in India) mark clothes with black oleoresin extracted from the nut of *Semecarpus anacardium*. Boiling does not destroy the ink, and it causes "dhobi itch" at sites of contact, especially the nape of the neck.

Drug allergy (DA): Drug hypersensitivity reactions (DHR) are of four types: type I (IgE-mediated), type II (IgG/IgM-mediated cytotoxicity), type III (immune complex-mediated), and type IV (T cell-mediated). Type IV is further divided into four subtypes (a-d).[8] The most common DHR types are type I and IV. Immediate DHRs include urticaria (hives), angioedema, or anaphylaxis; and nonimmediate DHRs include morbilliform or maculopapular eruptions (MPE), fixed drug eruption, SJS/TEN, acute generalized exanthematous pustulosis (AGEP), drug-induced hypersensitivity syndrome (DIHS), drug-induced liver disease (DILI), and others. Both large macromolecular drugs and small molecule drugs (molecular weight <1000 Da; act as hapten/prohapten and bind to tissue or blood proteins, such as penicillin) can cause DHRs. Pharmacological interaction with immune receptors (Pi) is a new concept in which direct reversible binding of drugs (lacking hapten characteristics) with antigen-specific T-cell receptors causes T-cell stimulation and the appearance of symptoms even without previous sensitization. DIHS, SJS, TEN, and other HLA-linked DHRs are thought to be Pi-mediated. In DHRs, the skin is predominantly involved because of its richness in memory T cells, which are in close apposition to MHC-expressing dendritic cells.

MPE is the most common of all DHRs. Common causes of MPEs include aminopenicillin, cephalosporin, sulfonamide, allopurinol, and antiepileptic drugs. Urticaria is the second most common. Urticaria is superficial, limited to the epidermis. Angioedema is deep, involving dermal and subcutaneous tissue, and can involve the mucosa of the respiratory and gastrointestinal tracts. While anaphylaxis occurs through IgE-specific antibodies, a few drugs cause mediator release directly (anaphylactoid reaction). NSAIDs like aspirin and radiocontrast media can cause direct mast cell degranulation and result in an anaphylactoid reaction. Red man syndrome, a histamine-related anaphylactoid reaction, is caused by vancomycin. It is characterized by diffuse MPE, flushing, and hypotension. Serum sickness presents with fever and arthralgia, and is commonly seen with monoclonal antibodies (MABs).

DIHS is associated with pyrexia, diffuse rash (morbilliform), facial edema, involvement of different organs, and hematological features like eosinophilia and atypical lymphocytosis. Relapse of DIHS is seen 2–4 weeks after acute symptoms, which coincides with reactivation of herpesviruses such as human herpesvirus 6,

Epstein–Barr virus (EBV), and cytomegalovirus (CMV). Myocarditis and CMV reactivation are common causes of death in DIHS, and mortality is up to 10%. The pathogenesis of DIHS involves both CD4 and CD8 T cells. HLA class I alleles have a strong association with DIHS, for example, HLA-B*32:01 and vancomycin, HLA-B*58:01 and allopurinol, and HLA-B*13:01 and dapsone.

SJS/TEN usually presents with fever, sore throat, conjunctivitis, painful dusky, atypical target-like lesions, and blisters. In SJS, the total body surface area involved is <10%, while in TEN, it is >30%. Drugs commonly involved are sulfonamides, allopurinol, antiepileptics, oxicam NSAIDs, beta-lactam antibiotics, and other antibiotics. SJS/TEN is associated with full-thickness epidermal detachment and mucosal or epidermal necrosis but usually lacks dermal inflammation. It is thought that keratinocyte apoptosis in SJS/TEN occurs through T-cell-mediated interaction of Fas-Fas ligands and their receptors, and the release of chemicals like perforin, granzyme B, and granulysin.[9] Cytotoxic CD8 T lymphocytes release perforin, which punches holes in the target-cell membrane through which granzymes (serine esterases) can enter and induce apoptosis of keratinocytes.

AGEP is associated with high spiking fever, diffuse erythema, and the subsequent development of innumerable pinpoint pustules overlying the erythema. Drugs associated with AGEP include beta-lactam antibiotics, calcium channel blockers, macrolides, radiocontrast agents, dialysates, and others. Skin erosions in AGEP are more superficial than in SJS, with a lack of prominent mucosal involvement. Some patients develop overlap hypersensitivity syndromes, such as DIHS with TEN, DIHS with AGEP, and AGEP with TEN.

Cross-sensitivity is seen among chemically related drugs (e.g., aromatic antiepileptics). In some cases of DHR, enhanced susceptibility to another drug has no explanation, such as enhanced susceptibility to sulfonamides over cephalosporins in penicillin-allergic patients. As severe DHRs are often associated with HLA genes, first-degree relatives should avoid offending drugs. Genetic polymorphism, and HIV and EBV infections can increase the risk of DHRs. Excipients of drugs or vaccines can cause allergies, and they should be considered in cases of multiple unrelated DAs. Correct diagnosis of DA is important, as a majority of self- or physician-reported DAs are found to be nonallergic after testing.

Single organ HRs include DILI and drug-induced acute interstitial nephritis (DI-AIN). DI-AIN manifests 7–10 days after drug exposure and causes acute kidney injury, especially in hospitalized patients.[10] DI-AIN needs differentiation from nephrotoxic acute tubular necrosis, as they have differences in pathophysiology and treatment. Drugs responsible for DI-AIN include antibiotics (e.g., amoxicillin, ciprofloxacin, azithromycin), proton pump inhibitors, NSAIDs, 5-aminosalicylates, diuretics, allopurinol, antiepileptics, H2 receptor antagonists, and others.[10] Symptoms of DI-AIN are nonspecific. Kidney biopsy confirms the diagnosis. The drug should be discontinued before the development of irreversible fibrosis. Corticosteroids are useful in the treatment of DI-AIN.

DILI may be due to idiosyncratic mechanisms or intrinsic mechanisms (e.g., acetaminophen-induced apoptosis and necrosis of hepatocytes). Idiosyncratic DILI is caused by antibiotics (e.g., amoxicillin-clavulanate, sulfonamides, ciprofloxacin, isoniazid, rifampicin), NSAIDs, herbal and dietary supplements, amiodarone, valproate, phenytoin, and others. Most cases of DILI are benign and improve after drug withdrawal. Glucocorticoids have a limited role and are used only when the histological appearance of DILI resembles autoimmune hepatitis.

Food allergy (FA): FA may manifest with cutaneous, respiratory, and gastrointestinal features, and with severe anaphylactic reactions. It is the leading cause of nondrug-related anaphylaxis. In class 1 FA, sensitization to food allergens occurs in the gastrointestinal tract, while class 2 FA is due to cross-reactivity to structurally homologous inhalant allergens. Class 2 FA is also called pollen food syndrome (PFS) or oral allergy syndrome (OAS). PFS is more common but causes milder symptoms. In OAS or PFS, cross-reacting allergens are found in pollen as well as in raw fruits, tree nuts, and vegetables. It causes a contact allergic reaction in the mouth and throat with mild symptoms like itchiness and swelling. In class 2 FA, allergens are heat-labile, are digested, and do not cause gastrointestinal sensitization, but they can cause allergic reactions in already sensitized patients. Acute FA is usually mediated by IgE. FAs in children commonly include eggs, soy, milk, wheat, or peanuts, and in adults, FAs include crustaceans, fish, tree nuts, peanuts, etc. FA is seen more commonly in children than adults. Some children outgrow their FAs (especially egg, milk, and soy) as they get older. Sometimes, HRs caused by various food allergens hidden in the composition of medicines can mistakenly be diagnosed as DAs. Corn/maize allergy can cause hand dermatitis caused by corn starch contained in medical gloves, or it may mimic DA when corn starch is used as an excipient. Thus, the initial diagnosis of DA may be changed to that of FA after investigation.[11] Vaccines cultured in eggs or chick embryos (e.g., influenza, rabies, yellow fever) may also cause allergy due to their egg component. Alpha-gal syndrome (AGS) is a life-threatening IgE-mediated FA in which α-gal, an oligosaccharide, causes anaphylaxis following red meat consumption in patients with tick bites. A tick bite transfers α-gal into the body and causes sensitization. α-gal presents in mammalian meats and other products made from mammals. α-gal is also an ingredient in drugs like cancer chemotherapeutics, such as cetuximab. The B antigen on human red blood cells has structural homology to α-gal and can be protective for AGS. AGS has not yet been reported in India.

FA needs differentiation from food intolerance. In food intolerance, a small amount may not cause a problem, but in FA, a minute amount of food can trigger an allergic reaction. FA retards the quality of life and causes malnutrition and social isolation.

Latex allergy (LA): Natural rubber latex can cause IgE-mediated type 1 HR or delayed ACD; however, synthetic latex, found in latex paint, does not cause symptoms. Breathing in fibers of latex (even small amounts) can cause allergic reactions, such as urticaria, rhinitis, conjunctivitis, asthma, and anaphylaxis. Occupational asthma can occur with repeated latex exposure. Health care workers (HCWs), food handlers, restaurant workers, hairdressers, and painters who frequently use catheters containing latex can develop LA. However, new cases of LA are not common due to the use of nonlatex gloves and products. Some fruits can cross-react with latex, as they have proteins similar to those in rubber tree sap. They cause latex food allergy syndrome or latex-fruit syndrome, and it is seen in about 30–50% of people with LA, commonly in fruits like banana, tomato, avocado, peach, fig, kiwi, etc.

Physical allergy: Physical allergy is usually IgE-mediated and occurs due to exposure to cold, heat, ultraviolet (UV) radiation, exercise, mechanical stimuli, etc. The pathogenesis is not yet clear. It may be due to unknown exogenous allergens or may have an autoimmune origin triggered by physical stimuli. Cholinergic urticaria is precipitated by fever, hot baths or showers, or exercise, and it presents with small-sized (1–2 mm) pruritic wheels surrounded by large erythema. In dermographism, a linear wheal appears after a brisk stroke with a firm object. The wheal is surrounded by erythema. Pressure urticaria is due to sustained pressure from a seat belt or shoulder strap, prolonged running (at the feet), manual labor, etc. This type of urticaria

is often associated with chronic idiopathic urticaria. Exercise alone, or with ingestion of certain food prior to exercise, can precipitate exercise-induced anaphylaxis. An association is seen with IgE antibody against α-5 gliadin, which is present in wheat. Exercise after eating such foods may cause dizziness, flushing, erythema, urticaria, or anaphylaxis. Such foods should not be consumed for a couple of hours before exercising. In contrast to cholinergic urticaria, here wheals are of conventional size and not precipitated by passive heating. Cold urticaria occurs in low temperatures or on contact with cold objects. Immersion or swimming in cold water can cause vascular collapse in these patients. Vibratory urticaria is either occupational or idiopathic and may be accompanied by cholinergic urticaria. Aquagenic urticaria occurs after contact with water, which may be of any temperature, and is occasionally seen in patients with polycythemia vera. Photo-allergy may be an IgE-mediated immediate reaction (e.g., solar urticaria) or type IV delayed HR to exogenous chemicals. The combined effect of ultraviolet light (mainly UVA) and exogenous sensitizing chemicals leads to phototoxic or, less commonly, photoallergic reactions. In phototoxic reactions, highly reactive oxygen molecules induce skin changes resembling sunburn. Photoallergic eruptions are pruritic and resemble eczema. Chronic exposure to photoallergic drugs can lead to chronic actinic dermatitis. Light-sensitizing substances are contained in cosmetic preparations, preservatives, topical or systemic drugs (e.g., NSAIDs like ketoprofen; thiazides; sulfonamides; sulfonylureas; phenothiazines; fluoroquinolones; quinine; quinidine; tricyclic antidepressants; griseofulvin), some fragrances, and certain plants. Photoallergic reactions may induce occupational eczema in farmers, gardeners, fruit growers, and breeders due to pesticides, veterinary drugs, or light-sensitizing plants. Photoallergies can be diagnosed by photo-patch testing. Withdrawal of offending drugs, avoidance of sunlight, and use of sunscreens with UVA filters and topical steroids are helpful in photoallergic dermatitis.

Rarely, Kounis syndrome, a vasospastic acute coronary syndrome, is seen due to anaphylaxis triggered by food, insect bites, or drugs.[12] Systemic mastocytosis is associated with the infiltration of clonally derived MCs in different tissues like skin, liver, spleen, bone marrow, intestines, etc., and patients have intermittent flushing, rash, pruritus, abdominal pain, anaphylactoid reactions, and other systemic features. In idiopathic mast cell activation syndrome (MCAS), a vast number of triggers can induce allergic reactions, and patients experience recurrent IgE-mediated anaphylaxis, other allergic symptoms, and several systemic features.

Relation and Coincidence of Different Allergic Disorders

Different allergic diseases often occur simultaneously or subsequently (atopic march). Allergic rhinitis often precedes or coexists with asthma and is considered a spectrum of allergic airway syndrome.[13] The co-occurrence of allergic rhinitis and asthma is explained by the "one-airway theory," according to which there are similarities in inflammatory processes in the nasal and bronchial mucosa.[14] Patients with rhinitis without asthma can also have subclinical inflammation in the lower airways. Local allergic reactions cause systemic production of allergen-specific IgE. T-cells also migrate from regional lymph nodes to other tissues. Apart from asthma, allergic rhinitis often coexists with sinusitis (rhinosinusitis) and conjunctivitis.

FA occurs often in patients with atopic diseases. LA is seen in people with atopic disorders (e.g., allergic rhinitis) and FAs. In PFS and latex-fruit syndrome FA, respiratory or skin allergies coexist. DA is usually not associated with atopy or other allergic disorders, but atopy can aggravate its symptoms. However, atopy is seen to be a risk factor for NSAID hypersensitivity.[15]

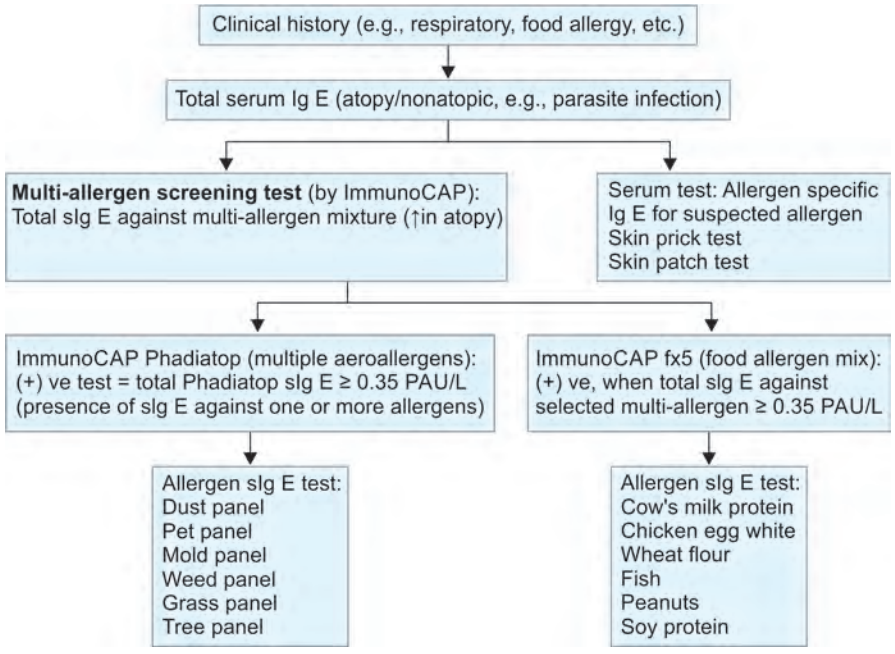
Allergic asthma, rhinitis, conjunctivitis, atopic dermatitis, and anaphylaxis are common in patients with shellfish allergy. Allergy to shellfish, including crustaceans and mollusks, occurs in children as well as in adults. Cross-allergic reactivity is seen between HDMs and shellfish. HDM contains tropomyosin, which has high sequence homology to shrimp tropomyosin. HDM allergens thus sensitize individuals for shrimp allergy, even in vegetarians.[16]

Different types of HRs (type 1-4) may occur simultaneously or subsequently in an individual patient. Simultaneous occurrences of type 1 HR and type IV HR have been reported in cases of atopic eczema and ACD despite the opposing effects of Th2 and Th1 responses.[17]

Diagnosis and Management

Allergy is diagnosed by skin prick tests or patch tests, and blood tests for total IgE and IgE specific for allergens. Flowchart 1 shows an approach for the diagnosis of atopic disorders. Biomarkers for allergic disorders are helpful for precision diagnosis, identification of disease endotypes and therapeutic targets, and monitoring of treatment efficacy.[18] Well-known biomarkers of allergy include serum IgE, blood or sputum eosinophils, and fractional exhaled nitric oxide (FeNO). Research is now focusing on novel biomarkers like pro-inflammatory mediators, epithelial barriers and microbiomes, genes, etc.

Flowchart 1: Approach for diagnosing atopy; PAU, Phadia arbitrary unit; sIgE, specific IgE; *ImmunoCAP, *in vitro* test for antigen-specific IgE utilizing fluoroenzyme immunoassay; **ImmunoCAP Phadiatop, a variant of the ImmunoCAP assay covering a mixture of common aeroallergens used for screening purposes; ***ImmunoCAP fx5, screening test for common food allergens



For preventing allergic reactions, the most important measure is the avoidance of triggers or allergens (Table 1). Avoidance of indoor allergens includes cleaning, vacuuming, hot washing, acaricide spraying, air-conditioning, high-efficiency particulate air (HEPA) filtration, and removing materials carrying allergens like fluffy toys, etc. HDMs get optimal temperature, humidity, and nutrients (human epithelia) in bedrooms, in beds and linen. They can be avoided using mite-proof beddings, impermeable bed and pillow covers, which prevent exposure to HDMs, their metabolites, and eggs. Breathing masks (e.g., N-95, N-99) prevent allergen exposure. Face masks and eyeglasses can provide protection for the airways and conjunctiva. Nasal filters are yet to be proven as protective against allergens. Mucosal barrier enhancement devices are promising.[19] Hypoallergenic nonlatex gloves (e.g., nitrile, neoprene, vinyl, cotton, bamboo, tencel, etc.) should be used to avoid latex allergy. To identify a trigger, keeping a diary will help, especially for tracking activities, foods, or drugs causing symptoms and helping to relieve symptoms.

Treatment of allergy includes antihistamines, antileukotrienes, MC stabilizers (e.g., cromolyn sodium), steroids, or biologics. Biologics include anti-IgE (omalizumab); anti-IL5 (mepolizumab and reslizumab); and anti-IL5 receptor α (benralizumab). Allergic therapy may be topical or systemic. Biologic therapy is found helpful, especially in allergic asthma (e.g., omalizumab, mepolizumab), chronic rhinosinusitis with nasal polyps (e.g., dupilumab), and atopic dermatitis (e.g., dupilumab against IL-4Rα; tralokinumab against IL-13). Biologics prevent exacerbations, but remission criteria are not yet defined. As anaphylaxis may be a biphasic reaction, patients need observation over 6–12 hours after the resolution of initial symptoms. Adrenaline is the first-line therapy in anaphylaxis. Epinephrine or epinephrine auto-injectors should be used, and it should be kept with the patient at all times. A medical alert bracelet (or necklace) may provide information in severe anaphylactic reactions when the patient is not communicative.

Steroids and immunosuppressants are helpful for antibody- and immune complex-mediated disorders and delayed HRs. In skin and eye allergies, topical therapies should include steroids, antiallergics, or skin emollients. In DA, all potentially offending drugs should be stopped. In DIHS, all potentially offending drugs introduced within 8 weeks before presentation are withdrawn. Systemic corticosteroids are the mainstay for

Table 1: Allergens and strategies for preventing their exposure

S. no.	*Allergens*	*Predisposing conditions*	*Steps for preventing exposure*
1.	Outdoor allergens (respiratory)		
a.	Pollen	Pollen season/dry, windy days Peak-early morning	Stay indoors, shut windows, wear face mask, use air-conditioning and HEPA filter, remove pollen-exposed clothing, take shower, rinse nose, wear glasses, avoid gardening, follow pollen forecast
b.	Mold	Damp shady areas, decaying leaves, organic debris, stagnant bodies of water, hot and humid weather, rainy season	Remove dense vegetation, dead trees, damp leaves, and wet, rotten wood; divert water from foundation, fill low-lying areas, wear facemask, take shower after exposure
2.	Indoor allergens (respiratory)		(Avoid nonallergic triggers like tobacco smoke, chemical irritants, odor)
a.	HDM (e.g., *D pteronyssinus* and *D farina*) and storage mite	Humidity >50%, temperature 68–77°F Bed sheets, mattresses, pillows, carpets, furniture, animal fur, stuffed animals	Prefer bare floors; vacuum cleaning, wash bed clothes regularly over 130°F; use mite-proof bed and pillow cover; remove HDM habitats like carpets, upholstered furniture, nonwashable curtain and horizontal blinds; replace carpet with hard flooring material; keep humidity <50%
b.	Animals	Cat and dog dander and other pet allergens like proteins in urine, saliva, feces Bird feathers	Avoid animals in bedroom or bed; wash hands or take bath after touching pet; avoid down comforters/pillows/jackets; brush and bath pets regularly in a closed area
c.	Cockroach	Dead roach debris, roach droppings (frass), saliva, shedding body parts	Keep cockroaches out of home, for example, clean up food debris, use insecticides or boric acid power, caulk house cracks, use exterminator
d.	Mold	Doors, windows, crawl spaces, unsealed parts of building foundation. kitchen, bathroom, laundry, basement; indoor plants, old books, newspapers, furniture; humidity >70%	Clean mold-covered surfaces with bleach; fix water leaks; use dehumidifier (keep moisture <60%, better 35–50%); exhaust fans for attics, kitchens, laundry rooms, bath-rooms, basements; minimize indoor plants, old books, magazines, old beddings and firewood; declutter home; remove mold-impregnated carpet and upholstery
3.	Food allergens	Undeclared or unknown allergens in food, food intake at festivals/ceremonies/busy restaurants; foods cross-reacting with pollen	Avoids foods containing allergens; avoid fruits/foods cross-reacting with pollens; check food-level; precaution for inadvertent mixture; check restaurant menus and ask detailed explanation of ingredients.
4.	Drugs	Large molecule drugs, for example, immunoglobulin, MAB; small molecule drugs forming hapten like penicillin, drugs with similar structure of offending drug	Avoid offending drugs and drugs with close chemical structure. Alert close family members
5.	Skin allergens	Unprotected or uncovered skin, occupational exposure	Use nonlatex gloves, avoid contact with possible allergens, phytoallergens, occupational allergens

HEPA, high efficiency particulate air; HDM, house dust mite; MAB, monoclonal antibody

the treatment of DIHS, but steroid-sparing agents can also be tried, such as cyclosporine, intravenous immunoglobulin, etc. Continuous monitoring for CMV reactivation is essential.

Allergen immunotherapy (AIT) can modulate IgE-mediated allergic disorders like allergic rhinitis, asthma, venom hypersensitivity, FAs, etc.[20] It reduces allergen sensitivity by giving increasing doses of antigens sequentially to the patients. It shifts the immunological response from Th2 to Th1. Though AIT can be administered via different routes, only subcutaneous (SCIT) and sublingual (SLIT) have sufficient evidence. SCIT is commonly used. SLIT needs a larger dose and is not yet approved in India. SLIT with peanut powder was recently approved by the FDA. Oral solutions are not yet considered. Currently, in India, only allergenic extracts from natural sources are used for SCIT. Fewer build-up injections and less frequent maintenance dosing are possible with depot and hypoallergenic formulations. Nasal AIT seems to be beneficial for allergic rhinitis. AIT is usually continued for 3–5 years. Emergency desensitization is used when the offending agent causing IgE-mediated hypersensitivity is essential for life, like anti-snake venom.

Epidemiological Trend

The prevalence of allergic disorders has increased significantly since the industrial revolution. Asthma prevalence is still rising in developing countries, but has begun to decline in some developed countries.[21,22] Allergic rhinitis affects 10–30% of the global population. In a study from Delhi, allergic rhinitis was found to affect 11% of the population, and among them, 33.3% also had asthma.[23]

FA is common in early childhood and becomes less common with increasing age. FA seems to be increasing in prevalence, and more food groups are increasingly detected to have FA, though objective data on this are scarce.[24,25] IgE-mediated FA prevalence is between 5–10% in developed countries.[25] Family history of atopy, Asian ethnicity, and male sex are at higher risk of FA. FA commonly has oral allergy symptoms, followed by skin involvement and rhinoconjunctivitis.[26]

Overall data on the epidemiology of DHRs are scarce, except for individual drugs. DHRs seem to be increasing. National surveys in the pediatric and adult Spanish population showed an increasing trend of DA, allergic rhinitis, and FA, except for asthma, the frequency of which has decreased in both children and adult patients.[21,22] Non-IgE-mediated DHRs (e.g., SJS/TEN, MPE) are more common than IgE-mediated DHRs.[27] DA in children, based on parental perception, is high (3.38% in Krakow) and needs a complete diagnostic workup to confirm or exclude DA.[28] Only about 10% of self-reported DHR patients are positive for allergy tests.[29] Both self-reported and proven DHRs are higher among adults than children.[30,31] Anaphylaxis is most commonly linked to drugs, followed by foods.

At least 20% of the world population is suffering from allergic conjunctivitis, and the prevalence of rhino-conjunctivitis is increasing.[32,33] The prevalence of allergic disorders, including perennial and seasonal conjunctivitis, varies in different countries and regions, with higher prevalence in Africa, Latin America, and Japan.[33,34] The prevalence of atopic dermatitis among children is approximately 20%, and among adults, it ranges between 7 and 14%.[35] The global prevalence of ACD and atopic dermatitis is also gradually increasing.[36]

Factors Related to Changed Prevalence

The rise of allergic diseases is related to westernized lifestyle, urbanization, pollution, and climate change. Factors responsible for the increased prevalence are mentioned in Table 2.

Climate change due to global warming enhances the reproductive effects of plants and produces more pollen due to the high carbon dioxide levels in the atmosphere. Climate change may increase the duration of the pollen season and possibly increase the allergenicity of pollen as well.[37] Climate change leads to land coverage changes, and human habitat encroaching on forest areas results in more exposure to allergens of animal, plant, and fungal origin. Fossil fuel burning and traffic-related emissions enhance the frequency and severity of asthma and rhinitis.[38] The chances of exposure to allergens increase due to climate-related migration of humans and plants. HDMs favor hot and humid weather. Mold proliferation is increased in excessive rainfall, humidity, and floods, both indoors and outdoors. Production and distribution of aeroallergens are altered by thunderstorms and floods. Thunderstorms cause the dissemination of pollen. During thunderstorms, pollen grains absorb moisture and burst into smaller fragments, which are easily dispersed by wind, triggering thunderstorm asthma.

Epithelial barrier hypothesis: Skin and mucosal barriers protect host tissues from allergens. Physical and functional impairment of these barriers causes allergen sensitization. Dysbiotic microbiota cross damaged barriers and trigger allergic disorders. Industrialization and the adoption of modern lifestyles often damage epithelial barriers. A defective epithelial barrier is reported in rhinitis, asthma, atopic eczema, etc.[39]

Hygiene hypothesis: A high standard of hygiene reduces exposure to microbial substances during childhood and predisposes to allergy.[40] Lack of beneficial microbiota in the gut increases FA. Apart from excess sanitation and purification of foods and drinks, FA is also related to the lack of early introduction of allergenic foods during the weaning period and to vitamin D deficiency. Allergenic foods should be introduced early for allergy prevention after a period of exclusive breastfeeding, as per recommendations from different guidelines.[41] Childhood pet exposure reduces the incidence of atopy and allergic rhinitis; growing up on a farm and early exposure to other children are also

Table 2: Factors responsible for epidemic of allergic disorders

S. no.	*Factors*	*Explanations*
1.	Climate change	Consequences of global warming due to greenhouse gas emissions
2.	Pollution	Industrial and traffic related
3.	Hygiene hypothesis	Excessive concern on sterility and sanitization
4.	Absence of early life allergen exposure	Lack of development of immune tolerance
5.	Epithelial barrier hypothesis	Discontinuation of epithelium causes more exposure to allergens
6.	Genetics and epigenetics	Genetic polymorphism and environmental influence on epigenetics
7.	Drugs and antibiotics	Increased availability and use of small molecule drugs and biologics
8.	Foods and food habits	Westernization of food habit
9.	Dysbiosis of gut, skin, and respiratory tract	From pollution, antibiotics

Factors influence each other along with their direct effects on allergy

seen as helpful for allergy prevention.[40,42] It is hypothesized that, since IgE requirement is reduced now to protect against parasitic diseases due to lower incidence, especially in the Western world, the IgE-mast cell axis has evolved into a type I HR.[43]

Dysbiosis due to modern lifestyle is seen in the gut, skin, and respiratory tract, and it adversely affects allergic disorders. Exposure to maternal microbes during vaginal delivery and breastfeeding helps create a pool of healthy gut microbiota and supports immune system development early in life. Changes in lifestyle, indiscriminate use of antibiotics, and preference for cesarean section adversely affect the gut microbiota.[44] Changes in gut microbiota affect oral tolerance of antigens through interactions of gut microbial antigens with pattern recognition receptors of gut immune cells. Production of short-chain fatty acids by intestinal microbes is reduced in gut microbial dysbiosis, and their protective effects on FA are diminished.

Changes in eating habits, increased consumption of processed foods and imported products, and frequent travel contribute to the increased prevalence of FAs. The prevalence of DA has risen due to the increased use of drugs and antibiotics. Large molecule biologics have a high immunogenic potential.

Quality of Care and Barriers

Table 3 shows different barriers to controlling allergic disorders. Suboptimal allergy care is due to a paucity of allergy specialists, inadequate training, and an insufficient multidisciplinary approach. Clinical inertia, lack of evidence-based treatment, and a research gap are other contributing factors. The field of allergy is not an independent specialty in India and is dealt with separately by chest specialists, otorhinolaryngologists, dermatologists, and ophthalmologists. As a result, allergy care is fragmented. The knowledge gap also leads to delayed recognition or nonrecognition of anaphylaxis and other HRs.

Diagnosis of allergy can often be confused with other conditions, as elevated eosinophil and IgE levels are also seen in parasitic infections, especially in developing countries. In presumed allergic disorders, a definite cause is sometimes not determined, leading to uncertainty in diagnosis. This can be problematic, as an unknown trigger may cause a sudden, life-threatening anaphylactic reaction. Despite this, epinephrine is often underused in anaphylaxis, and auto-injectors are not commonly available. Immunotherapy is still not widely practiced, and biologics, which can be crucial in managing severe allergies, remain unaffordable and often unavailable at the point of care.

Antibiotic allergy is rarely confirmed with appropriate testing or graded rechallenge. Withholding an effective antibiotic on suspicion of drug allergy (DA) leads to suboptimal therapy, and patients experience side effects from second-line drugs, exaggerated treatment failures, increased healthcare costs, and the development of antibiotic-resistant infections. So, active antibiotic allergy delabelling programs are essential.[45] Apart from antibiotics, other effective drugs are also underused due to DA misdiagnosis. Information regarding DA is often incomplete, inaccurate, and not up to date in records. Proper allergy documentation and systematic reconciliation of information are critical to ensure patient safety.

Occupational allergic disorders (OAD), like asthma, rhinitis, dermatitis, HSP, and anaphylactic shock, can lead to work interruptions, job loss, and legal consequences.[6,46] OADs may become intractable with continuous exposure to allergens. A study from Alappuzha, Kerala revealed a high incidence (90%) of nasobronchial allergy among symptomatic coir workers (coconut husk); however, bronchial challenge testing was not done.[47] OADs receive poor attention in India. India has no OAD-related policy despite its urgent requirement because of high socioeconomic, health, and legal implications.

Apart from knowledge gaps, a second translational gap—i.e., the time between the acquisition of new knowledge and its application in practice—is also wide, and evidence is poorly adopted in the practice of allergic disorders.

Table 3: Barriers of controlling allergic disorders

S. no.	*Barriers*
1.	Lack of awareness among patients and healthcare workers
2.	Knowledge gap of physicians regarding pathogenesis and management
3.	Lack of allergy training
4.	Less number of allergists
5.	Lack of speciality department of allergy
6.	Inadequate research
7.	Nonavailability of epinephrine autoinjector
8.	Cost of biologics
9.	Immunotherapy: incomplete development or poor standardization
10.	Poor intercaregiver communication and lack of multidisciplinary approach
11.	Allergen free food—expensive; difficult to access; preparation time consuming
12.	Faulty perception in identifying allergy: over or underdiagnosis
13.	Social myth regarding hygiene and avoidance of early life allergen exposure

Strategies and Future Direction

Dedicated allergy training is essential, which should include anaphylaxis education and training regarding the use of adrenaline or adrenaline autoinjectors.

Newer insights regarding the effects of climate change, the hygiene hypothesis, the epithelial barrier hypothesis, and the role of dysbiosis on allergy should be addressed adequately for long-term policy making. Proper mitigation and adaptation measures are required for climate change-related allergic disorders. Physicians should take preventive and therapeutic actions and promote a healthy lifestyle as per the changing environment.

Confirming the proper time to introduce complementary foods in infancy is essential for developing immune tolerance from early allergen exposure. To ensure adequate exposure to maternal microbiota and enhance the number of beneficial microbiota in the gut, respiratory tract, and skin of infants, vaginal delivery and breastfeeding should be encouraged. Indiscriminate use of antibiotics should be stopped.

Further research is essential to understand the role of gut microbiota in allergy (especially FA) and the anti-allergic effect of fecal microbiota implantation. Baked milk and egg may be well tolerated in milk and egg allergies due to heating and interactions with the food matrix in baked goods.[48] Regular use of baked milk and egg can work like immunotherapy, but their safety needs further confirmation.

Na^+/H^+ exchanger regulatory factor 1 is shown to promote airway inflammation in an HDM extract-induced asthma in mice. Further research in the field may lead to the development of new therapeutic strategies.[49] A promising role for CD2 in the regulation

of Th2-associated allergic asthma is shown in another animal study.[50] As several CC chemokines activate a common receptor, CCR3, antagonists targeting CCR3 can inhibit the actions of chemokines on eosinophils and other inflammatory cells.[51,52] Further research in the field is promising. Recently, it has been proposed that sphingolipids, especially S1P, have important roles in the pathogenesis of allergic diseases.[53] S1P is a signaling molecule generated upon IgE-FcεRI crosslinking, which enhances activation of MCs. Regulating S1P has the potential to control allergic disorders. Inhibition of complement may also prove therapeutic in type I HR, for example, anti-C5 antibody eculizumab, which can attenuate allergen-induced airway responses in mild asthma.[54]

Conclusion

A better understanding of pathogenesis, novel technologies for diagnosis and treatment, and the adoption of proper lifestyle and preventive measures from birth will help improve allergy management and reduce the prevalence of allergic diseases and life-threatening anaphylactic reactions.

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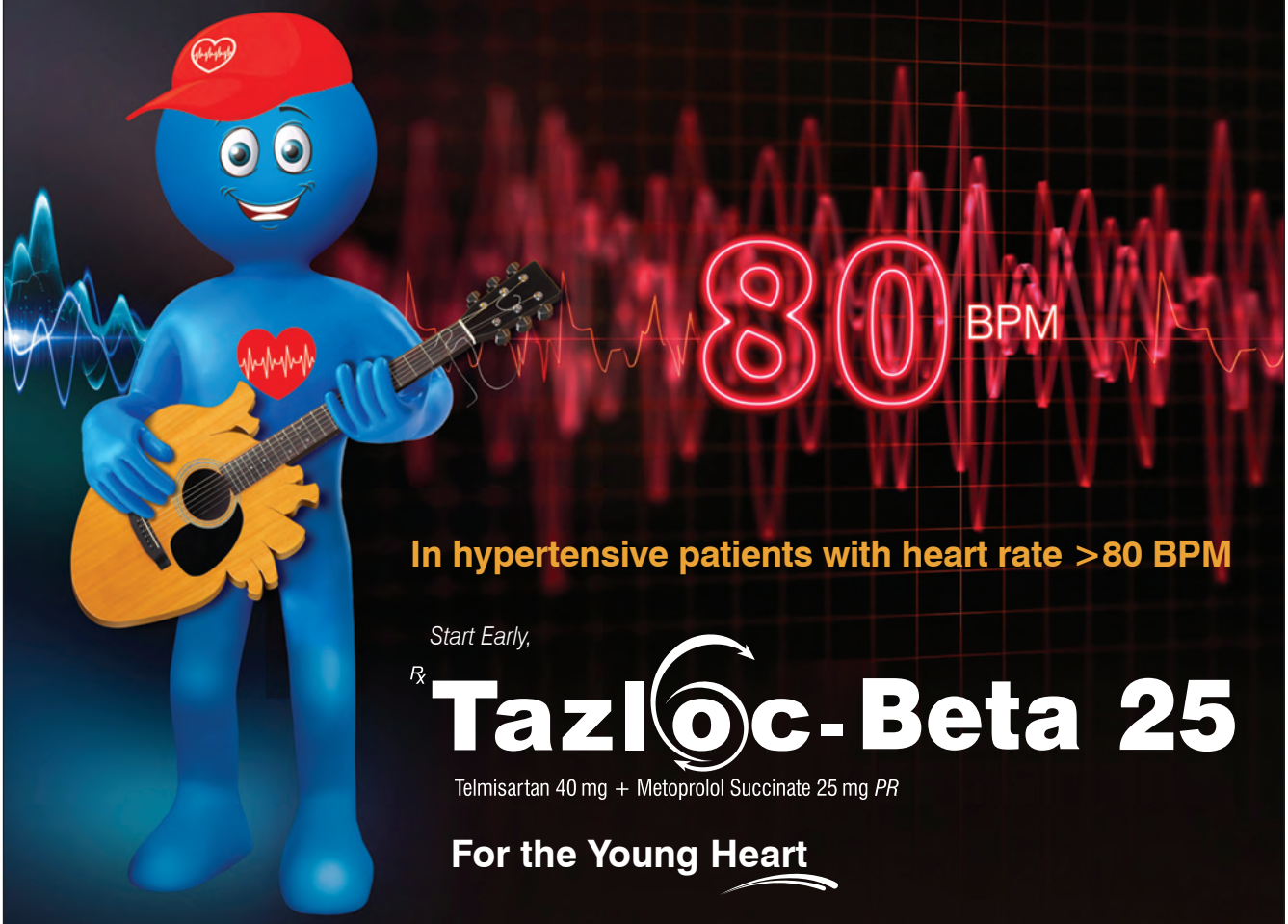

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References:

1. European Heart Journal (2024) 00, 1–10. **2.** 2023 ESH Guidelines for the management of arterial hypertension.

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CASE REPORT

Paroxysmal Hypertension: A Grave Cause

Shyam S Kothari[1*], Sahil Agarwal[2], Vishal Sharma[3]

Received: 06 June 2023; *Accepted:* 21 September 2023

Abstract

A 62-year-old lady was referred with the diagnosis of hypertensive encephalopathy. She had episodes of paroxysms of hypertension while on the ventilator with normal saturations. She underwent a battery of tests to identify the cause of the paroxysms. Eventually, a very unusual cause was found that should have been identified if the label of hypertensive encephalopathy had not been put at the beginning. A diligent history and examination remain important even in the modern day with high-technology care.

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Introduction

Hypertension remains the most common cardiovascular disease. When a hypertensive patient presents with hypertension and hypokalemia, the differential diagnosis is wide and interesting. Sometimes, a mislabeling of the disease can create havoc, and a systematic analysis of the patient's history is always important. We present a case that allowed the opportunity to highlight the approach to paroxysmal hypertension and underline the fundamental importance of clinical approach, even as it was initially missed.

Case Description

A 62-year-old diabetic lady reported to our emergency services with atypical chest pain, breathlessness, and hypertension. Two weeks earlier, she was admitted to a local facility with similar complaints and was diagnosed as having hypertensive urgency. She was not known to have hypertension earlier. She was treated with amlodipine, losartan, hydrochlorothiazide, metoprolol, and sertraline [a selective serotonergic reuptake inhibitor (SSRI)] with moderate blood pressure control. However, four days before presenting to us, she had another episode of severe hypertension with disorientation. An MRI of the brain was normal. She was treated with the addition of intravenous mannitol and furosemide to the antihypertensive drugs and was transferred to our emergency facility. Other details were not available.

On presentation, she was conscious, in distress, and confused. Her heart rate was 65/minute, blood pressure was 160/117 mm Hg, and chest auscultation showed isolated crackles and a few rhonchi. Her electrocardiogram (ECG) (Fig. 1A) showed ST-T changes with QT prolongation, and the chest X-ray showed increased bronchovascular markings with mild pulmonary venous hypertension (Fig. 2). The troponin I was negative, and saturation was 88%. She was treated with bilevel positive airway pressure (BiPAP) support, intravenous nitroglycerin, and oral antihypertensives. Her serum sodium was 110 mEq/L, and serum potassium was 2.6 mEq/L. The blood sugar, liver function tests, renal function tests, and thyroid function tests were within normal limits. The echocardiogram showed normal left ventricular function and mild left ventricular hypertrophy.

She was electively intubated. The hyponatremia and hypokalemia were corrected over 3 days with 3% saline and intravenous potassium replacement as advised by a nephrologist. Her pro BNP was reported to be 218 pg/mL (normal for <75 years of age—125 pg/mL). The blood pressure was well controlled, and ECG changes normalized (Fig. 1B). However, she could not be extubated. Intermittently, she showed episodes of flushing, sweating, disorientation, and hypertension. Blood pressures were 170–190/90–100 mm Hg during these episodes. The monitor showed heart rates varying from 80–110, and saturations were 95–96%. During those times, the endotracheal tube was well in position, the ventilatory settings were not altered, and the episodes were not related to endobronchial suctioning. The blood sugar levels were normal. The daytime pressures, otherwise, were 120–130/70–80 mm Hg. The antihypertensive therapy was continued. During the hospitalization, there was an episode of chest infection that was treated with colistin and gentamicin. Biochemical parameters, including serum electrolytes, serum calcium, phosphorus, and magnesium levels, were normal (Table 1). There was no history of hypertension, sudden death, or endocrine disorders in the patient's family. The patient did not have any significant medical history except for the history of mild seasonal bronchial asthma in the last three years, intermittently treated with bronchodilators.

The patient underwent a series of tests to uncover the cause of paroxysmal hypertension. The abdominal ultrasound showed normally sized kidneys, and both renal arteries Doppler studies were normal. A 24-hour urinary vanillylmandelic acid (VMA) was 10.3 mg (normal—<13.2 mg), and plasma metanephrine was 58 pg/mL (normal values—<65 pg/mL). The abdominal contrast-enhanced computed tomography (CECT) (Fig. 3) did not reveal any mass, lymphadenopathy, or any significant abnormality. Colonic diverticulae were noted. Both adrenals were normal. The CECT chest (Fig. 4) was also done and showed minor pulmonary emboli that did not account for symptoms. There were no paragangliomas. The venous Doppler of the lower limbs was normal. She had a normal MRI and a normal carotid artery Doppler. The tests for carcinoid syndrome were not available, and the diagnosis was considered unlikely. There was no suspicion of the use of illicit drugs or toxin ingestion. The aldosterone and renin profiling were not pursued further as the imaging studies were normal and electrolytes remained normal after initial stabilization.

The tendon reflexes were normal. There were no abnormal movements, eyeball uprolling, or myoclonic jerks during the episodes. The patient was planned for an electroencephalogram (EEG). However, during one of the episodes, when we were transiently able to extubate her, it appeared that the patient had difficulty keeping her eyes open. On questioning the caregiver, he reported that for the last two months, she couldn't keep her eyes open when the blood pressure was

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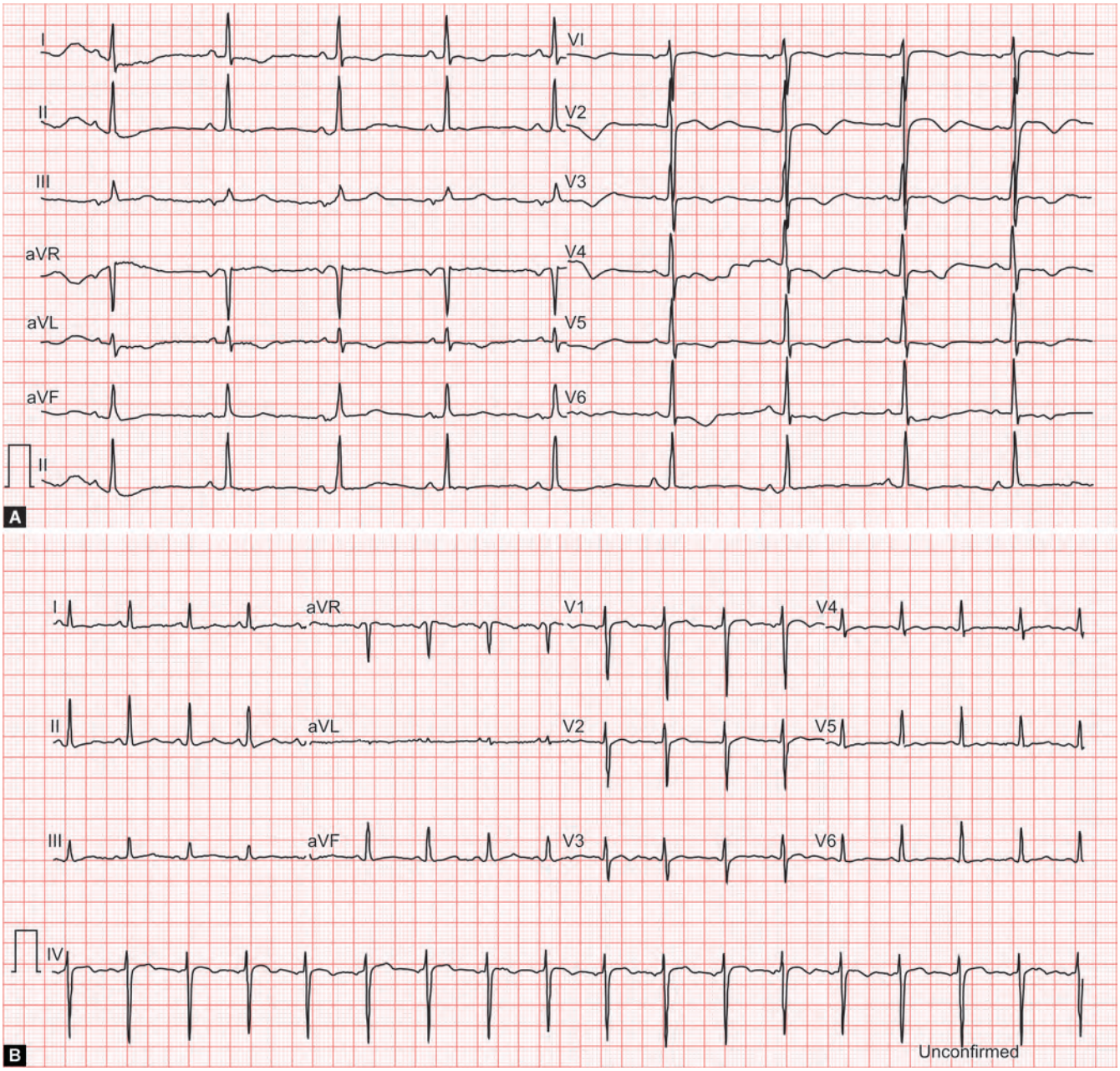

Figs 1A and B: (A) ECG at presentation showing widespread ST-T changes and a QT interval of 500 ms; (B) ECG after correction of electrolyte abnormality within normal limits

high. This story, coupled with the raised dome of the diaphragm on a subsequent X-ray (Fig. 5), initiated the consideration of reactionary hypertension to any respiratory difficulties. The arterial blood gases twice during the episodes showed PCO_2 of 70 and 75 mm Hg and an increased alveolar-arterial gradient for oxygen. The arterial blood gases at other times were within normal range. The test for acetylcholine receptor antibodies for myasthenia gravis was strongly positive (patient—8 nmol/L, normal values—<0.4 nmol/L). She was shifted to a neurology facility for further management, but unfortunately, she succumbed to her illness shortly thereafter with sepsis and multiorgan failure.

Discussion

The initial priority in the management of the patient was to treat severe hyponatremia and hypokalemia that were due to excessive diuretic use in the mistaken belief of hypertensive encephalopathy by the referring physicians. It might be useful to remember that treatment of hypokalemia in this setting will also elevate serum sodium; thus, serum electrolytes require close monitoring.[1] Hypertension may be a cause or consequence of ischemia or acute heart failure, and that should be remembered in medical emergency settings. During the course of her illness, the paroxysms of hypertension and difficulty in extubation were encountered.

The approach to a patient with paroxysmal hypertension may be difficult (Table 2).[2] The episodes of headache, sweating, palpitations, and severe hypertension often dictate the investigations for a pheochromocytoma, but such a diagnosis is found in fewer than 2% of the patients in whom it is suspected. In fact, patients with pheochromocytoma do not typically have flushing; they appear pale during the episodes. Hypertension and

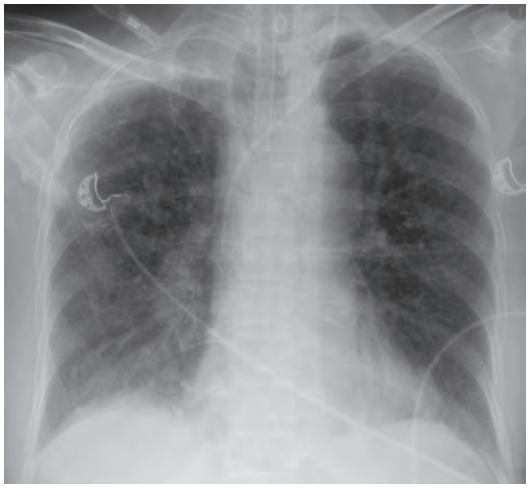

Fig. 2: Bedside chest X-ray AP view showed increased bronchovascular markings with mild pulmonary venous hypertension

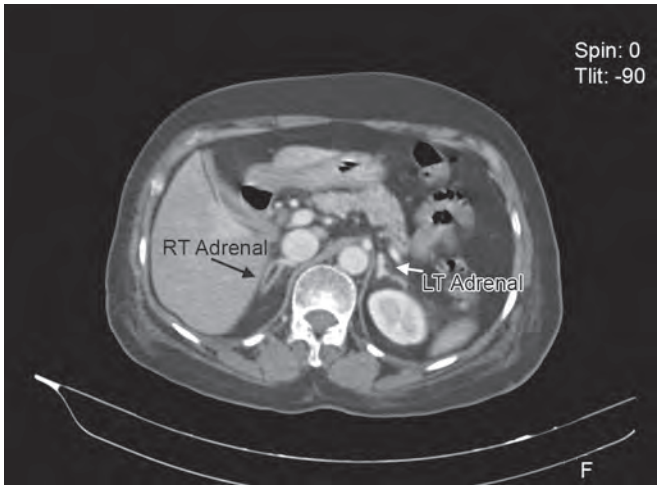

Fig. 3: Axial contrast CT abdomen image showing normal adrenals

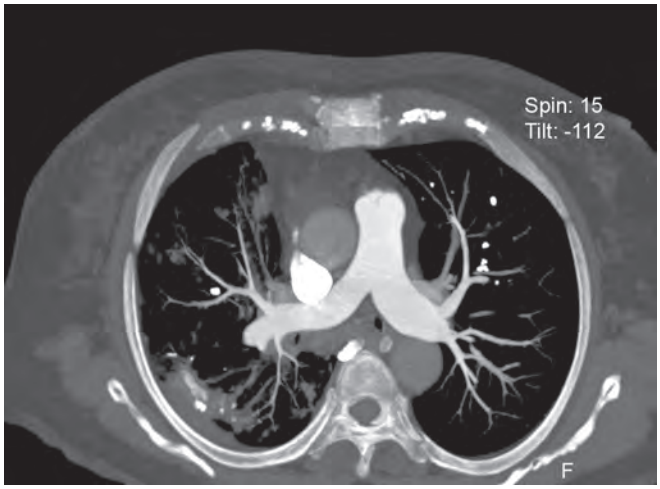

Fig. 4: Maximal intensity projection axial CT pulmonary angiography image showing normal MPA, RPA, and LPA and subpleural fibrotic changes

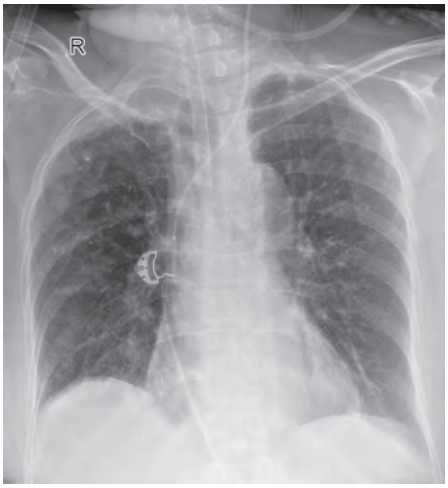

Fig. 5: A subsequent chest X-ray during the clinical course showing raised right dome of the diaphragm

Table 1: Lab investigations

Hemoglobin (gm/dL)	13.6
TLC (/mm^3)	13500
Platelet count (/mm^3)	42800
Blood urea (mg/dL)	21.4
Creatinine (mg/dL)	0.65
Sodium (mEq/L)	137
Potassium (mEq/L)	4.2
Chloride (mEq/L)	97
Calcium (mg/dL)	8.4
Phosphorus (mg/dL)	3.7
Magnesium (mg/dL)	1.8
RBS (mg/dL)	138
CRP (mg/L)	1.4
Procalcitonin (ng/mL)	0.03
Troponin I	8.7
CPK MB (U/L)	38
CPK total (U/L)	43
NT-proBNP (pg/mL)	218
Bilirubin total (mg/dL)	0.5
ALT (U/L)	19
AST (U/L)	18
ALP(U/L)	109
Protein total (gm/dL)	7.2
Albumin (gm/dL)	4.2
Globulin (gm/dL)	3
Plasma-free metanephrine (pg/mL)	10.3
24 hours urine VMA (mg/24 hours)	1
INR	1.01
APTT second	42.8
HbA1c	9%

disproportionate hypokalemia (in this case possibly induced by overzealous diuretic use) might suggest a hyperreninemic state. Hyperaldosteronism and renal artery stenosis should be excluded. These disorders are generally considered in patients with resistant hypertension, but rarely may they cause paroxysmal hypertension.[3,4] Variations in the autonomic state of the individual might conceivably cause the paroxysm in these conditions, although no systematic studies are available regarding the paroxysmal nature

Table 2: Causes of paroxysmal hypertension

A) Secondary to sympathetic drive in patients with myocardial ischemia, hypoglycemia, or respiratory insufficiency
B) Classic causes
Pheochromocytoma
Drugs and toxins
Clonidine withdrawal
Erratic antihypertensive treatment
Binge drinking
Labile hypertension
Renal artery stenosis#, adrenal adenoma#
Neurogenic hypertension
Autonomic seizures
Panic attacks
Rare systemic illnesses like—carcinoid syndrome*, systemic porphyria, systemic mastocytosis*

#Typically present with resistant hypertension, but rarely may present with paroxysms; *commonly hypotension, but rarely may present with hypertension

of hypertension in renal artery stenosis or adrenal adenoma.

Unusual causes of paroxysmal hypertension, like pseudopheochromocytoma, were considered.[5] Often, such patients have a history of traumatic stress disorder and mount a hypertensive response to any stressor—psychological or physical. Our patient was on an SSRI, although there was no past history of any major psychiatric illness or stress disorder. Alternatively, other causes of neurogenic hypertension, like autonomic seizures, were also considered. There was no evidence of any drug ingestion or toxins. Sometimes, the episodes of paroxysms of hypertension might be due to systemic illness, like systemic mastocytosis or porphyria.[6] It is often reasonable to revisit the entire story for missing links when faced with a clinical dilemma.

Labile hypertension and paroxysmal hypertension may be difficult to distinguish.[2] Although fluctuations of blood pressure in patients with essential hypertension are on the order of 25 mm Hg,[2] the fluctuations might be greater in the elderly. The presence of distinct symptomatic episodes with distress makes labile hypertension less likely.

The final diagnosis in this patient was myasthenic crisis. Myasthenic crisis may rarely be the initial manifestation of myasthenia gravis. The diagnosis of myasthenia was entirely missed, and the patient was labeled as a case of hypertensive encephalopathy initially. All the later evaluations were targeted at unraveling the cause of the paroxysm of hypertension. What alterations were precisely used to trigger the crisis while the patient was on the ventilator remains unclear. Diuretic-induced hypokalemia initially, along with antibiotics and other drugs used subsequently in the management of the patient, could have worsened the myasthenic weakness. The lack of hypoxia on the monitor during the episodes was related to the high FIO_2 that she was receiving. Arterial blood gas analysis during the episodes was not considered in the absence of hypoxia on the monitor. Once the clinical context was realized, the arterial blood gas did show CO_2 retention during the episodes.

Hypertension secondary to sympathetic overdrive due to hypoglycemia, myocardial ischemia, or respiratory insufficiency may masquerade as hypertensive emergency, and the real illness may be missed. This case illustrates the value of clinical evaluation in the era of technology dependence. An earlier appraisal of her clinical story could have alerted to the correct cause of the paroxysms of hypertension, possibly sparing unnecessary investigations and prompting appropriate therapy. Unfortunately, this scenario is not uncommon nowadays, with physicians adhering more to the monitors than to the patients' faces. Thus, raising the correct clinical context from clinical history and physical examination remains a central aspect of clinical decision-making.

Conclusion

Paroxysmal hypertension in a patient may result from numerous clinical conditions. Hypertension secondary to sympathetic overdrive due to hypoglycemia, myocardial ischemia, or respiratory insufficiency may masquerade as hypertensive emergency, and the real illness may be missed. Thus, raising the correct clinical context from clinical history and physical examination remains a central aspect of clinical decision-making.

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CASE REPORT

An Interesting Case of Alcohol-related Myelopathy

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Abstract

The most accurately described causes of alcohol-related myelopathy are cases of hepatic myelopathy, which is myelopathy in the setting of either liver cell failure or portosystemic failure resulting in toxic myelopathy in the absence of liver failure. One of the few descriptions of myelopathy completely attributed to toxic effects of alcohol or its metabolites alone is by Sage et al., who reported five patients with the condition who had no evidence of hepatic involvement, portal hypertension, or nutritional deficiency. We report one of the first cases from India where an alcoholic presented with acute onset myelopathy with sphincter disturbances in the absence of liver cell involvement or portosystemic shunting.

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Introduction

Chronic alcohol consumption can present with a multitude of neurological symptoms. Among the manifestations that affect the motor system, alcohol-related myelopathy is relatively rare. Most of the cases described in literature allude to myelopathy in the setting of alcoholic liver disease and myelopathy secondary to portosystemic shunting.[1] The cases resulting from direct neurotoxic effect of ethanol have been reported only in a handful of studies, and there are none from India.[2] Here, we report an interesting case of myelopathy in an alcoholic without any evidence of chronic liver disease (CLD) or portosystemic shunt.

Case Report

A 35-year-old male presented with difficulty in walking and involuntary passage of urine for 15 days. He was apparently well 15 days back when he insidiously noted difficulty in clearing ground, which was associated with stiffness in both legs. He also noted involuntary passage of urine with increased frequency. He was able to feel bladder filling sensation, and there was no associated bowel incontinence or constipation. He is a chronic alcoholic with an average daily consumption of 360–720 mL of brandy and recent history of binge drinking for 5 days; his last drink was 2 days before onset of symptoms. He does not have any other comorbidities, and he was not on any medications. Examination revealed normal higher mental function and normal cranial nerves. Motor examination revealed bilateral spastic weakness of both lower limbs with brisk reflexes in all limbs. Sensory examination was normal, and there were no cerebellar signs. He was provisionally diagnosed as a case of probable noncompressive myelopathy. As part of evaluation, he underwent magnetic resonance imaging (MRI) of the brain to rule out osmotic brainstem demyelination and Wernicke's encephalopathy, and it was normal. MRI of the whole spine screening was done, and it showed normal cord signals with no compressive lesions. Routine laboratory investigations including complete blood count (CBC), renal function test (RFT), liver function test (LFT), random blood sugar (RBS) were normal. There was no evidence of CLD in ultrasonography (USG) of the abdomen. Serum ammonia levels were normal. Peripheral smear showed macrocytes. Serum folate levels were reduced, whereas serum methyl cobalamin and copper levels were normal (Table 1). Nerve conduction study was also normal. Cerebrospinal fluid (CSF) study was done, which was also normal, and hence ruled out infective and immune-mediated causes of myelopathy. Serology for common viral antigens was negative. Anti-human T-cell lymphotropic virus (HTLV) was not done as it did not fit the clinical picture of acute myelopathy. The patient was treated with high-dose parenteral thiamine and folate supplementation, and at the end of 7 days, he was able to walk independently with complete resolution of bladder symptoms.

Discussion

The clinical features and investigations in our case were suggestive of a noncompressive myelopathy of probable metabolic or toxic etiology. Despite working up for common causes of the same, we could not find any etiology except reduced folate levels and macrocytosis suggesting a nutritional cause. However, myelopathy secondary to folate deficiency usually has a subacute onset as opposed to the acute onset in our case, which points to another trigger for acute cytotoxicity. Given the history of binge drinking prior to onset of symptoms, direct neurotoxic effect of ethanol and its metabolites needs to be considered.

A review of literature revealed that most cases of noncompressive myelopathy in the setting of chronic alcohol intake were secondary to CLD[3] and subsequent toxin-induced damage to spinal cord neurons and tracts, particularly demyelination of the lateral corticospinal tracts with an overlap of varying degrees of axonopathy. The cases independent of CLD were attributed to nutritional deficiency secondary to chronic alcoholism, and only few cases in a singular case report were said to result directly from toxic effects of alcohol on the spinal cord neurons. However, very few patients have presented in such acute manner and with isolated pyramidal involvement[4] and sphincter involvement, which makes our case unique. Other rare causes apart from folate to B12 deficiency include vitamin E and copper deficiencies, which may occur secondary to poor diet associated with alcoholism. The exact pathology in cases independent of hepatic disease is not well studied due to lesser case numbers, but it is purported to be toxic damage to corticospinal tracts.

Acute ethanol toxicity has been linked to delayed recovery from traumatic spinal cord injury.[5] The mechanism is hypothesized to be a reduction in cell integrity mediated by ethanol toxicity.[6]

Sphincter involvement in noncompressive myelopathy is rare and has not been reported so far in alcohol-induced myelopathy; however, it was noted in our patient. The possible mechanism could be an early autonomic involvement or involvement of the reticulospinal tract along with corticospinal tract. Complete recovery of urinary symptoms following nutritional supplementation and

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Table 1: Patient characteristics

Investigations	*Result*
Hemoglobin	15.3
RBC	4.6
Hematocrit	41
Total count	6,900
MCV	87
MCH	33
MCHC	38
Platelet	2.7
Liver function tests	
Bilirubin (total)	0.4
Bilirubin (direct)	0.2
Bilirubin (indirect)	0.2
SGOT	21
SGPT	14
ALP	78
Protein	7.7
Albumin	4.5
Globulin	3.2
A:G	1.41
Renal function test	
Urea	14
Creatinine	1.0
Uric acid	9.8
Serum electrolytes	
Sodium	145
Potassium	3.9
Chloride	109
Peripheral smear	• RBCs: Predominantly macrocytes noted along with normocytic normochromic RBCs • WBCs: Neutrophilic predominance • Platelets: Adequate in number • Impression: Normal study
Urine examination	• Urine albumin: Trace • Urine sugar: Nil • Pus cells: 2–3 • RBCs: Nil • Epithelial cells: 2–3 • Cast: Nil • Crystals: Nil
Ammonia	17.2 (normal range: 31–123 µg/mL)
Serum copper	70 µg/dL (64–158 µg/dL)
Folate	2.0 (3.0–17.0)
ANA	Negative
Vitamin B12	462 (normal range: 200–1100 pg/mL)
CSF	• Acellular • Biochemistry: protein 30 • Glucose: 60 • c/s negative
Nerve conduction study	Normal all four limbs

A:G, albumin:globulin ratio; ALP, alkaline phosphatase; ANA, antinuclear antibodies; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; WBC, white blood cell

ethanol cessation confirms the metabolic etiology of the same.

Our case probably reflects a multifactorial etiopathogenesis wherein a myelopathy due to folate deficiency was exacerbated due to binge drinking and ensuing direct ethanol toxicity, presenting with predominant pyramidal involvement with complete sparing of sensory tracts and a rare involvement of bladder.

Accurate identification of nutritional deficiency and timely ethanol cessation is of utmost importance in this completely preventable disease.

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CASE REPORT

Unveiling the Enigma: A Peculiar Encounter of Concurrent Anti-*N*-methyl-D-aspartate Receptor and Anti-Hu Antibody Positive Paraneoplastic Syndrome in Small Cell Lung Cancer

Archana Rajan[1*], Abhinav Sengupta[2]

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Abstract

Paraneoplastic neurological syndromes (PNS) are mostly immune-mediated, tumor-associated disorders. Earlier the 2004 PNS criteria were used which are now partially outdated due to advances in PNS research and also identification of new phenotypes and antibodies that have transformed the diagnostic approach to PNS; hence, a new criterion was proposed in 2016. They can have multifarious presentations, ranging from behavioral abnormalities to altered sensorium and coma. They can precede, be synchronous with, or follow the diagnosis of malignancy. Treatment depends on the underlying antibody and malignancy. We hereby describe an unusual presentation with dual antibody positivity in a patient who was diagnosed with lung cancer in a hospital in the same presentation.

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Introduction

Paraneoplastic limbic encephalitis (PLE) is a rare paraneoplastic neurological syndrome (PNS) that selectively affects limbic system structures, including the hippocampus, hypothalamus, and amygdala. Typically, patients present with cognitive impairment, personality change, short-term memory loss, and seizures.[1] It is associated with antineuronal antibodies. Classical limbic encephalitis (LE) with temporal lobe seizures is associated with onconeural antibodies directed against intracellular antigens, including anti-Hu, anti-Ma2, anti-amphiphysin, and anti-CRMP5.[2–4] Patients might be classified as "seronegative" but may end up testing positive for autoantibodies to neuronal extracellular epitopes, such as the voltage-gated potassium channel (VGKC) complex, *N*-methyl-d-aspartate receptor (NMDAR), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), and gamma-aminobutyric acid B receptor ($GABA_BR$).[2]

N-methyl-d-aspartate receptor encephalitis is most commonly associated with ovarian teratoma. Tumors related to NMDAR encephalitis generally have a relatively benign nature, although neuroendocrine tumors and lung cancers with a high risk of metastasis are rare.[5,6]

Treatment options include immunotherapy and anticancer therapy. Among the immunomodulators, intravenous immunoglobulin, and steroids have shown promising results in patients with better performance status, though prognosis remains guarded.

Case Description

A 73-year-old male known smoker with no prior comorbidities developed progressive cough since 3 months and shortness of breath since 1.5 months. There was no history of chest pain, hemoptysis, sputum production, abdominal pain, jaundice, seizures, loss of consciousness, or focal neurological deficits. Patient was detected to have right-sided pleural effusion, transudative in nature, and was in follow-up in another hospital. He had undergone a contrast-enhanced computed tomography (CECT) Chest which was suggestive of a neoplastic process, suspicious of small cell lung carcinoma with right bronchus intermedius obstruction and subsequent collapse and pleural effusion (Fig. 1). He presented to us with history of altered sensorium which had progressed over the previous 4 days. It is associated with altered behavior in terms of increased sleepiness and past history of memory deficits. With the above complaints, the patient was admitted for further evaluation and tissue confirmation.

On examination, the patient was hemodynamically stable, maintaining saturation on room air. On presentation, his Glasgow Coma Scale (GCS) was E4pV4M5. Limb power was at least 3/5 on the Medical Research Council (MRC) scale in all limbs. His pupils were bilaterally 4 mm, that is equal in size and reactive to light. Deep tendon reflexes were bilaterally present in all limbs and equal, plantar reflexes were mute bilaterally. Normal fundi were seen on ophthalmoscopy. His sensory system, cerebellar signs, and gait could not be assessed. There was no evidence of focal neurological deficits, cranial nerve palsies, abnormal or stereotypical movements, seizures, or autonomic dysfunction. CT head and contrast-enhanced magnetic resonance imaging (CEMRI) brain was performed which revealed no infective, inflammatory, or neoplastic etiology. Due to persistent altered state, cerebrospinal fluid (CSF) study was sent which was significant for increased proteins and no cells. Infective workup including cultures, India ink examination, cryptococcal antigen, Ziehl–Neelsen (ZN) stain, Genexpert, and malignant cytology were negative (Table 1). Metabolic parameters at presentation including sodium, calcium, hepatic, and renal function tests were normal at presentation (Table 2). Pleural fluid evaluation as suggestive of transudative effusion with negative malignant cytology (Table 3).

On day 3 of admission, the patient had progressive worsening of sensorium with GCS of E2V1M5 and had to be endotracheally intubated for protection of airway. Bronchoscopy-guided needle aspirate was taken from right-sided endobronchial lesion. Transbronchial needle aspiration (TBNA) was suggestive of small cell carcinoma of lung. With the above knowledge, paraneoplastic

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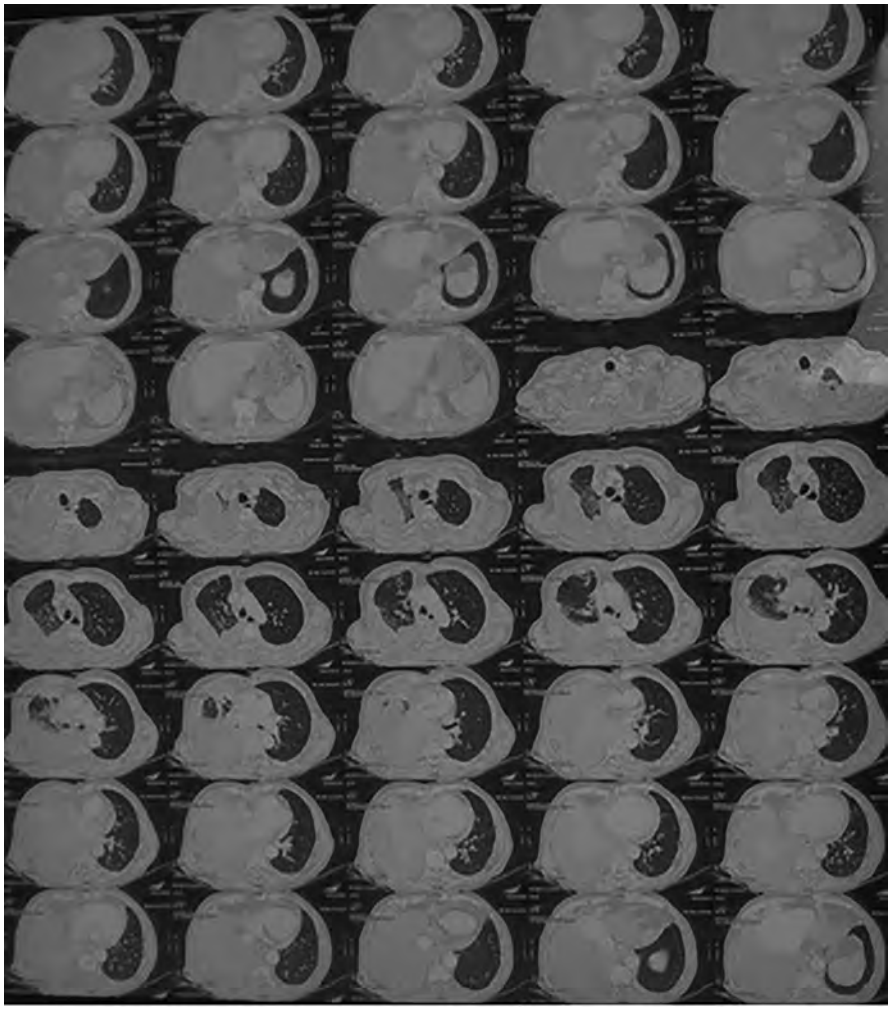

Fig. 1: CECT chest demonstrating right hilar mass with right pleural effusion

and autoimmune encephalitis panel was advised, which revealed anti-Hu (serum and CSF) and anti-NMDA (serum and CSF) antibodies positive.

The patient was tracheostomized in view of persistent altered mental status. Neurology opinion and medical oncology opinion were taken; however, they advised supportive care in view of poor performance status. In hospital, course was complicated by progressive hyponatremia due to a syndrome of inappropriate antidiuretic hormone (SIADH), aspiration pneumonitis, and catheter-associated urinary tract infection (CA-UTI). In view of difficulty in weaning and persistent right pleural effusion, in spite of repeated therapeutic taps, an intercostal drain was placed. He was successfully weaned off ventilator. After explaining prognosis to family members, the patient was discharged on request with advice for the best supportive care at home.

Investigations

Computed Tomography Brain

Diffuse age-related cerebral atrophy seen with small ill-defined hypodensities in deep white matter and lacunar infarct in bilateral

Table 1: CSF analysis of patient

RBC (CSF)	240/mm^3
TLC (CSF)	Nil
DLC (CSF)	Nil
CSF protein	108 mg/dL
CSF glucose	57 mg/dL
Bacterial culture	Sterile
Organism	Nil
CSF GeneXpert	Not detected
Cryptococcal antigen	Negative
Cryptococcal culture, India Ink preparation	Negative
CSF malignant cytology	Negative

DLC, differential leukocyte count

Table 2: Biochemical workup of patient at presentation

TLC	4.57 × 10^3/µL
DLC	N68 L20 M10 E2
Hb	12.6 gm/dL
HCT	38.2%
Platelet count	242 × 10^3/µL
ESR	15 mm in 1st hour
Urea	31 mg/dL
Creatinine	0.7 mg/dL
Uric acid	4.2 mg/dL
Calcium	9.1 mg/dL
Phosphorous	4.6 mg/dL
Sodium	136 mEq/mL
Potassium	5.0 mEq/mL
T bilirubin	0.54 mg/dL
D bilirubin	0.31 mg/dL
I bilirubin	0.23 mg/dL
ALT	14 U/L
AST	18 U/L
ALP	101 U/L
Total protein	7.2 gm/dL
Albumin	4.2 gm/dL
Globulin	3.2 gm/dL
Iron	28 µg/dL
Transferrin	87 mg/dL
Ferritin	487 ng/mL
TIBC	113 µg/dL
Vit B12	1584 pg/mL
Folate	9.38 ng/mL
HIV 1,2	**Nonreactive**
HBS Ag	**Nonreactive**
Anti-HCV Ab	**Nonreactive**
Blood culture	Sterile

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D bilirubin, direct bilirubin; Hb, hemoglobin; HBS Ag, hepatitis B surface antigen; HIV 1,2, human immunodeficiency virus 1 and 2; I bilirubin, indirect bilirubin; T bilirubin, total bilirubin

Table 3: Pleural fluid workup of patient

Pleural for albumin	1.4 gm/dL
Pleural for glucose	120 mg/dL
Pleural ror protein	3.5 gm/dL
DLC	Monocytes 90 Neutrophils10
RBC	120/mm^3
TLC	100/mm^3
Culture	No pathogenic organism grown
Gram stain	Nil
Fungal culture/direct KOH	Sample negative for fungal elements
GeneXpert	Not detected
Pleural fluid cytology	No malignant cells detected

basal ganglia and external capsule s/o microangiopathic ischemic changes. No evidence of metastasis.

Contrast-enhanced Magnetic Resonance Imaging Brain

Age-related cortical atrophy with periventricular ischemic demyelination changes. No abnormal areas of meningeal or parenchymal enhancement were seen to suggest meningitis, meningoencephalitis, or metastasis.

Positron Emission Tomography-Computed Tomography Whole Body with Brain Positron Emission Tomography

Hypermetabolism in both basal ganglia and mesial temporal cortices with hypometabolism in both prefrontal, parietal, and occipital cortices-likely paraneoplastic.

Metabolically active mass in the right lung bronchus intermedius with tiny irregular nodules seen in right upper lung-primary with bilateral pleural effusion (Fig. 2).

Transbronchial Needle Aspiration-biopsy of Bronchial Mass

Bronchoscopy-guided biopsy from right lung shows predominantly necrosis with one of the fragments showing tumor infiltration composed of sheets of tumor cells which are predominantly small with condensed chromatin and nuclear molding. Brisk mitosis, numerous apoptotic bodies, and evidence of Azzopardi phenomenon are noted. The tumor cells are immunopositive for synaptophysin and chromogranin. Overall features compatible with small cell carcinoma of lung.

Discussion

Limbic encephalitis was first reported in 1960 by Brierly et al. with three patients described as having subacute encephalitis of later adult life, mainly affecting the limbic area with two patients having evidence of cancer in autopsy.[7] However, a causative association was not suspected or proven at the time. With improved neuroimaging and discovery of multiple antibodies to different paraneoplastic antibodies, it is now known that it is a more general affliction of the brain with pathology not limited to the limbic areas.

The classic syndrome of limbic encephalitis as described by Tuzun and Dalmau includes rapid development of irritability, depression, sleep disturbances, seizures, hallucinations, and short-term memory loss.[5] It has a subacute development of short-term memory deficits which is considered a hallmark. Many atypical presentations of limbic encephalitis have been reported associated with different antibodies. Our case was performing normal activities of daily living until 4 days since he resented when he became increasingly difficult to arouse. When he presented to us, he was stuporous with no other significant neurologic abnormalities on examination or any evidence of subtle seizures. In the series of 50 PLE patients by Gultekin et al., they reported lethargy and stupor in six of their patients.[1]

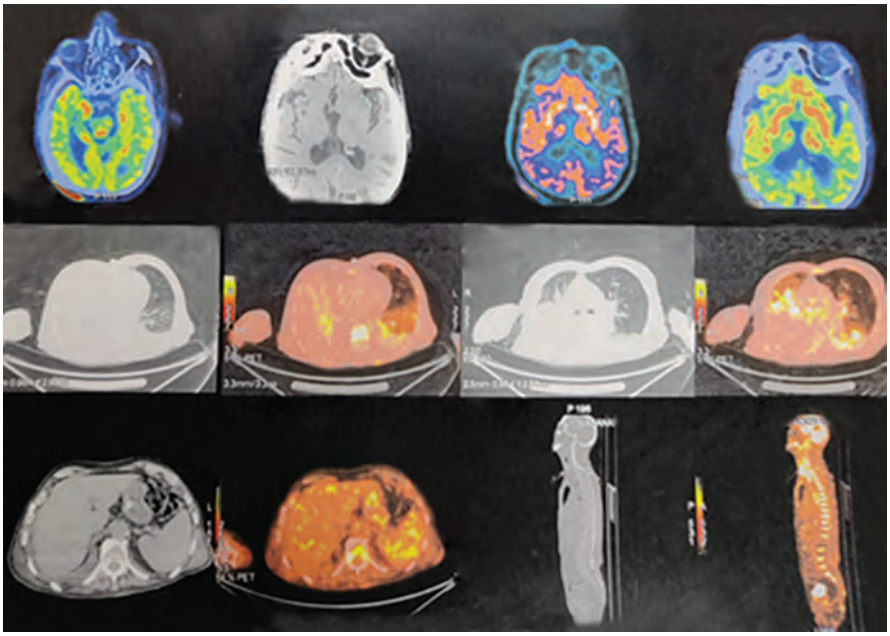

Fig. 2: Whole body FDG PET-CT scan with brain PET-CT

Anti-Hu antibody was described by Graus et al. in 1985 in two patients with small cell lung carcinoma (SCLC).[2] In the PNS Euronetwork Database it was the most frequent onconeural antibody seen at 38.8%, with a plethora of paraneoplastic manifestations, most commonly involving the sensory system (54%), and limbic system in 22%.[8] It is most commonly associated with SCLC with no cancer seen in 15%. Prompt antitumor therapy is most useful in stabilizing the disease and in some cases immunotherapy also helps.

Anti-NMDAR encephalitis is a young disease described in the last 15 years with a typical clinical course. It most commonly occurs in young women, presenting with viral prodrome followed by psychiatric symptoms progressing into dysautonomia, seizures, and ultimately coma. The diagnostic criteria proposed by Graus et al. in 2016 focus on a rapid course with psychiatric, speech, movement, and autonomic disorders with decreased levels of consciousness and seizures.[2] It also harks on the importance of a positive antibody test in the CSF confirming pathogenesis. In the series of 98 patients by Dalmau et al., 58 patients had a tumor with 55 being a teratoma, most common being mature teratoma of ovary.[5]

Anti-NMDAR encephalitis has special implications in older patients where it occurs in equal frequency among the sexes, with association with various cancers, and has a longer time till diagnosis and treatment. Small cell lung cancer has been rarely reported till now with four cases and one case with both anti-NMDAR and anti-AMPAR.[9–13] None of the patients had tumor removal. Three of the patients received immunotherapy with one showing neurological improvement and the other stabilization of disease; the other died during treatment course from infectious complications. In one of the cases, the SCLC cells expressed the NMDA receptor on the surface purporting a causative role.

Concurrence of anti-Hu and anti-NMDAR in the same patient is an even rarer occurrence. Extensive search on yielded two reported cases. Pohley et al. reported a 32-year-old male with headaches, muscle pain, and weight loss followed by seizures, hallucinations, oculomotor disturbances, ataxia, and polyneuropathy. After a delay of 2 years, the patient was found to have serum tests of anti-Hu and anti-NMDAR (CSF positivity has not been mentioned). The patient underwent a diagnostic thymectomy which revealed a primary mediastinal seminoma.[14] The other was reported by Awasthy et al. in a 52-year-old male presenting with gradually progressive behavioral disturbances, sensory loss in lower limbs, tremulousness followed by proximal

weakness, involuntary posturing of neck and left upper limb, and swallowing difficulty. Electromyography (EMG) was suggestive of pure axonal sensory neuronopathy with normal CEMRI and whole-body PET-CT. They discovered both anti-NMDAR and anti-Hu in the patient and held them causative.[15]

Our case study also highlights that NMDAR encephalitis may occur with metastatic cancer and metastasis might even be the initial presentation of the cancer.[16] Moreover, the underlying cancer in NMDAR encephalitis may show a very insidious course and may potentially affect the lifetime survival rate and prognosis of the patient.

Conclusion

Altered sensorium is a common presentation in patients with advanced malignancy, metabolic complications being common cause. Paraneoplastic limbic encephalitis should be suspected in patients with subacute course, behavioral abnormalities, or seizures. Presence of multiple antibodies is rare but can guide management and prognosis. As per our review, this is the first reported case of anti-Hu and NMDA dual positivity in lung cancer presenting with limbic encephalitis. This unique finding, absent in prior literature, underscores the importance of recognizing and elucidating uncommon associations in clinical contexts, highlighting the need for further exploration.

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CASE REPORT

Syringomyelia Mimicking as Bibrachial Variant of Motor Neuron Disease

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Abstract

Introduction: Syringomyelia is a slowly progressive degenerative disorder of the spinal cord. Clinical features of syringomyelia vary from weakness in limbs to positive sensory symptoms and dissociative sensory loss. Thus, early and prompt diagnosis becomes crucial for reducing the morbidity associated with the disease.

Case description: Here, we present a case of 52-year-old male presenting with progressive weakness in bilateral upper limbs without any sensory involvement which is an atypical presentation for syringomyelia.

Conclusion: Motor neuron disease (MND) like presentation in syringomyelia is a rare entity. This can make diagnosis of syringomyelia difficult. Hence, any patient presenting with pure motor weakness of bilateral upper limb should also be suspected of syringomyelia.

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Introduction

Syringomyelia is described as cavitary expansion in the central canal of the spinal cord. Most of the cases are because of developmental anomalies of the spinal canal, like Arnold–Chiari type I malformations. The remaining cases of syringomyelia are idiopathic in nature or secondary to disease of spinal cord like myelitis of any etiology and infarction of spinal cord. It presents classically as weakness and wasting of the hands and arms with segmental dissociative sensory loss. Pain is a symptom in majority of the patients of syringomyelia, it is usually unilateral and severe in intensity. The classic presentation in most of cases of syringomyelia is so characteristic that diagnosis is seldom in doubt. But sometimes the disease may present atypically and may be missed. So here, we are reporting a rare presentation of syringomyelia, in which, a 52-year-old male presented with isolated motor weakness in bilateral upper arms was clinically diagnosed as motor neuron disease (MND) but later, on doing magnetic resonance imaging (MRI), he was diagnosed with syringomyelia.

Case Description

Here, we are reporting a 52-year-old male, who presented to the neurology department with a 1.5-year history of progressive weakness in the left upper limb followed by right upper limb after 6 months duration. He was unable to do his routine activities, like combing hair, reaching for high objects, dressing, and undressing but he had no difficulty in buttoning and unbuttoning his clothes. He was able to eat with his hands, write, and lift small objects with his hands. He also had no difficulty in walking or squatting. He also observed the reduced muscle mass of upper back, shoulder, and upper arm areas. There is no history of any abnormal sensations, decreased sensation in the body, abnormal body movements, or loss of consciousness. No history of fasciculations or twitching of muscles. No history of any distal muscle or lower limb weakness.

The patient is a known case of hypertension for the last 6 months and is taking treatment for it regularly. He had a history of road traffic accident 25 years back when he had head and spine injury for which he was bedridden for 2 months.

During an examination of the patient, the higher mental function and cranial nerve were normal. His motor system examination revealed atrophy of supraspinatus, infraspinatus, deltoid, and biceps muscles (Fig. 1). There was also reduced tone in the corresponding muscles. His muscle power was 2/5 power at left shoulder joint to 3/5 power at right shoulder joint as per Medical Research Council scale. Sensory system examinations including superficial and deep senses were normal. His deep tendon reflexes were absent in bilateral upper limbs and normal in lower limbs. The planter reflex was bilateral flexor in response. There was absence of muscle fasciculation and no evidence of upper motor neuron signs. Rest of the neurological examination was within normal limits. Other neurological and systemic examinations were unremarkable.

In view of pure motor asymmetrical proximal weakness with atrophy of muscle, a provisional diagnosis of bibrachial variant of MND was kept. All the routine

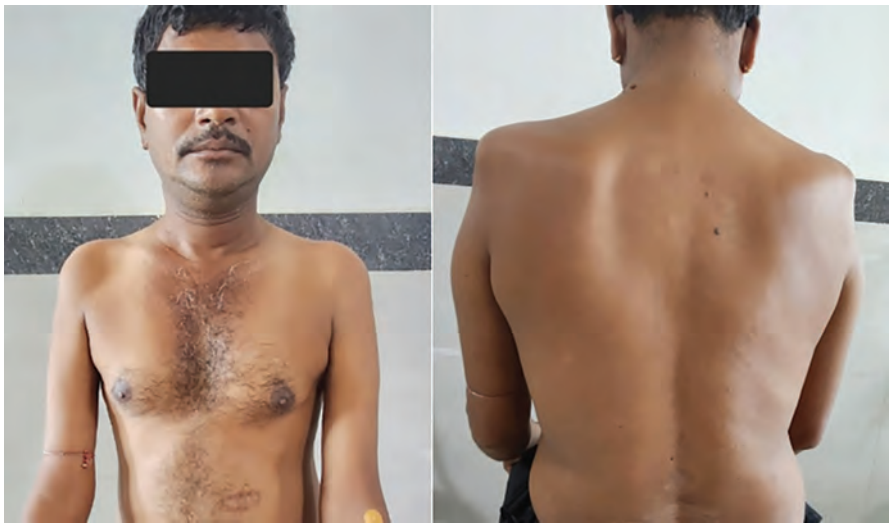

Fig. 1: Showing atrophy of supraspinatus, infraspinatus, deltoid, and biceps muscles

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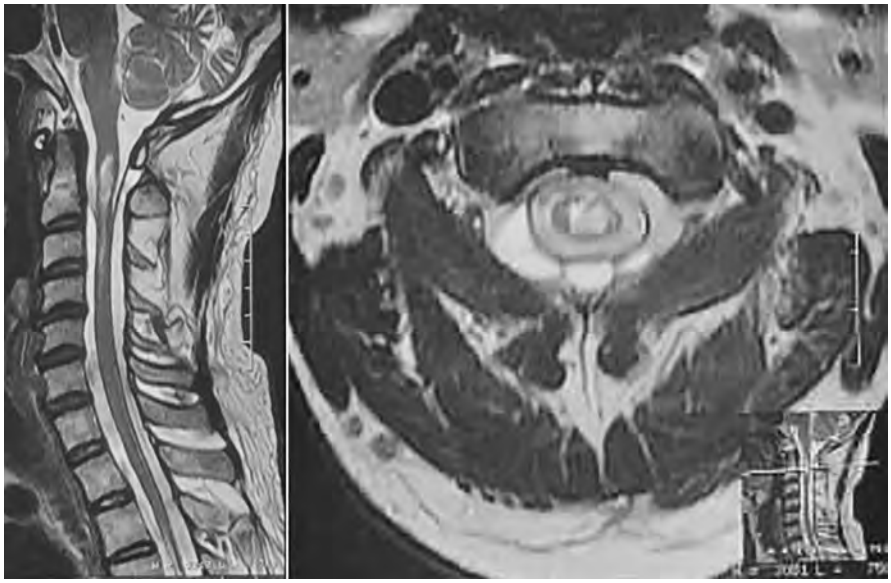

Fig. 2: MRI revealed nonenhancing abnormal signals in the central cord extending from C2 to T1 levels suggestive of focal syrinx

investigations were sent which came out within normal limits. The cerebrospinal fluid (CSF) examination for protein, glucose, cell count, and cell types was also sent which was also within normal limits. The patient was advised MRI cervical spine and electroneuromyography (ENMG).

His MRI revealed nonenhancing abnormal signals in the central cord extending from C2 to C6 levels suggestive of focal syrinx (Fig. 2) and his ENMG was suggestive of neurogenic pattern. The patient was then diagnosed with syringomyelia.

Discussion

Syringomyelia is defined as an abnormal dilatation of central spinal canal which dissects into the surrounding white matter forming a cavity. The specific features of syringomyelia are the combination of lower motor neuron signs at the level of the lesion, a dissociated sensory loss, and upper motor neuron signs below the level of the lesion. The sensory features are described as impaired pain and temperature sensation but preserved light touch, vibration, and position sense in a cape or hemi cape like distribution.[1]

Common complaints of syringomyelia patients includes neck pain, suboccipital headache, back pain, radicular pain, and segmental dysesthesia.[1,2] The etiology of syrinx is variable with almost 70% of nonidiopathic syrinx being caused by Arnold–Chairi type I malformation. Approximately, 25–60% of intramedullary spinal tumors are associated with syringomyelia while only 8–16% of syrinx are caused by tumors.[3] Syrinx can occur in a variety of conditions like serious spinal cord injury, delayed myelitis, or spinal cord ischemia in late phase.[3,4] The prevalence of syringes after trauma varies from 1–7%.[5,6] Symptoms of syrinx formation usually develop over a median duration of 9–15 years after the acute traumatic myelopathy.[7] In our patient also, there was a history of head and spine injury 25 years back. But the duration was >15 years and there was no pain or sensory features, so the syringomyelia was not suspected initially.

A close differential to syringomyelia as in our case is anterior horn cell disease which presents as a progressive disorder with asymmetrical wasting and weakness in proximal or distal group of muscles depending on the type and severity of disease and presence of fasciculations is a classical feature of MND. There are no features of sensory abnormalities, sphincter disturbances, dementia, extrapyramidal signs, and autonomic dysfunction.[8] Because our patient also had bilateral asymmetrical motor weakness, without sensory involvement, he was diagnosed clinically as bibrachial variant of MND. The MRI was done to see secondary causes and routine evaluation, and found that nonenhancing abnormal signals in the central cord extending from C2 to T1 levels suggestive of focal syrinx. So, the whole diagnosis was changed to syringomyelia. The treatment for syringomyelia is difficult.[9] It is primarily surgical if the patient is having progressive weakness. The main aim of surgery is to reestablish normal CSF flow through areas of narrowing due to dural scar, adhesions, and spinal cord tethering. These include creating syringo–peritoneal or syringe–pleural shunts, laminectomy with intradural exploration, lysis of adhesions, and widening of the CSF space using duraplasty.[10]

Conclusion

Syringomyelia is a rare devastating neurologic condition with vague and complicated symptoms that can mimic MND. The main aim of this case presentation is to sensitize that any patient presenting with bibrachial weakness should be advised MRI to rule out structural diseases of spinal cord like syringomyelia as in our case and patients can be treated by a surgery as there is still no treatment available for MND.

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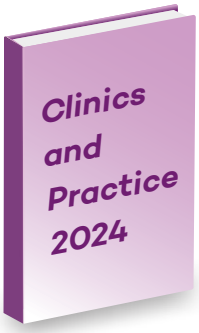

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CASE REPORT

Nutcracker Syndrome and its Exceptional Occurrence with Pulmonary Tuberculosis: A Case Report

Shiv Charan Jelia[1], Devendra Ajmera[2], Divya Airan[3*], Yogesh Meena[4], Ranjeet Bairwa[5]

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Abstract

Nutcracker syndrome (NCS), also known as left renal vein (LRV) entrapment syndrome, is a condition resulting due to compression of LRV between the aorta and superior mesenteric artery (SMA), with dilatation of the distal portion of LRV. We present a case of an elderly female presenting with left lumbar pain for 1 year. Initial investigations revealed microscopic hematuria and mild ascites. Further investigations revealed compression of LRV between the aorta and SMA, with aorto-SMA angle reduced up to 12°, suggesting a diagnosis of NCS. Along with this, cystic bronchiectasis with multiple centrilobular nodules with tree-in-bud pattern was seen in bilateral lung fields, suggestive of pulmonary tuberculosis. Ziehl–Neelsen (ZN) staining and cartridge-based nucleic acid amplification test (CBNAAT) confirmed our diagnosis of NCS with pulmonary tuberculosis.

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Introduction

Nutcracker syndrome (NCS), also known as left renal vein (LRV) entrapment syndrome is defined as compression of LRV between the aorta and superior mesenteric artery (SMA), resulting in compromised outflow from LRV into the inferior vena cava.[1] Most cases of NCS present with atypical left flank pain that worsens with standing. This might divert our attention toward musculoskeletal etiology. Some patients present with microscopic hematuria and orthostatic proteinuria. Others present with infertility, dyspareunia, and other gynecological symptoms. The rest present with varicocele and varicose veins in the lower limbs up to the knees. Other rarer presentations include orthostatic hypotension, vague abdominal pain, and fatigue.[2]

Case Description

In this case report, we present a case of a 74-year-old female who presented with recurrent left lumbar pain for 1 year and abdominal distension for the past 1 month. The patient did not give a history of comorbidities. The patient did not have any other associated symptoms such as fever, constipation, diarrhea, vomiting, and dysuria. However, the patient did have loosening of clothes, suggesting weight loss in recent times.

On examination, heart rate was 78 beats per minute, blood pressure was 100/70 mm Hg, temperature was 36.4°C, and respiratory rate was 18 per minute. Systemic examination was within normal limits except for abdominal examination. On per abdomen examination, the patient had tenderness in the left lumbar region along with a distended abdomen.

The patient's routine tests such as complete blood counts, renal function tests, liver function tests, and serum electrolytes were within normal limits. Urine examination showed 5–10 erythrocytes/high power field.

Ultrasonography (USG) of whole abdomen was performed, which was suggestive of mild ascites.

The contrast-enhanced computed tomography (CECT) scan was ordered (Figs 1 and 2) which was suggestive of marked compression of LRV while traversing between the SMA and aorta. The aorto-SMA angle was also reduced up to 12°. It also showed dilation of left ovarian vein up to 10 mm with multiple varicosities seen in the pelvic region. Along with this, cystic bronchiectatic changes with multiple centrilobular nodules with tree-in-bud pattern were seen in bilateral lung fields. We sent Ziehl–Neelsen (ZN) stain for acid-fast bacilli and also ordered cartridge-based nucleic acid amplification test (CBNAAT)

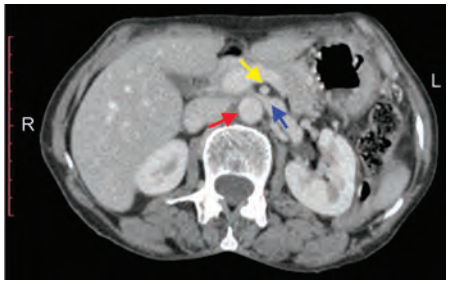

Fig. 1: Contrast-enhanced CT scan showing compression of LRV between the aorta and SMA. (Yellow arrow is showing SMA. Red arrow is showing aorta. Blue arrow is showing LRV)

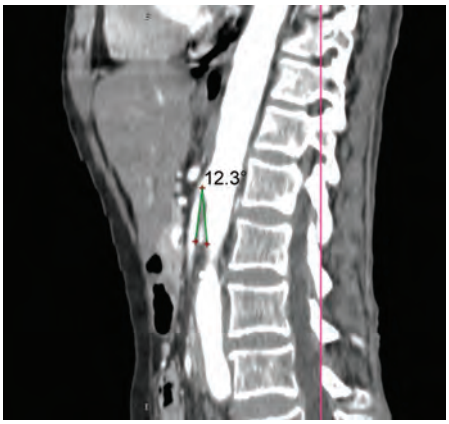

Fig. 2: Contrast-enhanced CT scan showing reduced aorto-SMA angle

for sputum. ZN stain was positive for acid-fast bacilli (+2), and CBNAAT also detected Mycobacterium tuberculosis without rifampicin resistance. The final diagnosis of NCS with pulmonary tuberculosis was made.

The patient was advised operative treatment but patient refused, so conservative management was advised to the patient. The patient was treated symptomatically. Antitubercular therapy was also started for management of tuberculosis. To improve renal perfusion, the patient was also started on angiotensin-converting enzyme inhibitor—enalapril 10 mg.

Discussion

Earlier, NCS was considered a rare disease, but nowadays many patients presenting with hematuria or proteinuria are beingidentified as NCS. Still, the exact prevalence of NCS is not known. The prevalence of NCS is slightly higher in females.[1,3] NCS can affect any age range starting from childhood to the seventh decade but most of the patients present in their second or third decade of life, during puberty when

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body height increases rapidly. This, along with the maturation of vertebral bodies, leads to narrowing of angle between SMA and aorta.[1,3]

The most common presenting symptoms of NCS are hematuria, abdominal pain, and proteinuria. Abnormal aorto-SMA angle leads to an increase in LRV pressure. It is believed that LRV hypertension triggers inflammatory activity, which leads to abdominal pain. One should suspect NCS in children presenting with isolated hematuria. In our case, the presenting complaint was pain abdomen.[4]

The diagnosis of NCS is confirmed mainly by imaging such as magnetic resonance imaging (MRI) of the abdomen, CECT scan, phlebography, intravascular ultrasound (IVUS), and color Doppler study. The initial investigation when suspecting for NCS is ultrasound scan followed by color Doppler study followed by CT scan or MRI scan. Both CECT scan and MRI can demonstrate compression of LRV between abdominal aorta and SMA. CT scan showing LRV diameter ratio (hilar to aorto-mesenteric ratio) >4.9 is suggestive of NCS with a specificity of 100%. The presence of "beak sign" is also seen in axial imaging.[1,5]

Management of NCS mainly depends on the severity of symptoms. Patients presenting with orthostatic proteinuria can be given angiotensin-converting enzyme inhibitors as they improve orthostatic proteinuria based on the release of angiotensin II.[5] In patients with mild or no hematuria, conservative management is considered.[5] Asymptomatic patients can be managed conservatively too. In patients presenting with gross hematuria, recurrent hematuria, abdominal pain, or persistent orthostatic hypotension, surgery may be considered.[4,5] If the patient does not improve with 24 months of supportive treatment in patients younger than 18 years of age and 6 months of treatment in adult patients, surgery can be considered.[4,5]

In our case, the patient was managed conservatively as the patient had mild abdominal pain and did not opt for surgery.

Percutaneous endovascular stenting has shown good outcomes. Other surgical interventions are renocaval reimplantation, fibrous tissue resection, aortomesenteric angle wedge placement, LRV transposition, SMA transposition, autotransplantation of the kidney, laparoscopic ligation of splenorenal vein, and in few cases nephrectomy.[6]

Conclusion

Due to broad range of symptoms and lack of systemic approach, NCS is difficult to diagnose. There is a lack of information about clinical features, course of disease, and treatment of disease. Our case presented with lumbar pain with microscopic hematuria and ascites. Abdominal imaging showed entrapping of LRV between the aorta and SMA, suggestive of NCS. Thoracic imaging suggested pulmonary tuberculosis. The patient opted for medical management and conservative treatment was started. Due to lack of clear diagnostic criteria, patients presenting with microscopic hematuria should be evaluated for NCS.

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CASE REPORT

Multiorgan Involvement: Is There a Relevant Pathogenetic Link?

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Abstract

Multisystem autoimmune disorders have different presenting symptoms with organ involvement phased over numerous years. We have a 56-year-old homemaker who is a known case of Graves' disease—post-thyroidectomy performed 20 years ago—and developed a volume overload state with exertional dyspnea for a period of 1.5 years. She was evaluated elsewhere and diagnosed with pulmonary arterial hypertension (PAH), the cause of which had not been established at the time. She presented to us with progressive dyspnea and abdominal distension of 1-week duration. A further diagnosis of biopsy-proven autoimmune hepatitis, chronic parenchymal liver disease (CLD), and noninfiltrative restrictive cardiomyopathy (RCM) was made. At follow-up, the patient complained of thickening and dryness of skin with similar antinuclear antibody (ANA) profile results 6 months apart. In the background of immune-mediated organ manifestations and laboratory picture, systemic sclerosis was diagnosed. This case report highlights that one should have a high index of suspicion while dealing with subsequent autoimmune manifestations of isolated organs as they might be part of a multisystem autoimmune disorder.

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Introduction

Multisystem autoimmune conditions pose a diagnostic challenge in general, and more so when there are atypical presentations. Systemic sclerosis (SSc) sine scleroderma is a rare subset of SSc wherein cutaneous manifestations are absent or occur after organ involvement. We present a case of multisystem autoimmune condition presenting a diagnostic challenge, which highlights the need for integration of clinical and laboratory evaluation.

Case Description

A 56-year-old homemaker presented with progressive exertional breathlessness for the past 1.5 years. She was evaluated outside and was recently diagnosed with pulmonary arterial hypertension (PAH). There was a history of abdominal distension for the past 1 week. She also complained of loss of sleep, loss of weight and appetite, and fatigue. She had a past history of Graves' disease, which was treated with total thyroidectomy 20 years ago.

General examination revealed bilateral pitting pedal edema. Jugular venous pulse was elevated. On auscultation, there were bilateral basal crackles and loud pulmonary heart sound. She also had abdominal erythema with ascites and the left lobe of the liver was palpable. The patient was in volume overload status, i.e., with features of right heart failure.

Investigations revealed normal serum angiotensin-converting enzyme (ACE), serum amylase, ferritin, and C3. Spot protein creatinine ratio and renal function tests were within normal limits ruling out renal involvement.

Ultrasound of the abdomen showed chronic liver parenchymal disease and moderate ascites. However, liver function tests were inconclusive with no active infections. Liver autoimmune markers were negative as well. Ascitic fluid analysis showed cloudy yellow liquid with raised lymphocyte levels indicating reactive effusion. Thus, liver biopsy was done for further evaluation, which showed features suggestive of autoimmune hepatitis (Figs 1A and B).

Electrocardiography was normal. Echocardiography revealed the presence of concentric left ventricular hypertrophy, right atrial collapse, grade 2 left ventricular diastolic dysfunction, PAH (right ventricular systolic pressure—60 mm Hg), and pericardial effusion. The patient was diagnosed with PAH and restrictive cardiomyopathy (RCM) as characterized by the nondilated ventricular diastolic dysfunction. She was treated with diuretics and advised salt and water restriction. High-resolution computed tomography of the chest showed moderate pleural effusion with subsegmental collapse, prominent pulmonary artery, and mild cardiomegaly. Further, cardiac magnetic resonance imaging (MRI) showed features in suspicion of an infiltrative pathology. There was an enlargement of bilateral atria and diffuse patchy enhancement of left ventricular myocardium and right ventricular wall (Fig. 2).

An infiltrative pathology or an autoimmune condition would explain the RCM with PAH. Technetium pyrophosphate scintigraphy scan ruled out amyloidosis. No thickening or enhancement was seen. There was, however, mild dilatation of bilateral atria. We did bone marrow aspiration, gingival biopsy, and rectal biopsy, which were also negative for amyloidosis on staining.

Antinuclear antibody (ANA) profile was positive for anti-Ro52 with cytoplasmic fibrillary pattern. Thus far, she was diagnosed with RCM, PAH, and chronic liver disease with portal hypertension presenting as autoimmune hepatitis with a past history of Graves' disease. Infiltrative pathology for RCM such as amyloidosis was ruled out.

Six months later, the patient presented with skin thickening and dryness. A repeat ANA profile showed similar results with positive anti-Ro52 antibody titers. After excluding the differentials, considering the age, sex, and history of autoimmunopathy with positive anti-Ro52 antibody, the patient was diagnosed with SSc.

She is now on regular follow-up with diuretics, vasodilators, and immunosuppressants. On follow-up, the patient was stable with normal renal function test levels.

Discussion

Systemic sclerosis is a rare, heterogeneous multisystem autoimmune connective tissue disorder affecting the lungs, gastrointestinal (GI) tract, and skin.[1] Mostly affecting young and middle-aged women, it is of two types: limited and diffuse. They usually present with a long history of Raynaud's phenomenon or with skin thickening. Early involvement of visceral organs is typical of SSc. This condition is characterized by

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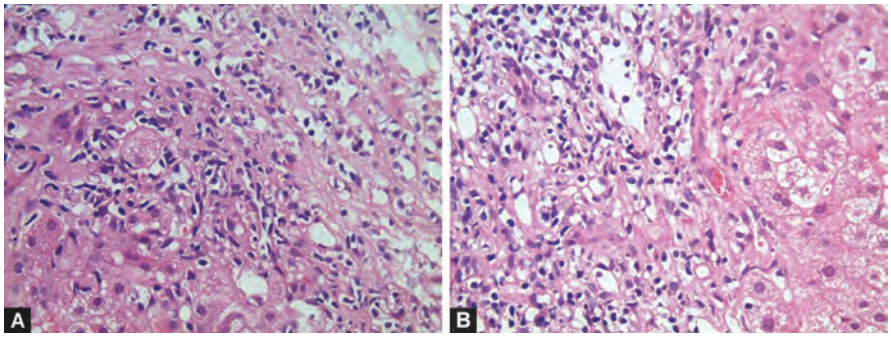

Figs 1A and B: Histopathology of liver biopsy showing lymphocytes and plasma cells in portal tract

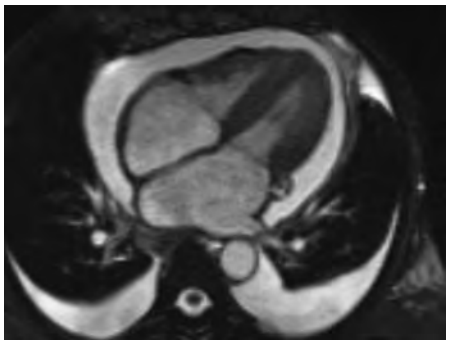

Fig. 2: Enlargement of bilateral atrium as seen in cardiac MRI

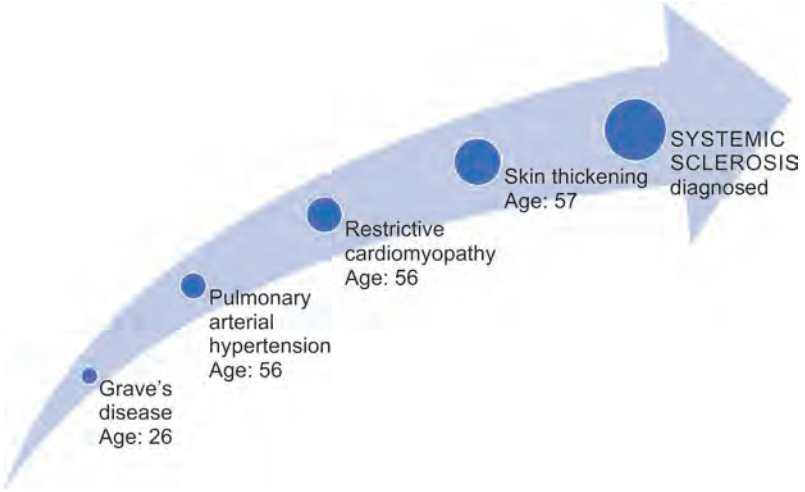

Fig. 3: Diagnoses organized as timeline

microvascular involvement, deposition of collagen, and skin induration. The common presentations include sclerodactyly, Raynaud's phenomenon, esophageal dysfunction, or interstitial pulmonary fibrosis. Although skin thickening is considered the hallmark for SSc, organ manifestation can occur without the phenotypic skin involvement.

Pulmonary involvement in SSc is prevalent in 90% of patients even though only 25% may present with respiratory symptoms. The most common cause of morbidity and mortality is interstitial pulmonary fibrosis leading to respiratory failure. PAH is seen in up to 12% of patients and may develop without evidence of interstitial fibrosis.[2] Pulmonary hypertension in scleroderma may be due to (1) primary vasculopathy of pulmonary vasculature, (2) secondary to interstitial pulmonary fibrosis, or (3) secondary to myocardial fibrosis leading to left ventricular systolic or diastolic dysfunction.[3] Its presence is an indicator of poor prognosis.

Though the probability of heart involvement is present in all patients, the clinical prevalence of the same is in only 30% of patients. Prevalence of cardiac manifestations in SSc is around 10%, with the most common conditions being valvular disease (60%), conduction abnormality (45%), and diastolic dysfunction (40%).[4] The inflammatory process in SSc causes myocardial fibrosis. It is caused by focal ischemic damage, which may lead to either systolic or diastolic dysfunction, the latter being more common. In our patient, RCM with diastolic dysfunction was seen as evidenced by volume overload status, echocardiographic, and cardiac MRI findings. Mechanical remodeling also occurs, which could further bring about arrhythmias and conduction abnormalities. These cardiac manifestations are best assessed with contrast-enhanced cardiac MRI. Delayed enhancement is seen as gadolinium contrast is retained in fibrosed tissue for longer.

Gastrointestinal involvement is observed in 90% of patients with SSc. Esophageal dysfunction is commonly noted. Primary biliary cirrhosis is the most common liver manifestation. However, in isolated case reports overlap syndrome with autoimmune hepatitis has also been noted.[5]

Thyroid involvement is not uncommon in SSc. Numerous studies have indicated the prevalence of thyroid autoimmunity in these patients including the presence of Graves' disease, Hashimoto's disease, or even malignancy.[6] In this case, there is a past history of Graves' disease, which was treated by total thyroidectomy with subsequent thyroid supplements.

Systemic sclerosis is associated with endothelial dysfunction that drives forward inflammation and fibrosis due to a combination of genetic and environmental factors. Several autoantibodies are associated with this, specifically anti-centromere, anti-topoisomerase, and anti-RNA polymerase antibodies. In our patient, the ANA profile revealed positive for anti-Ro52 antibody on two occasions 6 months apart. Anti-Ro52 antibody is also found to be positive in systemic lupus erythematosus (SLE), Sjogren's syndrome, and SSc.

Autoimmune conditions were chiefly considered. However, the main differential for our patient was an infiltrative pathology. The necessary investigations performed had ruled out amyloidosis and sarcoidosis as a cause for the RCM. SLE was excluded as the symptoms did not fulfill the European Alliance of Association for Rheumatology (EULAR) criteria. The presence of pulmonary hypertension and RCM was greatly in favor of SSc.

In the setting of multisystem presentations of autoimmune conditions, it is better to take into consideration Occam's razor. This principle suggests a unifying single explanation for the condition of the patient. After excluding the differentials, the diagnosis of SSc was made in our patient. In this case, the organ involvement occurred over a span of decades, allowing for a conclusive diagnosis to be made only later. This highlights that one should have a high index of suspicion while dealing with subsequent autoimmune manifestations of isolated organs as it might be part of a multisystem autoimmune disorder (Fig. 3).

Learning Points

- SSc is an important noninfiltrative cause of RCM.
- Symptoms of isolated organ involvement in multisystem autoimmune conditions can occur spanning over decades.

- In autoimmune presentations of one organ, investigating involvement of other organs at the time of presentation is vital.
- Regular follow-up of patients with any autoimmune organ involvement is necessary to rule out an impending multisystem autoimmune disorder.

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Announcement

JAPI will be going completely Green from March 2025 and will send the physical copies to the members on demand. Every member will have free access to the soft copy of the Journal on the Website. So, members who are interested in getting the physical copy (hard copy), please write to the JAPI office at – onlinejapi@gmail.com with your membership number, address for the delivery and mobile number.

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Unusual Presentation of Conidiobolomycosis

Jisha M K[1], Jayanthi Savio[2], Jananee Muralidharan[3], Julian Alphonse Crasta[4], Priyadarshini A Padaki[5*]

Received: 23 October 2023; *Accepted:* 17 August 2024

A 31-year-old gentleman, hailing from West Bengal, a farmer by occupation, with no known prior comorbidities, presented with a history of multiple painful swellings over the abdomen, thorax (back and front), and suprapubic region of 6 months' duration. The swelling started in the abdomen and subsequently involved the thorax. It also progressively increased in size over the 6 months. He had used analgesics for the management of the pain. He also reported significant weight loss and loss of appetite.

On questioning further, the patient gave a history of similar swelling over the right side of the abdomen 2.5 years ago, for which he underwent magnetic resonance imaging (MRI) of the abdomen. The MRI showed a large soft tissue swelling

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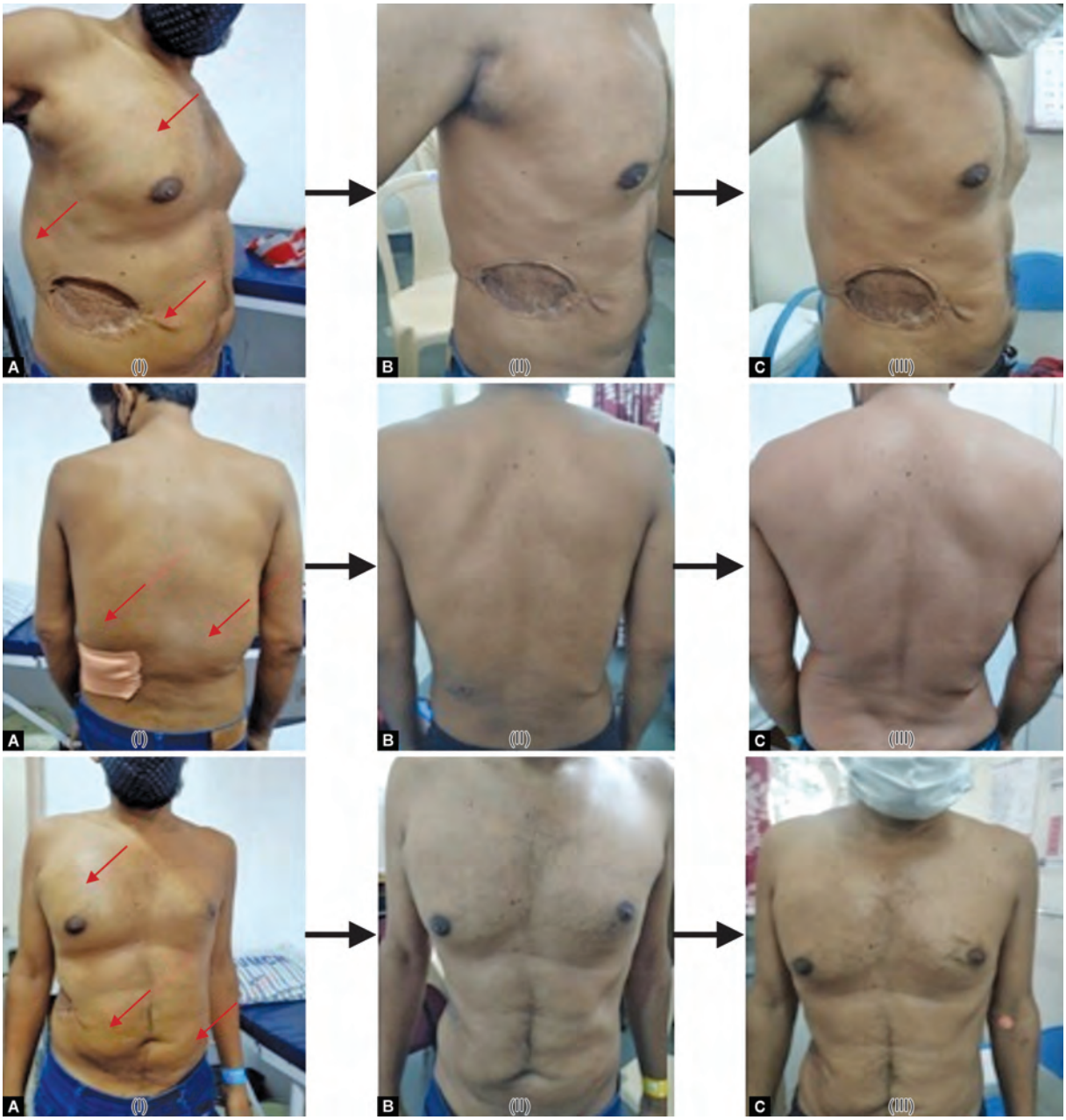

Figs 1A to C: (A) Patient at presentation; (B) On treatment—after 1 month; (C) On treatment—after 3 months

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involving the subcutaneous and superficial muscle layer of the right lateral and anterior abdominal wall, extending from the right hypochondriac region to the right iliac fossa region. The imaging showed fat stranding, muscle edema, and a small fluid collection. The patient was provisionally diagnosed with a soft tissue tumor, and an excision of the swelling followed by skin grafting was done. Histopathological examination of the swelling revealed necrotizing inflammation with eosinophilic granulomas, giant cells, and a foreign body reaction but no malignant cells; no further workup was done after that. There was no history of trauma or any other significant personal or family history.

On physical examination, he had pallor with no cyanosis, icterus, clubbing, lymphadenopathy, or pedal edema. He had multiple swellings present over the chest, abdomen, and back, which were firm to hard and tender on palpation. The skin over the swellings was fixed, with regular margins and a smooth surface. As depicted in Figure 1, the swellings ranged in size from 6 × 5 cm to 3 × 4 cm at the time of presentation. The right lumbar region had a 6 × 4 cm skin graft scar from the previous surgical procedure. Systemic examination was normal.

The patient was initially referred to the department of surgical oncology at our center in view of the initial diagnosis of a soft tissue tumor. Initial investigations showed normocytic hypochromic anemia with eosinophilia and an elevated creatinine level of 1.76 mg/dL. A fine needle aspiration of the swelling was done, and the histopathology showed inflammatory cell infiltrate with a predominance of eosinophils, foamy macrophage clusters, histiocytes, and multinucleated giant cells. A few fungal elements were also seen, but the typing of the fungal elements by mycological culture was inconclusive. Subsequently, the patient was referred to the department of medicine, where an excision biopsy was performed, and the sample was sent for both histopathological and microbiological analysis.

Histopathology showed fungal elements (Figs 2 and 3), and microbiological analysis (Figs 4 to 6) showed aseptate hyphae on the direct KOH + Calcofluor white preparation. A provisional working diagnosis of subcutaneous mycosis, most probably entomophthoromycosis, was made at this point in time. Culture grew a mold on sabouraud dextrose agar (SDA) within 72 hours, which was identified as *Conidiobolus coronatus* with the lactophenol cotton blue (LPCB) mount.

The patient was started on oral itraconazole at a dose of 200 mg administered twice a

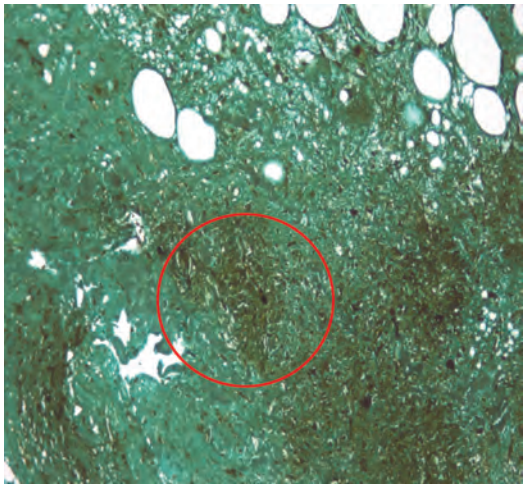

Fig. 2: Gomori methenamine silver (GMS) stains the polysaccharide component of the cell wall. Fungi appear black; background tissue takes pale green

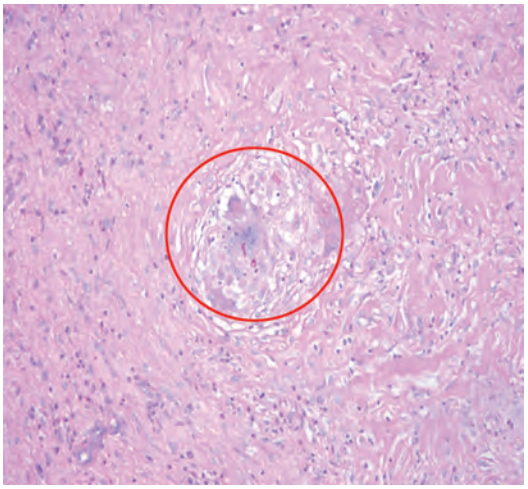

Fig. 3: Periodic acid–Schiff (PAS) stain—fungi appear deep pink; nuclei stain blue

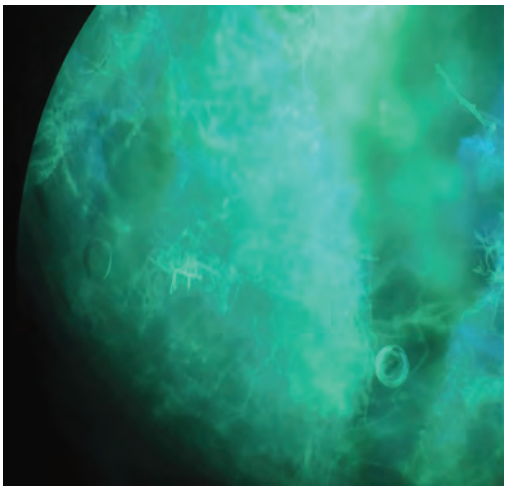

Fig. 4: Direct microscopic examination of the tissue sample: KOH-calcofluor revealed broad aseptate hyaline fungal hyphae

Fig. 5: Culture findings on Sabouraud's dextrose agar: Fungal culture on SDA yielded growth of waxy, expanding colonies with a cerebriform center, without aerial mycelium after 72 hours of incubation at both 25 and 37°C

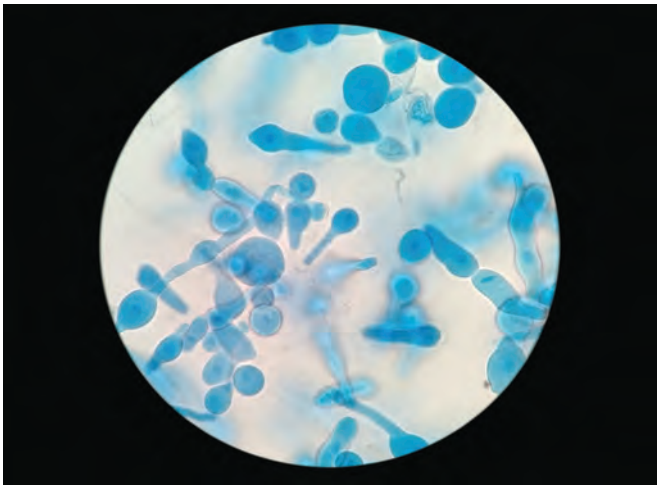

Fig. 6: Identification by lactophenol cotton blue mount: Aseptate hyphae bearing spherical conidia which forcibly discharge conidia (spores) and bear a projection called papilla after dehiscence

day. In view of the acute kidney injury (raised creatinine), which was attributed to the analgesic abuse, potassium iodide, as a treatment modality for subcutaneous mycoses, was not used, which is ideally the drug of choice. After initiation of antifungal therapy, the pain decreased in 1 week's time, and the size of the swelling decreased significantly on follow-up, as depicted in Figure 1. The patient completed 3 months of itraconazole therapy and has been asymptomatic at the time of the last follow-up.

Entomophthoromycosis is caused by mainly two genera: *Basidiobolus* and *Conidiobolus* spp. Conidiobolomycosis typically presents with painless swellings of the face and involvement of the nasal cavity.[1,2] Atypical presentations, like that in our case with painful swellings on the abdomen sparing the face, may lead to a missed diagnosis and highlight the importance of a broad differential when dealing with swellings on the body, which often get referred to the surgical departments. Surgical resection done previously at another center for this patient might have enhanced the spread of infection to larger areas on the abdomen.[3] An excision biopsy sent for both histopathological and microbiological analysis will help clinch the diagnosis of subcutaneous mycoses. Culture confirmation is essential to recognize fungi with uncommon presentations.[4] Owing to the fact that this patient was a farmer, we attributed the probable source to be the soil from where the fungus could have been implanted through minor trauma unnoticed by the patient. Appropriate antifungal therapy can cause significant improvement in symptoms and morbidity of the patient.

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Heart in the Brain

Somarajan Anandan[1*], Parameswaran Krishnan[2]

Received: 20 June 2024; *Accepted:* 27 July 2024

A 52-year-old man with a 5-year history of diabetes mellitus and chronic renal disease presented with sudden onset left upper limb weakness and numbness at 5 pm, which progressed to quadriplegia by the next day at 2:30 am. He had dysarthria at admission. There were no sensory symptoms in the lower limbs. There were no bladder symptoms. Examination showed bilateral tongue weakness and quadriplegia, with the left side more affected than the right. Reflexes were sluggish bilaterally. Plantars were extensor bilaterally. The sensory system was normal in all four limbs, including joint position sense and vibration. Diffusion-weighted magnetic resonance imaging (MRI) of the brain showed diffusion restriction in the bilateral medial medulla simulating a heart sign, suggestive of a bilateral medial medullary infarct (Figs 1 and 2). MR angiography showed left vertebral artery stenosis. He was treated as per stroke protocol and made partial recovery at follow-up.

Medial medullary infarction encompasses <1–1.5% of ischemic strokes, and bilateral medial medullary infarction (BMMI) is very rare. BMMI usually presents with tongue weakness, tetraplegia, and sensory loss, with or without respiratory failure. It can be confused with Guillain–Barré syndrome when there are no sensory symptoms or signs. The medullary pyramids, medial longitudinal fasciculus (MLF), medial lemniscus, and hypoglossal nucleus are nourished by paramedian branches of the anterior spinal artery, forming an airpod-shaped vascular territory. The most common etiology of BMMI is atherosclerosis affecting the vertebral and anterior spinal artery or its branches. The heart sign, airpod sign, or letter Y sign is classically seen in bilateral medial medullary infarct and is often due to type 2a anterior spinal artery occlusion, where a single anterior spinal artery comes off one vertebral artery, and occlusion causes bilateral medial medullary infarction.[1–4] The heart sign is seen in only two-thirds of patients with BMMI in the first 24 hours.

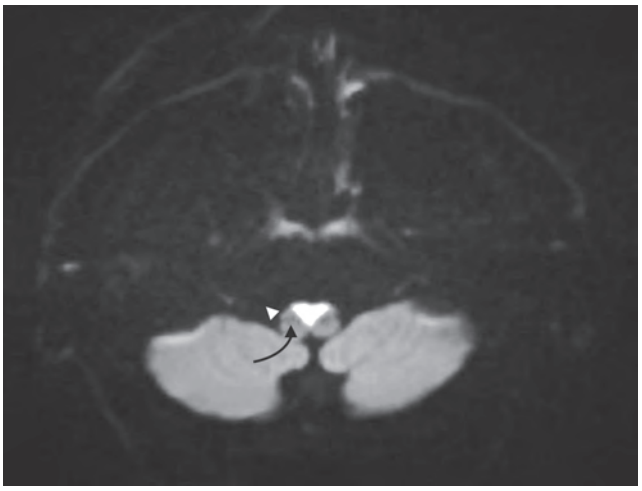

Fig. 1: Axial diffusion-weighted MRI of the brain showing heart-shaped diffusion restriction in the ventral medulla (heart sign)

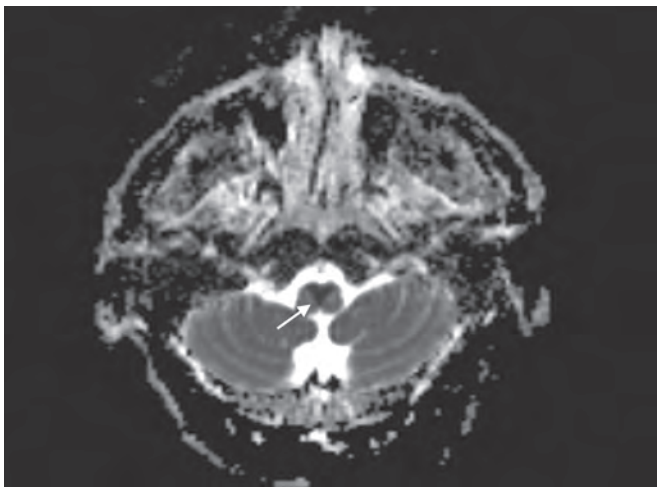

Fig. 2: Magnetic resonance imaging brain axial apparent diffusion coefficient image showing heart-shaped hypointensity in the ventral medulla

The heart appearance sign can also be seen in anteromedial infarction of the pons bilaterally and is attributed to thrombosis of the paramedian and short circumferential pontine arteries bilaterally, supplying the anteromedial pons.[5] It has also been reported in Wernekink's commissure syndrome due to infarct at the caudal paramedian midbrain tegmentum,[6] and in vitamin B_{12} deficiency at the rostral medulla in coronal MRI images.[7]

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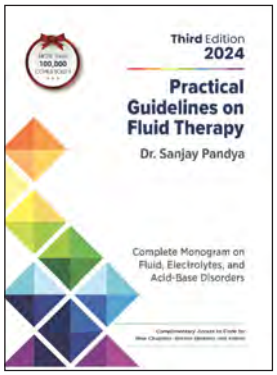
Book Review

Practical Guidelines on Fluid Therapy

By Dr Sanjay Pandya



Dr Sanjay Pandya's "Practical Guidelines on Fluid Therapy" stands as a beacon in the field, offering a remarkably simplified approach to understanding fluid, electrolyte, and acid-base disorders. This essential text is not only a learning tool but also a dynamic resource with an included access code for continuous updates, future chapters, and instructional videos.

The book meticulously details fluid management across various physiological states, from pregnancy to pediatrics, and addresses diverse disease states and postoperative care scenarios. Dr Pandya's clear explanations demystify the basics of IV fluids, solutions, and replacement strategies, making complex concepts accessible to practitioners at all levels.

Having known Dr Pandya for over two decades, I have witnessed his journey from Rajkot to his current global prominence. His commitment to patient education, exemplified by the widely accessible "Kidney Education for Patients" in over 40 languages, underscores his dedication to advancing medical knowledge worldwide.

The latest edition promises further improvement over its predecessors, aiming to meet and exceed expectations. For any practitioner seeking to deepen their understanding and refine their clinical practice in fluid therapy, this book is indispensable. Dr Pandya's expertise shines through every page, ensuring that readers not only satisfy their thirst for knowledge but also gain practical insights that enhance patient care.

"Practical Guidelines on Fluid Therapy" is more than just a book; it is a cornerstone resource that empowers healthcare professionals to navigate the complexities of fluid management confidently and effectively.

I strongly recommend you to grab your copies and motivate your students or colleagues to read it.

(Prof) Dr Agam Vora
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Sir Macfarlane Burnet-Immunologist

Jayant Pai-Dhungat

Sir Frank Macfarlane Burnet—Nobel Prize in Medicine or Physiology 1960

Stamps—Maldives 2000, Dominica 20**

Peter Medewar Nobel Prize in Medicine 1960. Stamp Guyana, 1995

Frank Macfarlane Burnet (1899–1985) was born in Victoria, Australia, and obtained his MD in 1924 from the University of Melbourne. Burnet spent 2 years in England at the Lister Institute, where he studied bacteriophages and earned a PhD in 1928. Returning to Australia, he worked at the Walter and Eliza Hall Institute; as a bacteriologist, he continued his research on phages. Burnet then made a significant contribution by devising a method for cultivating viruses in a living chick embryo (1932–33).

He was promoted to assistant director at the Hall Institute in 1934.

Burnet turned his attention to immunology in 1944. His work led him to the view that an animal's ability to produce antibodies to foreign antigens is not inborn but is developed during fetal life. He proposed that if foreign antigens are introduced into an embryo, then when the embryo develops into an independent individual, it will no longer have an immune response to those foreign antigens (1949). A few years later, a team led by Peter Medawar (1944–) at University College London confirmed Burnet's theory with experiments on mice (1956). Burnet called it acquired immunological tolerance.

This led to advances in the human immune response, allowing organ transplants and minimizing the possibilities of rejection. Burnet and Medawar shared the 1960 Nobel Prize in Physiology or Medicine for their work.

Burnet's major achievements in microbiology included developing assays for the isolation, culture, and detection of the influenza virus and describing the recombination of influenza strains. He also discovered the causative agents of Q fever and psittacosis. However, it is his work on immunology for which he is most remembered.

Burnet then introduced a hypothesis that in cellular immunity, lymphocytes respond to invading antigens using antigen receptors. Some receptors are a very precise match to antigens, while others are less precise to ensure some sort of immune response to virtually any invading pathogen. He proposed correctly that once precise antigen receptors meet the antigen they are programmed to fight, these lymphocytes make their own clones, producing a large-scale immune response to the particular invading antigen, which he named the clonal selection theory.

His theory led to the development of some of the most important treatments available today based on monoclonal antibodies; these are made by immune cells, all identical, that are clones of a single parent cell. Today, monoclonal antibodies can be made that bind specifically to almost any substance. Macfarlane Burnet died in 1985 of rectal cancer at the age of 85.

Professor of Medicine (Retd), Topiwala National Medical College and Bai Yamunabai Laxman Nair Charitable Hospital; Hon. Physician, Bhatia Hospital, Mumbai, Maharashtra, India

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Association of Diabetic Peripheral Neuropathy with Micronutrients: Letter to the Editor

Shah Aadil Shabbir[1], SV Dange[2], Saniya N Shah[3], Shaikh Zohra Neda[4]

[1]Senior Resident; [2]Professor; [3,4]Junior Resident, Department of Pharmacology, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pune, Maharashtra, India

Dear Editor,

We read with interest the article titled "Association of diabetic peripheral neuropathy with micronutrients" by Gautam et al. in your journal.[1]

We would like to congratulate them for this well-designed study.

The authors have estimated complete blood count, liver function test, kidney function test, hemoglobin A1c, blood sugar (fasting and postprandial), fasting lipid profile, and levels of zinc, copper, magnesium, and vitamin B12.

However, vitamin B6 levels have not been determined. It is well known that vitamin B6 is associated with peripheral diabetic neuropathy[2,3] and it would be interesting to know the vitamin B6 levels in this population.

Metformin is known to affect the absorption of vitamin B12, leading to its deficiency, which is dose- and duration-dependent.[4] This, along with dietary factors, could be contributing to the significant deficiency identified by the authors in the study. It is also recommended in the labeling documents of various metformin formulations to annually monitor and either stop metformin or supplement vitamin B12 as soon as deficiency is identified.[5,6]

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Avoiding Bias in Diagnostic Accuracy Studies

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[1]Junior Resident; [2]Assistant Professor, Department of Pulmonary Medicine; [3]Assistant Professor, Department of General Medicine, All India Institute of Medical Sciences, Rajkot, Gujarat, IndiaDiagnostic Accuracy Study and Bias

Sir,

We read with great interest the original article titled "Study of Diagnostic Yield of Nucleic Acid Amplification Test among Tuberculous Cervical Lymphadenitis in Immunocompetent Patients" published in the July 2024 issue of your esteemed journal. We congratulate the authors for studying the diagnostic yield of Truenat for the diagnosis of tubercular lymphadenitis as it's a challenge to perform diagnostic accuracy studies of extrapulmonary tuberculosis (TB) as there is no perfect gold standard. In this prospective study involving 50 participants, the authors have estimated the sensitivity and specificity of Truenat as 80.49 and 77.78%, respectively, when the reference standard taken was necrosis on fine-needle aspiration (FNA) cytology; 17.14 and 93.33%, respectively, when the reference standard taken was acid-fast bacilli (AFB) positivity on Ziehl–Neelsen (ZN) stain; and 74.29 and 33.33%, respectively, when the reference standard taken was lymph node necrosis on ultrasound (USG) neck.[1]

The authors must be commended for evaluating novel approaches like Truenat in resource-limited settings. However, the study design suffers from a high risk of bias. The reference or gold standard for the diagnosis of tuberculosis is culture. However, it is an imperfect standard for extrapulmonary TB due to its low sensitivity. The use of FNA cytology and necrosis on US or ZN stain in isolation has introduced classification bias in the above study affecting the sensitivity and specificity estimates of the index test. Composite reference standards, latent class models, or discrepant resolutions can be used for estimating diagnostic accuracy in the absence of a perfect reference standard. Discrepant resolution or discrepant analysis uses an additional test to resolve the discrepancy between the index test and the imperfect reference test. It has fallen out of favor as the accuracy estimates depend upon the results of the index test.[2] The latent class analysis approach uses a statistical model in which a minimum of three different tests are combined. The model adjusts for the accuracy of each of the imperfect component tests.[3] In a composite reference standard, two or three imperfect reference tests that are conditionally independent are combined. The new test is then compared against the composite reference standard. A composite reference standard comprising clinical, radiological, histopathological, and response to treatment findings would have given an accurate prediction of the diagnostic accuracy of Truenat.[2,4] Several different composite reference standards have been used in many diagnostic accuracy studies of TB and other diseases.[5,6]

If the pathologist assessing the cytology was not blinded to the Truenat results, it can be a source of diagnostic review bias. In the study, only those patients underwent Truenat who had evidence of granulomatous inflammation on FNA cytology introduced a spectrum or selection bias. Ideally, all patients with cervical lymphadenopathy who underwent FNA should have been subjected to Truenat. It is also unclear as to how invalid Truenat test results were handled. The Standards for Reporting Diagnostic accuracy studies (STARD) 2015 and quality assessment of diagnostic accuracy studies (QUADAS) tools help to improve the design and reporting of diagnostic accuracy studies.

We acknowledge the fact that the study does provide an indication that Truenat has good diagnostic accuracy for the diagnosis of TB lymphadenitis. However, a study with a better design that uses composite reference standard or latent class models with a fairly good sample size will give a more accurate estimate of

the diagnostic accuracy of Truenat for TB lymphadenitis.

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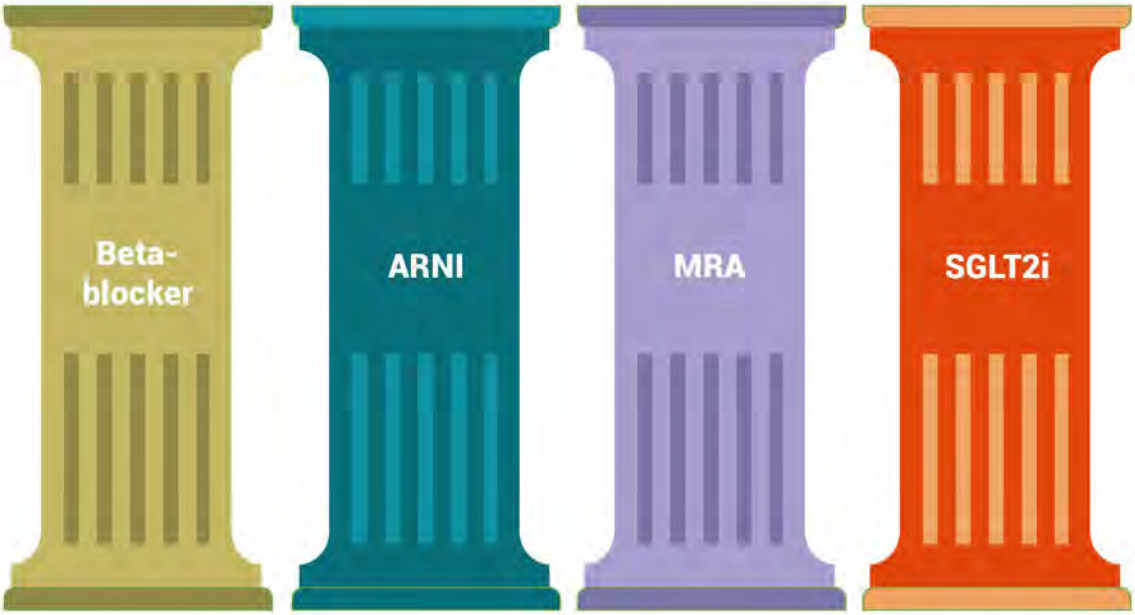

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ARNI: Angiotensin Receptor-Neprilysin Inhibitor, MRA: Mineralocorticoid receptor antagonist, SGLT2i: Sodium/glucose cotransporter-2 inhibitors, ESC: European Society of Cardiology, AHA: American heart association, ACC: American College of Cardiology, HFSA: Heart Failure Society of America, HFrEF: Heart Failure with reduced Ejection Fraction

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