

Journal of The Association of Physicians of India

VOL NO. 72 | ISSUE NO. I | JANUARY 2024 | ISSN: 0004 - 5772



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Telmisartan plus Metoprolol Succinate is contraindicated in severe bradycardia, second or third degree heart block, cardiogenic shock, decompensated cardiac failure, and sick sinus syndrome (unless a permanent pacemaker is in place). **Warnings and Precautions:** Telmisartan: Fetal Toxicity Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Telmisartan as soon as possible. Hypotension in patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with Telmisartan. Either correct this condition prior to administration of Telmisartan, or start treatment under close medical supervision with a reduced dose. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized. Hyperkalemia Hyperkalemia may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk. Impaired Hepatic Function As the majority of Telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Initiate Telmisartan at low doses and titrate slowly in these patients. Impaired Renal Function As a consequence of inhibiting the renin-angiotensin-aldosterone system, anticipate changes in renal function in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results have been reported with Telmisartan. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of Telmisartan in patients with unilateral or bilateral renal artery stenosis, but anticipate an effect similar to that seen with ACE inhibitors. Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAS) Dual blockade of the RAS with angiotensin-receptor blockers, ACE inhibitors, or aldosterone 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 aldosterone in patients with diabetes. Avoid concomitant use of aldosterone with Telmisartan in patients with renal impairment (GFR <60 mL/min/1.73 m²). Metoprolol succinate: 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 beta₁-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 beta₁-selectivity is not absolute, use the lowest possible dose of Metoprolol succinate. Bronchodilators, including beta₂-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-blocker 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 effects. 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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The dose may be uptitrated if necessary. **CONTRAINDICATIONS** The fixed dose combination of Telmisartan and Cilnidipine is contraindicated in: • Patients with known hypersensitivity to Telmisartan, Cilnidipine or any other component of this product. • Patients with diabetes who are co-administered aliskiren. • Conditions like cardiogenic shock; recent MI or acute unstable angina and severe aortic stenosis. • The concomitant use of fixed dose combination of Cilnidipine, Telmisartan and Chlorthalidone tablets with aliskiren-2 containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73m²). • Biliary obstructive disorders • Severe hepatic impairment • Pregnant Women **WARNINGS AND PRECAUTIONS** **TELMIASARTAN 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 assay 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). **CILNIDIPINE** **Pregnancy** Cilnidipine should not be administered to pregnant women as it has been reported that Cilnidipine prolongs the gestation period and delivery time in animal experiments (in rats). **Impaired Hepatic Function:** Close observation should be made and if any abnormality is observed appropriate measures, such as discontinuation of Cilnidipine, should be taken. **Elderly Patients:** Cilnidipine should be administered carefully under close observation of the patient's condition, start with low dose (5 mg) **Sudden Withdrawal:** It has been reported that sudden withdrawal of a calcium antagonist caused aggravation of certain symptoms. Therefore, if the discontinuation of Cilnidipine is necessary, appropriate measures, such as replacement with other antihypertensive agents, should be taken. **Effects on Ability to Drive and Operate Machine:** The symptoms, such as dizziness may occur because of the hypotensive action from this drug. It is hazardous to engage in activities which require alertness, such as working at a height, operating machinery or driving motor vehicles. **Others:** Precaution should also be exercised in patients with angina, chronic renal insufficiency, congestive heart failure, hypotension, liver dysfunction, or elevated liver enzymes, peripheral edema (confounding physical findings in congestive failure) and in patients with a history of serious adverse reactions to calcium antagonists. **USE IN SPECIFIC POPULATIONS Pregnancy:** Use of drugs that act on the renin-angiotensin system like Telmisartan, during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Cilnidipine has been reported to prolong the gestation period and delivery time in animal experiments (in rats). Therefore, the fixed dose combination of Telmisartan and Cilnidipine should be discontinued when pregnancy is detected, as soon as possible. **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. Transfer of Cilnidipine to mother's milk has been reported in animal experiments (in rats). Therefore it is advisable to avoid the administration of the fixed dose combination of Telmisartan and Cilnidipine to nursing mothers. **Pediatric Use:** Safety and effectiveness of both Telmisartan and Cilnidipine in pediatrics has not been established. Thus, the fixed dose combination of Telmisartan and Cilnidipine is not recommended in pediatrics. **Geriatric Use:** The fixed dose combination of Telmisartan and Cilnidipine should be administered carefully under close observation of the patient's condition. No dose adjustment is needed in elderly patients



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

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Published and Edited by

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

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

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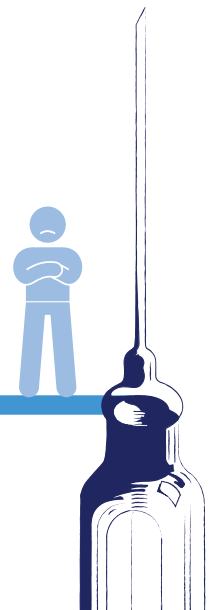
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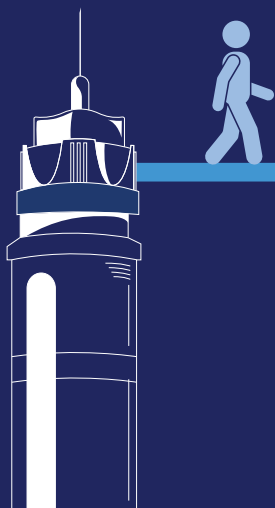
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Update on Primary Aldosteronism: Time to Screen All Hypertensives

Saba Samad Memon¹, Tushar Bandgar^{2*}

Primary aldosteronism (PA), characterized by autonomous renin-independent aldosterone production, is the most common endocrine cause of hypertension.¹ PA was initially considered a rare cause of secondary hypertension, as experts described 0.45–1% prevalence in mild to moderate hypertension when hypokalemia was an essential reason for screening.¹ However, recent data suggests that PA may be present even in patients with normokalemia, and 5–15% of patients in the hypertensive cohort have underlying overt PA.² The overall prevalence of PA in a cohort of hypertensives in primary care practice using aldosterone renin ratio (ARR) (>30 ng/dL per ng/mL/hour along with an aldosterone level >10 ng/dL) based cutoff had an overall 5.9% prevalence with 11.8% in patients with stage III hypertension.³ The studies done in the Indian population also reiterate the higher occurrence of PA. In our study performed in the diabetes and hypertensive cohort, the prevalence was at least 4.1% and an estimated 8.7%.⁴ In a study conducted in North India, PA was diagnosed in 17.8% of young hypertensives.⁵ Additionally, when prevalence was assessed using an aldosterone excretion rate of >12 µg/24 hours following an oral sodium loading test in a population with suppressed renin, irrespective of the presence or severity of hypertension, the prevalence ranged from 11.3% in normotensives to 22% in stage III hypertension.⁶ The latter study identifies and expands on the concept of evolving, not yet biochemically overt PA, but rather a continuum of PA pathophysiology.

Despite the high prevalence reported in the literature, the screening rate for PA remains dismal, with only 1–2% of the eligible population being screened.⁷ The low screening rate is due to a lack of awareness and testing. The Endocrine Society (ES) guidelines recommend screening patients with a high-risk of PA, namely, those with severe/resistant hypertension, spontaneous or drug-induced hypokalemia, adrenal mass, or family history.¹ As the risk of adverse cardiovascular and renal outcomes is higher in patients with PA than essential hypertension, the experts and guidelines from Japan suggest screening all hypertensives for PA.⁸

The ES guidelines recommend using plasma ARR as a screening test for PA and provide varied cutoff ranges.¹ Further, they recommend confirmatory testing (saline infusion, salt loading, captopril challenge, and fludrocortisone suppression test) in patients with positive ARR.¹ However, optimizing antihypertensive medication and collecting mid-morning sample with optimized salt intake are suggested before screening.¹ To simplify the process, experts suggest screening irrespective of medications [even mineralocorticoid antagonists (MRAs)] at any time of the day and interpreting renin and aldosterone separately.⁷ Further, inference from these reports should consider antihypertensive medications; for instance, suppressed renin, even on diuretics or angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, can be interpreted as a positive screen. In contrast, elevated renin on β -blockers assures the disease is less likely.⁹ In other cases, altering the drugs and repeating the screen is recommended. In patients with high pretest probability, suppressed renin can be assumed to be PA unless proven otherwise, and further investigations are to be undertaken as per degree of aldosterone elevation.⁷ In cases with lower pretest probability, confirmation with urinary aldosterone levels after oral salt loading is suggested.⁷ Serum aldosterone values have a high intraindividual variability. In patients with overt PA, aldosterone values varied by 31% and ARR by 45%; hence, repeated evaluation and a high suspicion index are necessary.¹⁰ This higher variability is observed even during adrenal vein sampling (AVS) and can lead to misclassification.¹¹ Thus, urinary aldosterone excretion, an integrated measure, may be more helpful.⁷

As per ES guidelines, an initial computed tomography (CT) scan is recommended in patients with PA to rule out adrenocortical carcinoma and mapping before lateralization.¹ Traditionally, PA pathophysiology has been divided into unilateral adenoma and bilateral hyperplasia.¹² However, with the advent of CYP11B2 staining, the histopathological characteristics of lateralized PA were identified as adenoma, nodules, micronodules, and hyperplasia per the histopathology of primary aldosteronism consensus.¹³ Thus, the

pathophysiology of PA is recognized as bilateral in the majority, with or without dominant secretion from one side, which necessitates using AVS to decide lateralization.¹⁴ However, as AVS requires expertise and has a cost constraint associated with it, patients should be carefully selected for it.¹⁴ Varied algorithms and predictive scores are available to guide whether to proceed with AVS based on a higher probability of lateralization.¹⁵ The ES guidelines recommend that patients desirous of surgery be offered AVS.¹

The aldosterone values obtained from the adrenal vein sample during AVS are corrected with cortisol values to overcome the dilution factor.¹⁴ However, concomitant cortisol secretion is increasingly recognized in PA.¹⁴ Associated cortisol excess is linked to a higher prevalence of metabolic and cardiovascular complications.¹⁶ This cortisol excess can interfere with interpreting AVS results in a few patients. Hence, other denominators like adrenal androgens and metanephrines are being studied.¹⁷ Further, the use of liquid chromatography-tandem mass spectrometry (LC-MS/MS) in AVS (11 β -hydroxyandrostenedione and 11-deoxycortisol to rescue failed baseline catheterization) and peripheral samples (aldosterone, 18-oxocortisol, and 11-deoxycorticosterone) also provides additional value in lateralization.¹⁸ Few centers also perform super-selective AVS, where a specific adrenal vein tributary is cannulated.¹⁹ These results can guide partial adrenalectomy based on AVS mapping.²⁰

The modalities for lateralization in PA are also evolving with the availability of nuclear scans. ⁶⁸Ga-Pentaxifor positron emission tomography (PET)/CT targets C-X-C chemokine receptor type 4 which colocalizes with CYP11B2. In a study of 120 patients

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How to cite this article: Memon SS, Bandgar T. Update on Primary Aldosteronism: Time to Screen All Hypertensives. J Assoc Physicians India 2024;72(1):11–13.

for lateralization of aldosterone-producing adenoma, ^{68}Ga -Pentaxifor PET/CT had a sensitivity of 92.4% and specificity of 94.4%; further, concordance with CYP11B2 stain was seen in 81.69%.²¹ In a prospective within-patient trial, ^{11}C -metomidate PET/CT was noninferior to AVS in the lateralization of PA. However, this tracer requires dexamethasone pretreatment and an onsite cyclotron due to its short half-life and, hence, is not widely available.²² NP-59 (131 I-6-biodomethyl-19-norcholesterol) adrenal scintigraph can also be used as an alternative. The data on nuclear scans is evolving and provides alternatives to AVS in patients unwilling or fit for AVS.²³

The dictum that treatment for lateralized PA is surgical adrenalectomy, while medical management for bilateral disease is also evolving. In patients with unilateral disease who are not fit for surgery, there are studies on using ethanol injection or radiofrequency ablation, which provide a 70% clinical success rate.^{24,25} Further, patients with bilateral disease with grossly asymmetric disease, known cardiovascular or renal disease, young age, and hypertension requiring multiple medications can be considered for noncurative unilateral adrenalectomy or even partial bilateral adrenalectomy to attenuate the severity of the disease.²⁶ In a data of 56 patients with bilateral disease subjected to adrenalectomy (unilateral or partial bilateral), complete or partial clinical success was observed in 84% and complete or partial biochemical success in 92%.²⁰

The drugs used to treat bilateral disease are MRA and potassium-sparing diuretics like amiloride and triamterene. The most widely used MRAs are spironolactone and eplerenone, with the latter having less potency but lower propensity for sexual side effects.¹² A newer generation MRA, namely esaxerenone, is available in Japan. It is nonsteroidal, has no active metabolites, and has a prolonged half-life of nearly 20 hours. Phase 2 and 3 studies of this drug have shown promising results.²⁷ Finerenone is another nonsteroidal MRA available in India for indication of prevention of the progression of diabetic nephropathy. This drug has equal distribution in the kidney and heart and, hence, a lower propensity for hyperkalemia, which can be a concern at lower epidermal growth factor receptor.²⁸ Other drugs in the pipeline are ocedurenone (MRA), baxdrostat, and lorundrostat [selective CYP11B2 (aldosterone synthase) inhibitors], currently in phase 2 trials.²⁷ The modalities to overcome hyperkalemia due to MRA use include loop diuretics, thiazides, potassium binding agents (patiomer), and concurrent use of sodium-glucose cotransporter-2

inhibitors. The biomarker for medical management should be not only the control of hypertension and potassium but also the normalization of renin.²⁷ Cardiometabolic outcomes and mortality are improved only in MRA therapy patients with plasma renin activity ≥ 1.0 ng/mL/hour.²⁹

The genetic spectrum of PA is also expanding. The germline mutations leading to familial hyperaldosteronism are now characterized into four types, namely FH-I to FH-IV (CYP11B1/2, CLCN2, KCNJ5, CACNA1H, and CACNA1D).³⁰ The current studies highlight that PA is a genetic disorder, with somatic mutations in the affected tissue identified in almost 90% of aldosterone-producing adenomas or micronodules at the site of CYP11B2 stain.³¹ These reemphasize the disease continuum of PA where somatic mutation drives nodule to adenoma and the severity from subclinical to overt primary aldosteronism.⁷ Further, each somatic mutation has a different signature and histologic feature, like *KCNJ5* being more common in Asian females, large tumor size, production of hybrid steroids (aldosterone, 18-oxocortisol, 18-hydroxycortisol), and clear cell dominant appearance on histopathology.³² In contrast, *ATP1A1* and *ATP2B3* are more common in males, have smaller tumor sizes, and have a compact cell-like appearance on histopathology.

To conclude, PA, a common cause of hypertension, contributes to cardiovascular, metabolic, and kidney disease, and treatment options like mineralocorticoid receptor antagonists and surgical adrenalectomy are available for effective management to reduce the excess cardiovascular risk. Screening tests should be strongly considered for diseases associated with higher morbidity and mortality, higher prevalence, easier availability of screening test, and effective treatment—PA qualifies for all of this. Thus, increasing awareness about screening tests for PA and interpretation is needed.

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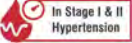


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Alarming Incidence of Gastric Outlet Obstruction Related to NSAIDs and Synthetic Opioid in North West India



Ashish Joshi^{1*}, Sushil Falodia², Arjun Vyas³, Naveen Kumar⁴

Received: 09 May 2020; Accepted: 10 July 2023

ABSTRACT

Background: In recent years, there has been an alarming increase in cases of gastric outlet obstruction (GOO) at our center due to drug abuse. So, we conducted this study to know the incidence of nonsteroidal anti-inflammatory drugs (NSAIDs) and synthetic opioid abuse in cases of GOO.

Methods: This was an observational study involving consecutive cases of GOO diagnosed from September 2017 to February 2019. A detailed history, including drug addiction history and clinical examination, was done. Investigations included routine biochemical and hematological tests, upper gastrointestinal endoscopy (UGIE), ultrasonography, rapid urease test (RUT), and histopathology of the diseased area.

Results: Among the 102 cases diagnosed with GOO, 62 (60.78%) cases had a history of drug addiction. The drug addiction history was as follows: NSAIDs and opioids in 56, opioids alone in four, and NSAIDs alone in two cases. The most common site of stricture was the second part of the duodenum. The features on histopathology were ulcerations of the mucosa infiltrated by eosinophils, plasma cells, and lymphocytes.

Conclusion: There is an alarming increase in the incidence of GOO due to NSAIDs and opioid abuse at our center. Efforts should be made to control the indiscriminate use of these over-the-counter drugs to prevent dreaded complications.

Journal of the Association of Physicians of India (2024); 10.59556/japi.71.0432

INTRODUCTION

Gastric outlet obstruction (GOO) is caused by obstruction of the pyloric channel or duodenum.¹ GOO may be defined more specifically as obstruction of the pylorus or pyloroduodenal area up to D2 (ampulla). The obstruction can be intrinsic or extrinsic to the pylorus and duodenum. The causes are mainly classified as benign or malignant. The benign causes are peptic ulcer disease (PUD), corrosive ingestion, tuberculosis, nonsteroidal anti-inflammatory drugs (NSAID), and opioid abuse.^{2,3} The most common cause of GOO in India is malignancy.⁴ Among the benign causes, PUD and corrosive ingestion are the leading causes.⁵ Intake of NSAIDs in excessive doses over a prolonged duration is known to cause ulceration of mucosa in the stomach and duodenum. NSAID and opioid abuse is a rare cause of GOO.^{3,6}

In this article, we are going to discuss the increasing incidence of drug abuse containing synthetic opioid preparations like tramadol or dextropropoxyphene either in combination with NSAID like diclofenac or non-NSAID drug like paracetamol in GOO patients.

METHODS

This was an observational study conducted in the gastroenterology department of

our institution from September 2017 to February 2019. Consecutive cases diagnosed with GOO in the department during this period were included in the study. GOO was defined as a complete or incomplete obstruction to the antrum, pylorus, or proximal duodenum up to the D2 (ampulla).¹ Patients with clinical features such as upper abdominal distension after food intake, nonbilious vomiting, and vomitus containing undigested food particles, along with an inability to pass a 9 mm gastroscope beyond the second part of the duodenum, were included in the study.

A detailed history was taken, including addiction and drug history, and a thorough clinical examination was done. Investigations included complete blood count, liver and renal function tests, ultrasonography of the abdomen, upper gastrointestinal endoscopy (UGIE), rapid urease test (RUT) for *Helicobacter pylori* (*H. pylori*), and histopathology. Endoscopic-guided biopsies were taken from the diseased area, and additional biopsies were taken from the body and antrum for RUT. The biopsy specimens were stained with hematoxylin and eosin and assessed by the histopathologist.

Informed consent was obtained from all patients, and the study was approved by the institutional ethical committee. Continuous variables were expressed as the mean and

standard deviation, while discrete variables were expressed as numbers and percentages.

RESULTS

The baseline characteristics of the cases are described in Table 1. A total of 102 patients were included in the study, out of which 71 (69.61%; 68 males and 33 females) had benign etiology and 31 (30.39%; 12 males and 19 females) had malignant cause for GOO. Among patients with benign etiologies, 62 patients had a drug history, while nine patients did not have any drug history; the latter included two patients with a history of corrosive ingestion. Out of 62 patients with a history of drug abuse, 56 were taking a combination of opioid and NSAID drugs, four patients were taking only opioid analgesics, and two patients were addicted to plain NSAIDs. Drug addiction was defined as the persistent use of drugs despite the harmful consequences, which may include negative physical, psychological, or social effects. The frequency and dose of the drugs were not specifically quantified in this study due to challenges in obtaining accurate and reliable data from patients due to variations in proprietary preparations. Out of 62 patients with a drug history, 28 (45%) had a past history of opium addiction. The mean duration of opium addiction was 5.16 years. The mean duration of drug abuse was 3.23 years. A total of 49 patients with a history of drug abuse were from the Northern part of Rajasthan state (39 from Hanumangarh district). On UGIE of patients with a drug history, there were retained food particles in the stomach with multiple ulcerations and strictures in

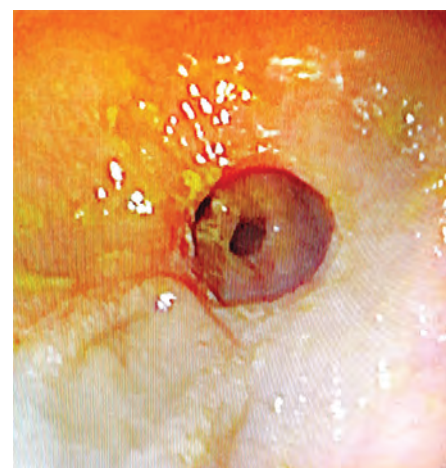
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How to cite this article: Joshi A, Falodia S, Vyas A, et al. Alarming Incidence of Gastric Outlet Obstruction Related to NSAIDs and Synthetic Opioid in North West India. *J Assoc Physicians India* 2024;72(1):14–16.

Table 1: Baseline characteristics and clinical profile of cases

Parameters	Benign		Malignant (n = 31)
	Drug-induced (n = 62)	No history of drug abuse (n = 09)	
Mean age	33.62 ± 10.12	48.71 ± 15.78	58.71 ± 15.78
Sex	M: 61 (98.38%) F: 1 (1.61%)	M: 7 (77.78%) F: 2 (22.22%)	M: 12 (38.71%) F: 19 (61.29%)
Residence			
Rural	50 (80.64%)	07 (77.78%)	22 (70.96%)
Urban	12 (19.35%)	02 (22.22%)	09 (29.04%)
Addiction			
Alcohol	10 (14.49%)	01 (11.12%)	0
Smoking	16 (23.18%)	02 (22.22%)	05 (16.12%)
Opium	28 (45.16%)	0	0
Comorbidities	06 (9.67%)	01 (11.12%)	09 (29.03%)
History of surgery	10 (16.12%)	0	02 (6.45%)
Clinical features			
Pain abdomen	56 (90.32%)	06 (66.67%)	20 (64.51%)
Vomiting	59 (95.16%)	07 (77.78%)	29 (93.54%)
Abdominal distension	45 (72.58%)	04 (44.44%)	16 (51.61%)
Constipation	07 (11.29%)	02 (22.22%)	14 (45.61%)
Weight loss	33 (53.22%)	04 (44.44%)	16 (51.61%)
Hematemesis	03 (4.83%)	0	0

**Fig. 1:** Upper GI endoscopy (UGIE) pictures showing ulcerations and strictures in duodenum

malignancy (19.2%).¹⁰ However, our study found that drug abuse, particularly the use of opioids and NSAIDs, was the most common cause of GOO (54.9%) in the study population.

Overall, our study found that NSAID/opioid use is a major cause of GOO, particularly in patients with a history of drug addiction.

DISCUSSION

The upper GI complications caused by NSAIDs are decreasing due to the use of proton pump inhibitors (PPI). However, the lower GI complications are increasing as PPI cannot protect the small intestine from NSAID-related injuries. In fact, the ratio of upper/lower GI complications due to NSAID has decreased from 4.1 to 1.4.⁷ We observed an increased incidence of NSAID-related upper GI complications due to abuse of the drugs containing synthetic opioid preparations in combination with NSAID. A similar observation was made in a study conducted in a North Indian institute.¹ Most of our cases came from Hanumangarh district, which is very close to Punjab state. Rajasthan and Punjab are among the top 10 states having population problems with opioid users (i.e., those using harmful or dependent patterns). There are approximately 10.3 lakh people who need help for opioid-related problems. Heroin is the most commonly used opioid, followed by pharmaceutical opioids and opium.¹¹

A retrospective analysis of the addiction history in these patients revealed that 45% of patients were opium addicts taking opium in the form of husk (local acronym: doda), the common variety of opium available in Rajasthan. Legal restrictions and difficulty in procuring opium led them to move to cheaper over-the-counter synthetic prescriptions of opioids like tramadol and dextromethorphan. Most of the preparations of these synthetic

Table 2: Location of benign ulcer/stricture in upper GI endoscopy and relationship with *H. pylori* test

Location of lesion	No. of patients	Positive RUT
Patient with a history of drug abuse (n = 62)		
D1–D2 junction and D2	24	13
Pyloric stenosis	16	10
Stomach and duodenum both (mainly D2)	22	13
Patient without a history of drug abuse (n = 7)		
D1 and D1–D2 junction	7	06
Patient with a history of corrosive ingestion (n = 2)		
Pyloric stenosis	2	1

the antrum, pylorus, and duodenum (Fig. 1). In patients with a history of drug addiction, the most common site of lesion was the D1–D2 junction and D2 (24/62; 38.7%). A total of 22 patients (35.4%) had lesions in both the stomach and the second part of the duodenum (Table 2). Seven patients without a history of drug addiction had lesions in the D1 and D1–D2 junctions, while two patients with a history of corrosive ingestion had pyloric stenosis.

Seven patients with a history of drug addiction had a history of surgery (gastrojejunostomy) in the past, but on endoscopy, there were still ulcerations in the pyloroduodenal area. The findings on histopathology were ulcerations of the mucosa infiltrated by eosinophils, plasma cells, and lymphocytes.

The claim of an alarming rise in GOO due to NSAID/opioid use is supported by previous studies. In a study by Lanas et al., the use of NSAIDs was found to be a major risk factor for GOO.⁷ Similarly, in a study by Shi et al., the incidence of GOO due to opioid use was found to be increasing over time.⁸ These studies support our finding that NSAID/opioid use is a major cause of GOO.

Comparative data from previous studies showed that the most common causes of GOO were PUD, malignancy, and postoperative adhesions. A study by Sachdeva et al. reported that PUD was the most common cause of GOO (41.1%), followed by malignancy (31.8%) and postoperative adhesions (23.3%).⁹ Another study by Ye et al. found that postoperative adhesions were the most common cause of GOO (44.7%), followed by PUD (24.6%) and

opioids come in combination with diclofenac, paracetamol, dicyclomine, and chlorpheniramine. The development of peptic ulcers and strictures in patients taking opioids along with NSAIDs can be explained by the known complications of NSAIDs on the upper GI tract. However, some patients were taking opioid preparations containing dicyclomine and paracetamol in combination. The development of duodenal strictures in these patients suggests that synthetic opioids may have similar adverse effects to NSAIDs on the upper GI tract.

Opioids are highly addictive narcotic drugs, and opioid dependence has adverse effects on all the systems of our body, like immune stimulation, depression of stem cell activity, inflammation, atherosclerosis, hypertension, coronary artery disease, and neuropsychiatric disorders.^{12–17} The adverse effects of opiates on the GI system are opioid-induced bowel dysfunction, narcotic bowel syndrome, and sphincter of Oddi dysfunction.^{18,19} Recently opium addiction causing small intestinal strictures has been reported by us.⁶ One recent study has shown opium abuse gastro enteropathy presenting as ulcer and ulcerated strictures, which respond poorly to medical management and endoscopic balloon dilation.²⁰

The actions of opioids on the GI tract are primarily through opioid receptors on the enteric nervous system and immune cells in the lamina propria. The opioids cause delayed gastric emptying, inhibit distension-induced peristaltic contractions, and elevate resting muscle tone in the antrum, pylorus, and duodenum. The opioids can directly activate the interstitial cell-muscle network through μ -receptors and cause an increase in the tone of the pylorus, disturb the migratory myoelectric complex, and delay the transit through the small and large intestine. The inhibitory action of opioids on the enteric nervous system causes a decrease in fluid, electrolyte, and bicarbonate secretion in the small intestine.^{18,21} The possible mechanism of ulcer formation by opioids may include the prolonged contact of the duodenal mucosa with acidic contents and inhibition of the pro secretory enteric reflexes by opioids. Tramadol also has similar action mediated through μ receptors.^{22,23}

Nonsteroidal anti-inflammatory drugs (NSAIDs) cause nonselective inhibition of cyclooxygenase, which leads to a reduction in bicarbonate secretion, reduced mucus production, increased acid secretion, and decreased epithelial cell proliferation. They also cause vasoconstriction and endothelial injury, leading to ischemia and ulceration.²⁴

The persistent inflammation and decreased stem cell activity due to opioid persistent ischemia and reduced prostaglandin synthesis by NSAIDs may lead to nonhealing ulcers in the duodenum. The consequences of these ulcers are anemia, hypoproteinemia, and the duodenal strictures causing GOO.

Chlorpheniramine is a first-generation antihistamine drug with abuse potential due to its effects on the central nervous system.²⁵ The addiction risk of tramadol is less when compared to traditional opioid preparations, but the combination of tramadol with chlorpheniramine and dicyclomine may have more addition risk than either preparation alone.^{18,21}

These patients can be managed by endoscopic dilatation of strictures or by gastrojejunostomy.³ The patients in our hospital were managed by surgery, and deaddiction therapy was also given. Further, follow-up is required to know the status of the lesion after surgery or endoscopic treatment and strict deaddiction therapy.

Regarding the outcomes of therapy in patients with GOO due to NSAID and opioid addiction, it is important to note that our study did not specifically investigate the response to different treatment modalities. Therefore, data on the effectiveness of proton pump inhibitors (PPIs), dilatation procedures, or surgery in this patient population are not available. Future research should aim to assess the outcomes of these therapeutic interventions in managing GOO in patients with NSAID and opioid addiction. Such investigations will contribute to optimizing treatment strategies and enhancing the overall prognosis of these individuals.

CONCLUSION

The most common cause of GOO in our center is NSAID and opioid addiction. Opium addicts are highly prone to duodenal ulcers due to abuse of NSAIDs along with opium. So, these patients should be evaluated for duodenal ulcers at the earliest suspicion to prevent further complications.

Legal efforts should be made to control the indiscriminate use of these over-the-counter drugs to prevent dreaded complications.

Institutional Ethical Committee approval was taken.

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Study of Glycemic Variability in Well-controlled Type 2 Diabetic Patients Using Continuous Glucose Monitoring System



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Received: 30 April 2023; Accepted: 25 July 2023

ABSTRACT

Introduction: The world has changed tremendously for patients suffering from diabetes mellitus with the development of cutting-edge technologies like continuous glucose monitoring and flash glucose monitoring systems. Now, the details of constant fluctuations of glucose in their blood can be monitored not only by medical professionals but also by patients, and this is called glycemic variability (GV). Traditional metrics of glycemic control measurement, such as glycated hemoglobin (HbA1c), fail to reflect various short-term glycemic changes like postprandial hyperglycemia and hypoglycemic episodes, paving the way to the occurrence of various diabetic complications even in asymptomatic, well-controlled diabetic patients. This need for advanced management of diabetes and effective monitoring of these swings in blood glucose can be met by using a continuous glucose monitoring system (CGMS).

Aim and objective: To evaluate the extent of GV in well-controlled type 2 diabetes mellitus (T2DM) patients using a flash CGMS and to assess the correlation between GV and HbA1c.

Materials and methods: A hospital-based prospective observational study was carried out from May 2020 to Oct 2021 at the Department of Medicine, SMS Hospital, Jaipur, Rajasthan (India), after approval from the Ethics Committee of the institution. A total of 30 patients with well-controlled T2DM (HbA1c was ≥ 6.5 , but ≤ 7.5) were included in the study using simple random techniques after written informed consent from patients. Patients were studied for glycemic excursions over a period of 7 days by using FreeStyle® Libre Pro™, which is a flash glucose monitoring system. The CGM sensor was attached to the left upper arm of the patient on day 0 and removed on day 7. The data recorded in the sensor was then retrieved using pre-installed computer software and analyzed using standard CGM metrics like standard deviation (SD), percentage coefficient of variation (%CV), time above range (TAR), time below range (TBR), and time in range (TIR), out of which %CV was used to quantify GV. %CV has been used to cluster patients into four cohorts from best to worst, namely: best/low CV $\leq 10\%$, intermediate CV from 10 to 20%, high CV from 20 to 30%, and very high CV of $>30\%$. Scatterplots are used to establish correlations between various parameters.

Result: Data from a total of 30 patients were analyzed using CGMS and thus used for calculating standard CGM metrics; glucose readings every 15 minutes were recorded consecutively for 7-day periods, making it a total of 672 readings for each patient. Interpreting the CGM data of all 30 patients, the following results were found: the mean blood glucose of all cases is 134.925 ± 22.323 mg/dL, the mean SD of blood glucose of all cases is 35.348 ± 9.388 mg/dL, the mean of %CV of all cases is $26.376 \pm 6.193\%$. CGM parameters of time are used in the form of percentages, and the following results were found: the mean of TAR, TBR, and TIR is 14.425 ± 13.211 , 5.771 ± 6.808 , and $82.594 \pm 12.888\%$, respectively. Clustering the patients into cohorts, the proportion of patients exhibiting best/low %CV (10%) is 0, intermediate %CV (10–20%) is 16.67% (five out of 30 patients), high %CV (20–30%) is 50% (15 out of 30 patients) and very high %CV ($>30\%$) is 33.33% (10 out of 30 patients). Also, there is no significant correlation found between HbA1c and %CV ($p = 0.076$, p -value = 0.690); a significant negative correlation was found between %CV and TIR ($p = -0.604$, $p < 0.001$); a positive correlation of %CV with TAR and TBR is significant ($p = 0.816$, p -value of < 0.001).

Conclusion: Using a flash CGMS device and considering %CV as the parameter and primary measure of GV, the study demonstrated the overall instability of a person's glycemic control, making note of unrecognized events of hypoglycemia and hyperglycemia in asymptomatic well-controlled T2DM patients, revealing the overall volatile glycemic control. The most important finding of this study is that even those diabetics who are considered well-controlled experience a great degree of GV as assessed by CGM-derived metrics. This study also demonstrated that there is no significant correlation between HbA1c and GV, suggesting that patients may not have optimal control of their diabetes despite having "normal HbA1c" values; hence, GV can be considered an HbA1c-independent danger factor, having more harmful effects than sustained hyperglycemia in the growth of diabetic complications. So, by using CGM-derived metrics, the measurement of GV has the potential to complement HbA1c data. In this manner, a more comprehensive assessment of glycemic excursions can be provided for better treatment decisions, thereby facilitating optimal glycemic control, which is essential for reducing overall complications and promoting good quality of life.

Journal of the Association of Physicians of India (2024): 10.59556/japi.71.0441

INTRODUCTION

According to International Diabetes Federation Diabetes Atlas, around half a billion people are living with type 2 diabetes (T2D), which makes up around 10.5% of the world population. By 2030, this will increase to 642 million, and by 2045, this could extend beyond 783 million.¹

Diabetes management has the main objective of maintaining effective glycemic control to prevent various micro- and macrovascular complications. Glycated hemoglobin (HbA1c) is considered the traditional measure of overall glycemic control, which shows average blood glucose levels over 2–3 months, but it fails to depict short-term glycemic changes, postprandial hyperglycemia, episodes of hypoglycemia,^{2–4} as well as the magnitude and frequency of intra- and inter-day glucose variation.⁵ Also, there are certain conditions like hemoglobinopathies, iron-deficiency anemia, and pregnancy that can confound HbA1c measurements. In order to fulfil the need for more advanced management of diabetes and to prevent various chronic complications, another glycemic metric beyond HbA1c, known as "glycemic variability (GV)," was introduced. GV is defined by the measurement of fluctuations in blood glucose or other related parameters of glucose homeostasis over a given period of time. In other words, it refers to swings in blood glucose levels⁶. These glycemic excursions result in vascular damage by two primary mechanisms: excessive protein glycation end products and activation of

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How to cite this article: Swami V, Yadav SK, Saxena P, et al. Study of Glycemic Variability in Well-controlled Type 2 Diabetic Patients Using Continuous Glucose Monitoring System. *J Assoc Physicians India* 2024;72(1):18–21.

oxidative stress.⁷ It is now evident that GV plays an important role in the pathogenesis of many diabetic microvascular as well as macrovascular complications, resulting in an independent risk factor in itself other than HbA1c.⁸

A 24-hour blood glucose excursion pattern can be determined by either perpetual finger prick "self-monitored blood glucose" (SMBG) measurements or a "continuous glucose monitoring system" (CGMS). Nocturnal hypoglycemia is a very prevalent complication in patients with tight control of diabetes, which is usually not detected by SMBG since SMBG provides a partial and incomplete picture of glycemic excursions⁹. Even in asymptomatic, well-controlled T2D, these wide glycemic excursions can occur, which can lead to a further overall decrease in quality of life. CGMS is considered one of the most trusted and accurate methods for assessing glycemic excursions in more detail, which are usually overlooked by the traditional methods of assessment of glycemia, such as self-monitoring blood glucose measurement and HbA1c.

A flash CGMS device is used in the study, and the CGM data thus collected is then utilized to derive meaningful interpretations and help us better understand the prevalence and extent of GV in well-controlled (HbA1c of ≥ 6.5 but ≤ 7.5) T2D and we will also find out whether GV is related to HbA1c or not.

MATERIALS AND METHODS

Study Participants

A hospital-based prospective observational study was conducted from May 2020 to Oct 2021 at the Department of General Medicine, SMS Hospital, Jaipur, Rajasthan, India, after approval by the ethics committee. The study included a sample of 30 patients of T2D mellitus (T2DM) with HbA1c of ≥ 6.5 but $\leq 7.5\%$ in the OPD and IPD of the General Medicine Department by simple random sampling. Patients who fulfilled the inclusion and exclusion criteria have received intensive training for approximately 1 hour to use CGMS.

Inclusion Criteria

- Patients who were willing to be a part of the study after giving informed consent.
- Patients aged between 18 and 70 years with T2DM are well-controlled, that is, HbA1c of ≥ 6.5 but ≤ 7.5 .

Exclusion Criteria

- Patients with a history of hepatic and/or renal dysfunction.
- Taking drugs that alter glucose metabolism (like diuretics, steroids, etc.).
- Pregnant females.

At screening, after a complete physical examination of each patient, the following baseline data were collected: the demographic profile, blood investigations including HbA1c, fasting plasma glucose, two-hour postprandial plasma glucose, and lipid profile [total cholesterol, serum triglycerides (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and very low-density lipoprotein (VLDL)].

Continuous Glucose Monitoring System

After assessing the participant's eligibility criteria, the FreeStyle® Libre Pro™ sensor (Flash Glucose Monitoring System) was applied to the back of the left upper arm on day 0 and removed on day 7. It does not require daily finger pricks for calibration as needed with an SMBG device. All sensors are inserted by one person, and each sensor is for single use only. The sensor has a flexible 4mm long tip inserted just under the skin (subcutaneously); it can be applied for up to 14 days, but our subjects were made to wear them for 7 days only. The thin filament of the electrochemical sensor continuously measures interstitial glucose levels in the 40–500 mg/dL range every 15 minutes during the entire wear period and stores them. The reader is used to gather data from the sensor, and the report can be generated by connecting the reader to a computer using LibreView software. In addition, patients were advised not to change their diabetes treatment during the study period and to continue with their normal lifestyle. All participants completed the CGMS integrity.

Glycemic Parameters Analysis Using Continuous Glucose Monitoring Data

Data analysis for 672 readings, which were recorded during consecutive 7 days, was done for each patient. As per the recommendation of the Advanced Technologies and Treatments for Diabetes Congress held in February 2019; standard CGM metrics were used in the study, which could be derived from CGM data, like standard deviation (SD), percentage coefficient of variation (%CV), time above range (TAR) (defined as the percent time with glucose level above 180 mg/dL), time in range (TIR) (defined as the percent time with glucose level between 70 and 180 mg/dL), time below range (TBR) (defined as the percent of the time with glucose level < 70 mg/dL).¹⁰ SD and %CV were used to quantify GV. SD is a measure of the spread in glucose readings around the average. %CV [calculated by the formula $(SD/\text{mean}) \times 100$] is used as the primary measure of GV as it adjusts the mean glucose value and is considered the metric of choice to describe GV.^{11,12}

Similar to a study done by Nwadiugwu et al.,¹³ in this study, %CV has been used to cluster patients into four cohorts from best to worst, namely: best CV of $\leq 10\%$, intermediate

CV from 10 to 20%, high CV from 20 to 30%, and very high CV of $> 30\%$ according to CV classification by Filho et al.¹⁴ The term "glucose control" was operationally defined by using the %CV range. Patients of diabetes mellitus were operationally defined as having the best glucose control with a %CV range between 0 and 10%; those having a %CV greater than 10% but $< 20\%$ were defined as having good control, while those with a %CV range greater than 20% but $< 30\%$ were defined as intermediate-to-poor glucose control, and above 30% were defined as poor/erroneous glucose control.

Statistical Analysis

Computer software (Statistical Package for the Social Sciences trial version 23 and primer) was used for statistical analysis. The quantitative data was expressed as mean and SD, while the qualitative data was expressed in proportion and percentage. The difference in proportion was analyzed by the Chi-squared test, and the difference in means among the groups was analyzed by the student's *t*-test. The correlation between quantitative outcomes was assessed by the Pearson correlation coefficient for parametric data and the Spearman correlation test for nonparametric data. A 5% probability level was considered statistically significant, that is, $p < 0.05$.

RESULTS

Baseline Parameters of Participants

A total of 30 subjects of well-controlled T2DM were enrolled in this study. The subjects were installed with a flash CGMS sensor (FreeStyle® Libre Pro™) for a period of 7 consecutive days. The baseline parameters of the participants are summarized in Table 1.

Continuous Glucose Monitoring Parameters of Glycemic Variability

Glucose readings every 15 minutes in the interstitial fluid were recorded consecutively for a period of 7 days, making it a total of 672 readings for each patient. This data was used to calculate the standard CGM metrics,¹⁰ as mentioned in Table 2.

The expression of time in the various ranges can be done as a percentage (%) of CGM readings, average hours and minutes spent in each range per day or both, depending on the circumstances as agreed by the consensus group.¹⁰ In this study, the CGM parameters of time were used in the form of percentages for the ease of interpretation of data.

Distribution of Cases in Various Cohorts Using Percentage Coefficient of Variation

In the study, the proportion of patients exhibiting low %CV ($< 10\%$) is 0, intermediate

%CV (10–20%) is 16.67% (five out of 30 patients), high %CV (20–30%) is 50% (15 out of 30 patients) and very high %CV (>30%) is 33.33% (10 out of 30 patients) as shown in Figure 1. The subjects having a %CV of <10 were considered most stable with low variability, which in this study was none, while

those with a %CV greater than 30 were the most unstable with very high variability.

Correlation between HbA1c and Glycemic Variability

There is no significant Correlation of HbA1c with %CV ($\rho = 0.076$, p -value = 0.690), and

similarly, no significant correlation was found between HbA1c and SD of blood glucose ($\rho = 0.126$, $p = 0.505$ NS) and also no significant correlation between HbA1c and mean of blood glucose ($\rho = 0.174$, $p = 0.356$ NS) was found.

There was a negative significant correlation of %CV with TIR ($\rho = -0.604$, $p < 0.0015$), and 28.9% of the change in TIR can be explained by the change in %CV.

There was a positive correlation of %CV with TAR and TBR, and with TBR, it is significant ($\rho = 0.816$, p -value of <0.001) and 37.1% of the change in TBR can be explained with change in %CV, although with TAR it is insignificant ($\rho = 0.250$, p -value = 0.191).

Various scatterplots have been displayed in Figure 2.

Table 1: Clinical and biochemical parameters of the study group

Baseline characteristics of the study population	
Parameter	Value
Number (male/female)	19/11
Age (years)	54.26 $\pm$ 16.26
Height (cm)	160.52 $\pm$ 30.67
Weight (kg)	69.32 $\pm$ 18.6
Body mass index (kg/m ²)	25.95 $\pm$ 3.794
HbA1c (%)	6.8 $\pm$ 1.29
Fasting glucose level (mg/dL)	127.19 $\pm$ 27.7
2-hour postprandial glucose (mg/dL)	183.47 $\pm$ 19.46
TG (mg/dL)	165.6 $\pm$ 63.56
HDL (mg/dL)	42.07 $\pm$ 9.1
LDL (mg/dL)	105.07 $\pm$ 38.15
VLDL (mg/dL)	30.3 $\pm$ 10.57
Cholesterol (mg/dL)	173.97 $\pm$ 43.76
Mean $\pm$ SD	

Table 2: Continuous glucose monitoring (CGM) parameters of the study group

	TAR (%)	TBR (%)	TIR (%)	Mean blood glucose (mg/dL)	SD blood glucose	%CV
Mean	14.425	5.771	82.594	134.925	35.348	26.376
SD	13.211	6.808	12.888	22.323	9.388	6.193

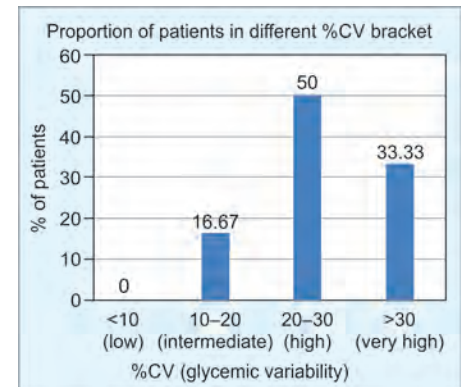


Fig. 1: Distribution of the cases according to GV

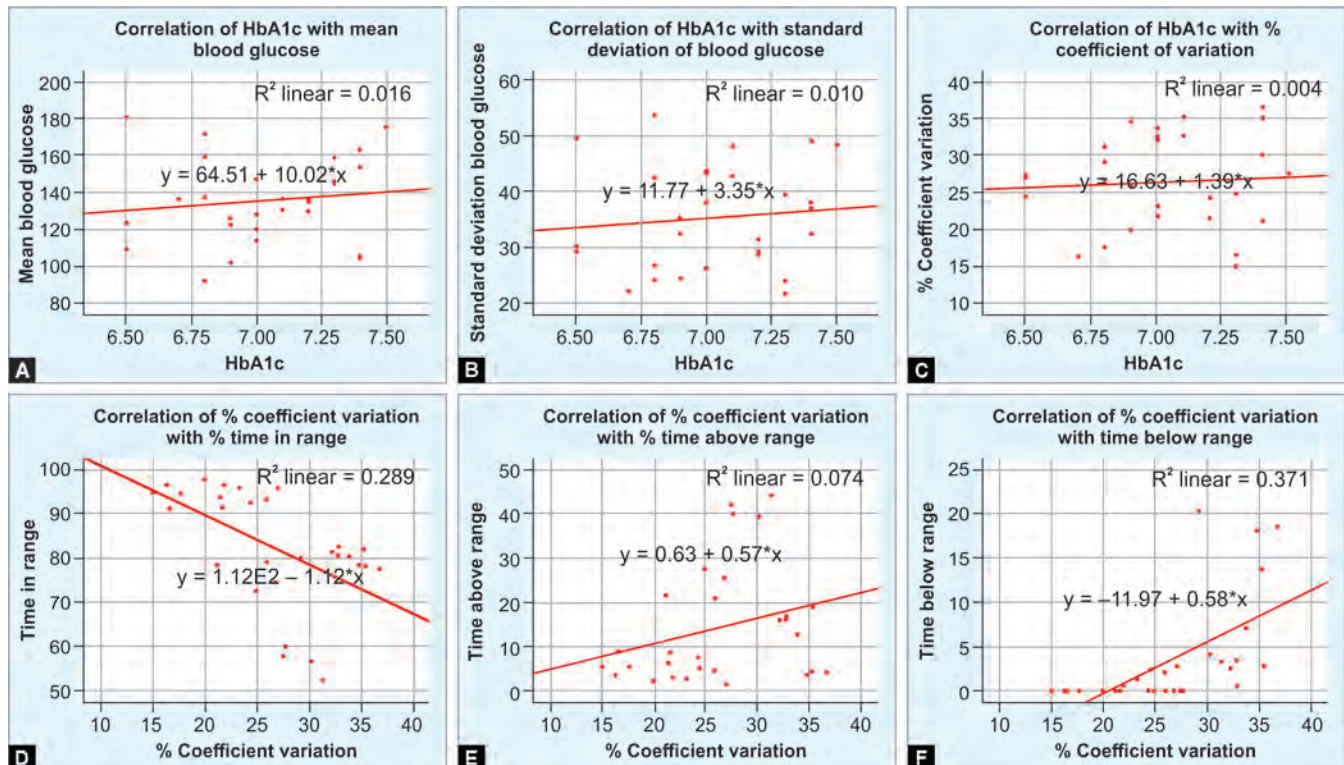


Fig. 2: Scatterplots to establish the correlation between various indices

Adverse Events during CGM Usage

No disconnection, local infection, allergy, bleeding, trauma, or other complications were observed in patients in the present study.

DISCUSSION

Glycemic variability (GV) indicates instability of the metabolic system, which can be expressed as frequent high and low glucose fluctuations, resulting in volatile glycemic control.¹⁵ By using a flash CGMS device, we demonstrated dynamic levels of glucose in the interstitial fluid within subcutaneous fatty tissue over a period of consecutive 7 days, making note of unrecognized events of hypoglycemia and hyperglycemia in asymptomatic well-controlled T2DM patients. The %CV was used as a primary measure of GV, as it is the parameter of choice according to various experts.^{11,12} The most important finding of our study was that even those diabetic patients whom we consider well-controlled experience a great degree of GV as assessed by CGM-derived measures.

Percentage coefficient of variation (%CV) is considered the metric of choice, as it is easily accessible and computable because the calculation does not depend on the average glucose level. Various brackets can be used to allow discrimination between cases on the basis of %CV so that we can devise a proper management plan to maintain glucose homeostasis in diabetes cases. In this study, although the mean %CV of all cases was $26.376 \pm 6.193\%$, one-third (10 out of 30) of study participants had an individual %CV of $>30\%$, that is, unstable with very high GV. These are the patients who need the utmost attention during diabetes care.

Hypoglycemia and hyperglycemia both affect the percentage of CV. The objective of CGM is to reduce the time spent in hypoglycemia (glucose levels <70 mg/dL) to <1 hour/day and time below glucose level 54 mg/dL to <15 minutes/day, equivalent to <4 and $<1\%$, respectively as the standard goal and to maintain TIR $>70\%$.¹¹ In this study, mean TAR, TBR, and TIR were 14.425 ± 13.211 , 5.771 ± 6.808 , and 82.594 ± 12.888 , respectively. It indicates that out of 20,160 observations of blood glucose levels, around 82% of all observations were within the normal range, and 6% were below the normal range, that is, hypoglycemic episodes, which are more dangerous in diabetic cases.

There is no significant correlation between HbA1C and %CV (a measure of GV), mean of the mean and SD of blood glucose level (p -value of >0.05), suggesting that patients may not have optimal control of their diabetes despite having "normal HbA1c" values.¹⁶ Hence, it can be said that GV is an HbA1C-independent danger factor, having more harmful effects than persisting hyperglycemia in the growth of diabetic complications. All the studies that have been done so far suggest no significant correlation between GV and HbA1C. Thus, relying on HbA1c alone in clinical practice is somewhat inadequate to prevent diabetes-related microvascular and macrovascular complications.

There was a negative significant correlation of %CV with TIR, a positive correlation of %CV with TAR and TBR, and with TBR, it is significant (p -value of <0.001), although with TAR it is insignificant (p -value = 0.191). With an increase in %CV, there was a decrease in TIR; as variation in mean blood glucose increases, there was a reduction in the proportion of readings below 70 mg/dL, and a 28.9% change in TIR can be explained with a change in %CV. While with the increase in %CV, there was an increase in the proportion of readings of blood glucose levels that deviated from the normal (70 – 180 mg/dL) range, and 37.1% of the change in TBR can be explained within %CV change.

Composite metrics (TIR and TBR) are to be suggested as complementary to HbA1c because TIR and HbA1c are not efficient for estimating the time in hypoglycemia (TBR).

CONCLUSION

Glucose monitoring has an important role in the proper management of diabetes. CGM provides a new option to patients for regular glucose level monitoring without any need for perpetual finger-sticks. The measurement of GV by using SMBG or CGM data has the potential to complement HbA1C data and also provide a more comprehensive assessment of glycemic excursions in order to inform treatment decisions in a better way, thereby facilitating optimal glycemic control, which is essential for reducing the complications and promoting good quality of life. The use of CGM-derived metrics in conjunction with HbA1C levels should be encouraged.

ACKNOWLEDGMENTS

We are grateful to all the participants in the study and the institution for permitting us to conduct the study.

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A Retrospective Study to Evaluate Real-world Evidence of Azelnidipine in Indian Patients (REDEFINE Study)



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Received: 05 December 2022; Accepted: 01 August 2023

ABSTRACT

Introduction: Azelnidipine, a selective calcium channel blocker, effectively lowers blood pressure (BP) and heart rate (HR) in hypertensive patients, as demonstrated in a retrospective real-world evidence (RWE) study in Indian patients.

Materials and methods: This was a retrospective cohort study that included 882 patients aged 18 years or older who had been on azelnidipine treatment for the last 3 months for mild to moderate hypertension (HTN). A structured proforma was utilized to gather data from prescribing physicians to assess the efficacy of azelnidipine (8 and 16 mg) as monotherapy or in combination with other antihypertensive drugs. The primary endpoints of the study were to capture changes in systolic blood pressure (SBP) and diastolic BP (DBP) from baseline to the subsequent visits (4 and 12 weeks), while the secondary endpoints were to measure similar changes in the diabetic group and to estimate the proportion of patients achieving target BP of <130/80 mm Hg and <140/90 mm Hg, respectively.

Results: The overall mean reduction of systolic/diastolic BP from baseline to 12 weeks was 13.92/7.91 mm Hg (p -value < 0.0001). The mean reduction of systolic/diastolic BP from baseline to 12 weeks was 11.77/7.43 mm Hg (p -value < 0.0001) in newly diagnosed HTN patients, while in known cases of HTN, it was 16.50/8.48 mm Hg (p -value < 0.0001). In the diabetic group, the mean reduction was 15.35/8.69 mm Hg (p -value < 0.0001). Overall the study showed that in 44 (4.99%) and 408 (46.26%) patients, target BP of <130/80 mm Hg and <140/90 mm Hg, respectively was achieved. The mean change in HR from baseline was a reduction of 5.22 beats/minute.

Conclusion: Azelnidipine can be an effective antihypertensive drug to treat mild to moderate HTN in Indian patients.

Journal of the Association of Physicians of India (2024); 10.59556/japi.71.0433

INTRODUCTION

Hypertension (HTN) is an established factor for increased risk of cardiovascular morbidity and mortality and for end-stage renal disease.¹ It remains the leading cause of death globally, accounting for 10.4 million deaths per year.² Fourth district-level health survey estimated HTN prevalence of 25.3% in India, with predominance in males (27.4%) compared to females (20%). This amounts to overall 207 million persons suffering from HTN in the country. According to the Global Burden of Diseases study, HTN led to 1.63 million deaths in India in 2016, representing an increase from 0.78 million (+108%) in 1990. Additionally, the disease burden measured in disability-adjusted life years attributable to HTN rose from 21 million in 1990 to 39 million (+89%) in 2016.^{3,4}

Treatment with antihypertensive drugs is effective in preventing or halting associated damage to target organs. According to the World Health Organization (WHO), the recommended target blood pressure (BP) treatment goal is <140/90 mm Hg for all hypertensive patients without comorbidities and <130 mm Hg for high-risk hypertensive

patients, including those with elevated cardiovascular disease risk, diabetes mellitus (DM), or chronic kidney disease (CKD).⁵ For adults requiring pharmacological treatment for HTN, WHO recommends the initial use of drugs such as thiazide and thiazide-like agents, angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers, and long-acting dihydropyridine calcium channel blockers (CCBs).^{6–8}

The antihypertensive effect of CCBs is primarily attributed to their inhibition of transmembrane Ca^{2+} influx through the voltage-dependent channels in vascular smooth muscles.⁹ Long-acting calcium antagonists are generally recommended due to the reported increased risk of ischemic heart disease associated with short-acting calcium antagonists, which can induce baroreflex-mediated sympathetic activation.¹⁰ Azelnidipine, a distinctive, long-acting, and selective L-type CCB, stands out as it does not trigger reflex tachycardia. Being lipophilic with a strong affinity for membranes of vascular smooth muscle cells, azelnidipine is retained in the vascular wall after blood clearance, providing a

sustained reduction in BP for individuals with mild to moderate HTN.^{11,12} Clinical studies have confirmed the significant efficacy of azelnidipine in reducing both BP and heart rate (HR) in hypertensive patients. There was a lack of evidence regarding the effectiveness of azelnidipine in hypertensive patients in India, and hence, in this real-world evidence (RWE) study, the effectiveness of azelnidipine in lowering BP in Indian patients with mild to moderate HTN was evaluated.

MATERIALS AND METHODS

Study Design

This was a retrospective cohort study that included a total of 1,095 patients aged 18 years or older who were on azelnidipine treatment for at least 3 months for mild to moderate HTN. This study was approved by the Suraksha Ethics Committee. Patients who fall into the following categories were excluded during the period of azelnidipine administration—noncompliant individuals, pregnant women, those with a history of hepatic or renal impairment, patients with comorbidities such as retinal hemorrhage, drug or alcohol dependency, evidence of secondary HTN, moderate or severe heart failure, recent myocardial infarction or cardiac surgery within the preceding 6 months, percutaneous transluminal coronary angioplasty or unstable angina within the preceding 3 months, individuals with cardiac arrhythmia,

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How to cite this article: Shah C, Tiwaskar M, Pakhale K, et al. A Retrospective Study to Evaluate Real-world Evidence of Azelnidipine in Indian Patients (REDEFINE Study). *J Assoc Physicians India* 2024;72(1):22–26.

hypertrophic obstructive cardiomyopathy, or aortic or mitral valve stenosis, as well as those undergoing dialysis.

Primary Outcomes

- Changes in systolic BP (SBP) from baseline (at the time of starting azelnidipine) to the subsequent visits (subsequent visits data for 2–3 visits was captured for a maximum of up to 12 weeks).
- Changes in diastolic BP (DBP) from baseline (at the time of starting azelnidipine) to the subsequent visits (subsequent visits data for 2–3 visits was captured for a maximum of up to 12 weeks).

Secondary Outcomes

- Changes in SBP and DBP from baseline to the subsequent visits in the diabetic group.
- Proportion of patients achieving target BP <130/80 and <140/90 mm Hg.

METHODS

Predesigned structured proforma was used to collect information from the prescribing physicians on the efficacy of azelnidipine (8 and 16 mg) when prescribed as monotherapy or with other antihypertensive drugs from their hospital records. Follow-up BP readings of patients were recorded.

Statistical Analysis

All analyses were performed using statistics and data (STATA) version 15.0 software with relevant statistics as per available data. A paired sample t-test was used to compare the mean BP at baseline with that at the end of the study. The proportion of patients achieving control within drug groups was compared using the χ^2 test.

RESULTS

Out of 1,095 patients, 882 patients fulfilled the inclusion criteria and formed our final study cohort. The baseline characteristics of study participants are depicted in Table 1. The mean

Table 1: Baseline characteristics of study participants

Parameter	Overall (n = 882)	Monotherapy (n = 583)	Dual therapy (n = 299)
Age (years)	47.63 ± 12.43	44.67 ± 11.77	53.40 ± 11.66
Gender, n (%)			
Male	452 (51.25%)	308 (52.83%)	144 (48.16%)
Female	427 (48.41%)	272 (46.66%)	155 (51.84%)
Data not available	3 (0.34%)	3 (0.51%)	0 (0.00%)
Weight (kg)	67.68 ± 12.53	67.40 ± 11.97	68.17 ± 13.45
HTN history, n (%)			
k/c/o HTN	401 (45.46%)	104 (17.84%)	297 (93.33%)
Newly diagnosed	481 (54.54%)	479 (82.16%)	2 (0.67%)
Duration of k/c/o HTN (in months)	105.15 ± 55.97	89.39 ± 50.83	110.67 ± 56.71
Concomitant medical history			
k/c/o DM, n (%)	216 (24.49%)	100 (17.15%)	116 (38.80%)
Duration of DM (in months)	82.37 ± 65.97	40.94 ± 43.87	118.08 ± 60.83
k/c/o CKD, n (%)	103 (11.68%)	72 (12.35%)	31 (10.37%)
Duration of CKD (in months)	30.18 ± 26.14	20.97 ± 20.81	51.58 ± 24.94
Angina	1 (0.11%)	1 (0.17%)	0 (0.00%)
Other concomitant antihypertensive medications, n (%)			
Azilsartan	25 (2.83%)	0 (0.00%)	25 (8.36%)
Captopril	1 (0.11%)	0 (0.00%)	1 (0.33%)
Carvedilol	8 (0.91%)	0 (0.00%)	8 (2.68%)
Losartan	35 (3.97%)	0 (0.00%)	35 (11.71%)
Metoprolol	40 (4.54%)	0 (0.00%)	40 (13.38%)
Olmesartan	23 (2.61%)	0 (0.00%)	23 (7.69%)
Prazosin	1 (0.11%)	0 (0.00%)	1 (0.33%)
Ramipril	5 (0.57%)	0 (0.00%)	5 (1.67%)
Telmisartan	161 (18.25%)	0 (0.00%)	161 (53.85%)
Concomitant medications other than antihypertensive medications, n (%)			
Aspirin	1 (0.11%)	0 (0.00%)	1 (0.33%)
Atorvastatin	6 (0.68%)	3 (0.51%)	3 (1.00%)
Rosuvastatin	1 (0.11%)	0 (0.00%)	1 (0.33%)
Ecosprin	1 (0.11%)	1 (0.17%)	0 (0.00%)
Dapagliflozin	37 (4.20%)	5 (0.86%)	32 (10.70%)
Metformin	1 (0.11%)	1 (0.17%)	0 (0.00%)
Cholecalciferol	1 (0.11%)	1 (0.17%)	0 (0.00%)
Esomeprazole	1 (0.11%)	1 (0.17%)	0 (0.00%)
Etizolam	1 (0.11%)	1 (0.17%)	0 (0.00%)
Fluconazole	1 (0.11%)	1 (0.17%)	0 (0.00%)

CKD, chronic kidney disease; k/c/o, known case of

study population age was 47.6 years, ranging from 23 to 82 years. The study included 452 (51.25%) male patients and 427 (48.41%) female patients. There were 401 (45.46%) patients who were known case(s) of (k/o) HTN, while 481 (54.54%) patients were newly diagnosed with HTN. The mean duration of HTN was 105.15 ± 55.97 months in the known case of (k/c/o) HTN group. There were 216 (24.49%) patients having DM with HTN with a mean duration of 82.37 ± 65.97 months. There were 103 (11.68%) patients who were suffering from CKD with a mean duration of 30.18 ± 26.14 months. About 583 patients received monotherapy of azelnidipine, and 299 patients received dual therapy of azelnidipine with other antihypertensive drugs. A total of 161 patients received telmisartan along with azelnidipine.

The mean baseline SBP of patients recorded was 152.50 ± 13.30 mm Hg, and DBP was 93.93 ± 8.99 mm Hg. During the first follow-up visit (4 weeks), the mean SBP recorded was 145.98 ± 12.77 mm Hg, and DBP was 90.08 ± 8.92 mm Hg. The mean reduction in SBP and DBP was $6.52/3.85$ mm Hg, which was highly significant ($p < 0.0001$). In the second follow-up visit (12 weeks), the mean SBP recorded was 138.58 ± 13.31 mm Hg, and DBP recorded was 86.02 ± 8.79 mm Hg. The mean reduction of SBP/DBP from baseline was $13.92/7.91$ mm Hg ($p < 0.0001$) (Table 2). Overall, in 44 (4.99%) and 408 (46.26%), patients target BP of $<130/80$ and $<140/90$ mm Hg, respectively was achieved (Table 3). The mean HR in the second visit was 84.11 ± 10.53 beats/minute. Mean change from baseline

was a reduction of 5.22 beats/minute (<0.0001) (Table 4).

The study showed a consistent reduction in mean SBP and DBP in both follow-up visits in both groups (newly diagnosed and old HTN). There was a reduction of 11.77 mm Hg and 7.43 mm Hg in SBP and DBP, respectively, after 12 weeks of follow-up visits in newly diagnosed hypertensive patients. Similarly, in k/c/o hypertensive patients, both SBP and DBP were reduced by 16.50 and 8.48 mm Hg, respectively, after 12 weeks of follow-up. The mean reduction in SBP/DBP was $12.39/7.71$ mm Hg in the azelnidipine monotherapy treatment group and $16.89/8.31$ mm Hg in the azelnidipine combination treatment group. The azelnidipine-telmisartan combination treatment group showed SBP/DBP reduction to 145.31 ± 10.52 and 90.59 ± 8.86 mm Hg, respectively at week 4 follow-up visit. At the week 12 follow-up visit, mean SBP was lowered to 136.86 ± 12.25 mm Hg, and DBP was lowered to 86.43 ± 8.47 mm Hg. This change in BP was highly significant in all groups (p -value < 0.0001) (Table 5). In the diabetic group, the overall mean reduction in BP was $15.35/8.69$ mm Hg (p -value < 0.0001) at week 12. With monotherapy, a reduction of $14.20/9.49$ mm Hg in BP was seen, while with dual therapy, a reduction of $16.34/8.01$ mm Hg was observed (Table 6).

DISCUSSION

In the present study, treatment with azelnidipine showed a significant reduction in the baseline BP after 12 weeks of treatment in Indian patients with mild to moderate HTN.

Various studies across the globe have reported conflicting findings on azelnidipine efficacy. A meta-analysis of 19 studies ($n = 1,482$) reported that there were no significant differences in the reduction in SBP when azelnidipine was compared to amlodipine in mild to moderate hypertensive patients (relative risk = 1.00, 95% confidence interval 0.92–1.10).¹³ In ALPS-J study conducted by Kojima et al., it was observed that over 48 weeks, the azelnidipine lowered mean SBP from 138.5 ± 16.9 to 129.1 ± 16.7 mm Hg ($p = 0.003$) and the amlodipine lowered it from 138.3 ± 15.0 to 127.2 ± 15.4 mm Hg ($p < 0.001$).¹⁴ Zhao et al. found that patients receiving azelnidipine showed a better reduction in SBP and DBP compared to those receiving amlodipine for 8 weeks.¹⁵ The findings were reiterated in the present study, with a significant mean reduction of SBP and DBP (p -value < 0.0001) in the overall study cohort.

Azelnidipine is known to decrease HR by inhibiting sympathetic nerve activity while it lowers BP as a vasodilator.¹⁶ Inomata

Table 2: Summary statistics of BP (mm Hg)

Parameter	Overall (n = 882)
Baseline visit	
SBP (mm Hg)	152.50 ± 13.30
DBP (mm Hg)	93.93 ± 8.99
Follow-up visit 1 (week 4)	
SBP (mmHg) (mean $\pm$ standard deviation)	145.98 ± 12.77
DBP (mmHg) (mean $\pm$ standard deviation)	90.08 ± 8.92
Mean change in SBP from baseline (mm Hg) (p -value)	$-6.52 (<0.0001)$
Mean change in DBP from baseline (mm Hg) (p -value)	$-3.85 (<0.0001)$
Follow-up visit 2 (week 12)	
SBP (mm Hg) (mean $\pm$ standard deviation)	138.58 ± 13.31
DBP (mm Hg) (mean $\pm$ standard deviation)	86.02 ± 8.79
Mean change in SBP from baseline (mm Hg) (p -value)	$-13.92 (<0.0001)$
Mean change in DBP from baseline (mm Hg) (p -value)	$-7.91 (<0.0001)$

DBP, diastolic blood pressure; SBP, systolic blood pressure

Table 3: Summary statistics of proportion of patients achieving targeted BP

Parameter	Overall (n = 882)
Targeted BP, n (%)	
Targeted BP $<130/80$ (mm Hg)	44 (4.99%)
Targeted BP $<140/90$ (mm Hg)	408 (46.26%)

BP, blood pressure

Table 4: Summary statistics of HR/minute

Parameter	Overall (n = 882)
Baseline visit	
Mean $\pm$ standard deviation	89.33 ± 11.83
Follow-up visit 1 (week 4)	
Mean $\pm$ standard deviation	88.23 ± 11.86
Mean change from baseline (p -value)	$-1.1 (<0.0001)$
Follow-up visit 2 (week 12)	
Mean $\pm$ standard deviation	84.11 ± 10.53
Mean change from baseline (p -value)	$-5.22 (<0.0001)$

et al. found a significant difference in muscle sympathetic nerve activity between amlodipine group and azelnidipine group (60.1 ± 9.7 vs 47.8 ± 16.6 bursts/100 beats, $p < 0.05$).¹⁷ Yamagishi suggested that oral azelnidipine may be effective for chronic morning HTN and home pulse rate (PR) control, as it decreased mean PR by 6.4 ± 8.3 beats/minute.¹⁸ In the present study, HR was found to be lowered by 5.22 beats/minute with azelnidipine.

Azelnidipine, besides its antihypertensive properties, also has organ protective effects by attenuating angiotensin-II-induced peritubular ischemia and possessing antioxidative properties, potentially aiding in renal injury. The reduction of inflammation by azelnidipine probably contributes to delaying the progression of atherosclerosis and/or diabetic nephropathy.¹⁹ Abe et al. suggested that azelnidipine, when combined with olmesartan, effectively reduces albuminuria

and oxidant stress in hypertensive diabetic patients with type 2 diabetes.²⁰

Azelnidipine plus telmisartan is a newer combination effective in stage II HTN.²¹ In the present study, the combination was effective in lowering SBP and DBP by 14.77 mm Hg and 7.99 mm Hg, respectively, suggesting a promising outcome of the combination. Further studies should be conducted to evaluate the efficacy of azelnidipine and telmisartan in treating hypertensive patients.

Table 5: Summary statistics of BP by subgroup

Parameter	Newly diagnosed HTN (n = 481)	K/c/o HTN (n = 401)	Azelnidipine + telmisartan (n = 161)	Monotherapy (n = 583)	Dual therapy (n = 299)
Baseline visit					
SBP (mm Hg)	152.58 $\pm$ 14.13	152.41 $\pm$ 12.25	151.63 $\pm$ 11.63	152.49 $\pm$ 13.60	152.51 $\pm$ 12.71
DBP (mm Hg)	93.41 $\pm$ 8.79	94.54 $\pm$ 9.19	94.42 $\pm$ 9.13	93.49 $\pm$ 8.57	94.77 $\pm$ 9.71
Follow-up visit 1 (week 4)					
SBP (mm Hg)	146.68 $\pm$ 13.80	145.17 $\pm$ 11.39	145.31 $\pm$ 10.52	146.19 $\pm$ 13.38	145.58 $\pm$ 11.52
DBP (mm Hg)	89.62 $\pm$ 8.82	90.61 $\pm$ 9.03	90.59 $\pm$ 8.86	89.58 $\pm$ 8.53	91.03 $\pm$ 9.57
Mean change in SBP from baseline (mm Hg) (intragroup <i>p</i> -value)	-5.9 (<0.0001)	-7.31 (<0.0001)	-6.32 (<0.0001)	-6.3 (<0.0001)	-6.93 (<0.0001)
Mean change in DBP from baseline (mm Hg) (intragroup <i>p</i> -value)	-3.79 (<0.0001)	-3.91 (<0.0001)	-3.83 (<0.0001)	-3.91 (<0.0001)	-3.74 (<0.0001)
Follow-up visit 2 (week 12)					
SBP (mm Hg)	140.81 $\pm$ 13.51	135.91 $\pm$ 12.58	136.86 $\pm$ 12.25	140.10 $\pm$ 13.18	135.62 $\pm$ 13.10
DBP (mm Hg)	85.98 $\pm$ 8.63	86.06 $\pm$ 8.99	86.43 $\pm$ 8.47	85.78 $\pm$ 8.48	86.46 $\pm$ 9.36
Mean change in SBP from baseline (mm Hg) (intragroup <i>p</i> -value)	-11.77 (<0.0001)	-16.50 (<0.0001)	-14.77 (<0.0001)	-12.39 (<0.0001)	-16.89 (<0.0001)
Mean change in DBP from baseline (mm Hg) (intragroup <i>p</i> -value)	-7.43 (<0.0001)	-8.48 (<0.0001)	-7.99 (<0.0001)	-7.71 (<0.0001)	-8.31 (<0.0001)

DBP, diastolic blood pressure; HTN, hypertension; k/c/o, known case of; SBP, systolic blood pressure

Table 6: Summary statistics of BP (mm Hg) in diabetic group

Parameter	Diabetic group (n = 216)	Diabetic group on monotherapy (n = 100)	Diabetic group on dual therapy (n = 116)	Newly diagnosed HTN with diabetes (n = 54)
Baseline visit				
SBP (mm Hg)	149.27 $\pm$ 12.87	145.34 $\pm$ 11.55	152.66 $\pm$ 13.04	139.72 $\pm$ 8.87
DBP (mm Hg)	92.73 $\pm$ 8.53	91.37 $\pm$ 6.95	93.91 $\pm$ 9.57	89.52 $\pm$ 6.75
Follow-up visit 1 (week 4)				
SBP (mm Hg)	141.50 $\pm$ 12.63	136.45 $\pm$ 11.94	145.86 $\pm$ 11.58	131.78 $\pm$ 10.27
DBP (mm Hg)	88.29 $\pm$ 8.07	85.75 $\pm$ 5.37	90.48 $\pm$ 9.31	83.83 $\pm$ 3.90
Mean change in SBP from baseline (mm Hg) (intragroup <i>p</i> -value)	-7.77 (<0.0001)	-8.89 (<0.0001)	-6.80 (<0.0001)	-7.94 (<0.0001)
Mean change in DBP from baseline (mm Hg) (intragroup <i>p</i> -value)	-4.44 (<0.0001)	-5.62 (<0.0001)	-3.43 (<0.0001)	-5.69 (<0.0001)
Follow-up visit 2 (week 12)				
SBP (mm Hg)	133.92 $\pm$ 11.88	131.14 $\pm$ 10.42	136.32 $\pm$ 12.57	127.50 $\pm$ 8.62
DBP (mm Hg)	84.04 $\pm$ 7.38	81.88 $\pm$ 4.84	85.90 $\pm$ 8.61	80.30 $\pm$ 3.87
Mean change in SBP from baseline (mm Hg) (intragroup <i>p</i> -value)	-15.35 (<0.0001)	-14.20 (<0.0001)	-16.34 (<0.0001)	-12.22 (<0.0001)
Mean change in DBP from baseline (mm Hg) (intragroup <i>p</i> -value)	-8.69 (<0.0001)	-9.49 (<0.0001)	-8.01 (<0.0001)	-9.22 (<0.0001)

DBP, diastolic blood pressure; HTN, hypertension; SBP, systolic blood pressure

The main limitation of the study was poor control over the exposure factors, covariates, and potential confounders as it was a retrospective study. The other limitations include a small sample size and lesser duration of follow-up that needs to be addressed in subsequent studies for more robust evidence.

CONCLUSION

Azelnidipine, a potent antihypertensive drug, has shown significant reductions in BP and HR in Indian patients with mild to moderate HTN, and hence, it can be an effective antihypertensive drug in Indian patients.

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Efficacy of Triglyceride Glucose Index–Neck Circumference and Triglyceride Glucose Index–Neck-to-Height Ratio in the Diagnosis of Cardiovascular Diseases and Metabolic Syndrome



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Received: 11 May 2023; Accepted: 03 October 2023

ABSTRACT

Background: A group of characteristics known as metabolic syndrome raises the chance of developing diabetes and cardiovascular disease. Insulin resistance (IR) and obesity are regarded as critical metabolic syndrome pathophysiology.

Objectives: The diagnostic accuracy of IR indicators, triglyceride (TG) glucose index–neck circumference (TyG-NC), and TG glucose index–neck-to-height ratio (TyG-NHtR) to be evaluated for the detection of cardiovascular diseases and metabolic syndrome in nondiabetic individuals.

Materials and methods: A cross-sectional study was conducted and passed by the Ethics Committee of the institute. The age should be 18 years or older, and subjects should not have diabetes. Each patient's clinical information was gathered, and lab tests were run. The study was done for a period of 1 year.

Results: The study has 100 participants. Around 74% of the group was women. Only 26.5% of the group had an obesity diagnosis. Poor fasting plasma glucose levels were found in 19.4% of the research team. Receiver operating characteristic (ROC)–area under the curve (AUC) testing revealed that all examined IR indices can differentiate individuals with metabolic syndrome from those who are healthy. Our analysis laid out the soaring high area under the ROC curve for TyG index and the low stunted area under the ROC curve for TyG-NC. For obesity, all indices showed appreciable diagnostic efficacy, indicating the maximum achieved area under the ROC curve for TyG index and the minimum recorded metabolic score for IR. The AUC in the case of the metabolic score for IR (METS-IR) male sample population was found to be not statistically compelling.

Conclusion: The exploration of indirect indices, the proposed ones, namely TyG-NC and TyG-NHtR, emphasized an intricate link between cardiovascular diseases and metabolic syndrome.

Journal of the Association of Physicians of India (2024); 10.59556/japi.71.0434

INTRODUCTION

A group of characteristics known as metabolic syndrome raises the chance of developing diabetes and cardiovascular disease.¹ Insulin resistance (IR) and obesity are regarded as critical metabolic syndrome pathophysiology.^{1,2} When the tissues of the body have reduced sensitivity to insulin, hindering its ability to effectively regulate sugar levels, it serves as a marker for IR. This can further cause cardiac and metabolic disturbances.³ During exogenous hyperinsulinemia, both the pancreas and liver's ability to produce glucose diminishes, and the release of glucose into the bloodstream reflects tissue absorption and indirectly establishes IR.⁴

Homeostatic model assessment for IR (HOMA-IR) is derived from fasting glucose and fasting insulin levels and is a frequently used indicator that literally signifies the relationship between IR and hyperinsulinemic-euglycemic clamp.⁴ Certainly, the TG–glucose index, calculated by putting values of glucose and TG concentrations, showcases

notable sensitivity as well as specificity in diagnosing IR. Its substantial connection with the hyperinsulinemic-euglycemic clamp reinforces its efficacy as an indicator for determining IR.⁵ TyG has also been found to have diagnostic relevance in the diagnosis of metabolic syndrome.⁶ The unfolding of new indicators like TG glucose–waist circumference (TyG-WC), TyG–waist-to-height ratio (WHtR), and TyG–body mass index (TyG-BMI), derived from putting together the anthropometric measurements, reflects ongoing efforts in the persona of providing valuable connection of metabolic health and the body composition.⁷

The TG/high-density lipoprotein cholesterol (HDLc) ratio is a straightforward measure of IR. It has also been suggested that cholesterol levels are a signal for the likelihood of developing type 2 DM and cardiac diseases.^{6,7} Moreover, it was shown that TG/HDLc is linked to hypertension. One anthropometric indication of obesity, as well as cardiovascular risk and metabolic syndrome, is neck circumference (NC). The

amalgam of NC and TyG index seems more promising, suggesting potential enhanced accuracy in the assessment of metabolic syndrome. This amalgamation brings into account various factors like increased weight, IR, and hypertension, thereby giving a comprehensive perspective on the complex interplay of these components in health evaluation. The study objective was to scrutinize the productiveness of indirect IR indicators; we proposed new markers for a metabolic syndrome called TyG index–NC (TyG-NC) and TyG index–neck-to-height ratio (TyG-NHtR).

MATERIALS AND METHODS

It was a cross-sectional study of 18 years of age or older among 100 individuals who did not have diabetes. People with previously identified diabetes who had fasting plasma glucose levels that exceeded 125 mg/dL were kept out of our study so that we may include just the sample of patients preceeding diabetes evolution. The study did not include people who were on lipid-lowering medications or who had hypertriglyceridemia (>500 mg/dL). The study was allowed by the Institute's Ethical Committee. Each patient's clinical information was gathered, and lab tests were run. The study was done for a period of 1 year.

Fasting plasma concentration of glucose (FPG), TG measurement, and high-density lipoprotein cholesterol values

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How to cite this article: Kumar A, Gupta A, Gupta A, et al. Efficacy of Triglyceride Glucose Index–Neck Circumference and Triglyceride Glucose Index–Neck-to-Height Ratio in the Diagnosis of Cardiovascular Diseases and Metabolic Syndrome. *J Assoc Physicians India* 2024;72(1):28–31.

were evaluated. The anthropometric measurements, including body height, WC, WHtR, and NHtR, were conducted in the morning after at least 12 hours of fasting. Body height was measured in standing posture with no footwear, with an accuracy of 0.5 cm. WC was approximated by noting the midpoint starting from the lower margin of the last palpable rib to the top of the iliac crest with the help of an unstretchable tape, recorded in centimeters. WHtR was defined as WC divided by body height, and NHtR as NC divided by body height.

Measurements of Insulin Resistance

Indicators of IR were computed using the following formulas:^{8,9}

$$\text{TyG} = \text{Ln}[\text{fasting TG}(\text{mg}\%) \times \text{FPG}(\text{mg}\%)/2]$$

$$\text{TyG-NC} = \text{TyG} \times \text{NC}$$

$$\text{TyG-NHtR} = \text{TyG} \times \text{NHtR}$$

$$\text{METS-IR} = \text{Ln}[2 \times \text{FPG}(\text{mg}\%) + \text{fasting TG}(\text{mg}\%) \times \text{BMI}(\text{kg}/\text{m}^2) / (\text{Ln}[\text{HDLc}(\text{mg}\%)])]$$

Criteria for Metabolic Syndrome

According to the International Diabetes Federation TaskForce on Epidemiology and Prevention in 2009 for Caucasians, important criteria set up for defining metabolic syndrome incorporate three out of five specific risk factors¹⁰:

- Triglycerides (TGs): ≥ 150 mg/dL.
- High-density lipoprotein cholesterol (HDLc): < 40 mg/dL in males, < 50 mg/dL in females.
- Blood pressure (BP): Systolic BP > 130 mm Hg or diastolic BP > 85 mm Hg, or treatment for previously diagnosed hypertension.
- Fasting plasma glucose (FPG): ≥ 100 mg/dL or previously diagnosed type 2 diabetes (diabetics were drawn out of study).
- Waist circumference (WC): ≥ 80 cm in females and ≥ 94 cm in males.¹⁰

Statistical Evaluation and Analysis

The statistical evaluation was performed using Statistical Package for the Social Sciences software for Windows version 22.0 (Mac and Linux). Findings were presented both in number and percentage and inspected by frequency, percentage, and Chi-squared tests. The association among variables was assessed using the Chi-squared test. A critical p -value of < 0.05 was contemplated, indicating the probability of a significant difference for comparison. The area under receiver operating characteristic (ROC) curves was utilized to determine the predictive diagnostic accuracy of the IR indexes.

RESULTS

Table 1 displays the results of anthropometric, lab, and indices of IR. This study has 100 participants. Around 74% of the group was women. Only 26.5% of the group had an obesity diagnosis. Poor fasting plasma glucose levels were found in 19.4% of the research team. The examined group had a hypertension diagnosis in 31.4% of the participants. About 35.2% of people met the metabolic syndrome criteria.

As per Table 2, out of 100 individuals, the computed results of the area under the ROC curve, the 95% confidence intervals (CI), and the corresponding sensitivity and specificity for every IR index for the total study sample are noted. ROC-area under the curve (AUC) testing revealed that all examined IR indexes can differentiate healthy individuals and those with metabolic syndrome.

As per Table 3, the outcome of the area under the ROC curve, the 95% CI, and the optimal thresholds, with corresponding sensitivity and specificity measurements for IR indices in the group with obesity, are hereby presented. All indices pulled off the greatest diagnostic ability with the most prominent curve for TyG index and least recorded for metabolic score of IR. The curve achieved for METS-IR did not give compelling statistical evidence.

DISCUSSION

Our investigation supports earlier findings that indirect measures of IR may be helpful in making a diagnosis of metabolic syndrome.^{6,7,11} It was interestingly demonstrated. HOMA-IR, which draws the importance of the indirect indicators of IR in regular routine practice, is less effective than TyG at predicting

Table 1: Demographic and clinical characteristics

Feature	Mean $\pm$ standard deviation	Median
Age (years)	43.9 $\pm$ 14.5	57.0
Weight (kg)	65.4 $\pm$ 15.2	73.5
Height (cm)	155.8 $\pm$ 9.1	165.0
WC (cm)	91.9 $\pm$ 14.2	92.0
BMI (kg/m ²)	25.4 $\pm$ 4.8	26.9
FPG (mg/dL)	90.4 $\pm$ 11.1	89.0
TC (mg/dL)	202.6 $\pm$ 42.0	201.0
HDLc (mg/dL)	65.9 $\pm$ 17.2	63.0
TG (mg/dL)	140.2 $\pm$ 78.2	125.0
Systolic BP (mm Hg)	123.6 $\pm$ 19.3	132.0
Diastolic BP (mm Hg)	80.9 $\pm$ 11.1	80.0
TyG	8.6 $\pm$ 0.6	8.6
TyG-NC	311.0 $\pm$ 42.3	309.5
TyG-NHtR	1.8 $\pm$ 0.2	1.9
METS-IR	38.2 $\pm$ 8.6	37.3

Table 2: Diagnostic accuracy for IR indexes

Index	AUC	95% CI	p-value	Sensitivity	Specificity
TyG	0.88	0.862–0.915	0.01	0.85	0.82
F	0.89	0.859–0.918	0.01	0.84	0.83
M	0.88	0.829–0.924	0.01	0.90	0.79
TyG-BMI	0.82	0.795–0.857	0.01	0.80	0.71
F	0.82	0.787–0.858	0.01	0.79	0.72
M	0.84	0.782–0.889	0.01	0.72	0.82
TyG-NC	0.79	0.757–0.825	0.01	0.90	0.56
F	0.84	0.812–0.879	0.01	0.87	0.73
M	0.82	0.766–0.876	0.01	0.90	0.68
TyG-NHtR	0.83	0.800–0.862	0.01	0.81	0.71
F	0.84	0.807–0.875	0.01	0.81	0.74
M	0.84	0.783–0.890	0.01	0.87	0.66
METS-IR	0.81	0.785–0.850	0.01	0.77	0.72
F	0.82	0.784–0.856	0.01	0.80	0.71
M	0.82	0.763–0.874	0.01	0.79	0.71

Table 3: Diagnostic accuracy for IR indexes in obese patients

Index	AUC	95% CI	p-value	Sensitivity	Specificity
TyG	0.88	0.840–0.920	0.01	0.86	0.79
F	0.88	0.819–0.926	0.01	0.86	0.79
M	0.89	0.826–0.949	0.01	0.92	0.80
TyG-BMI	0.83	0.781–0.874	0.01	0.83	0.70
F	0.82	0.757–0.881	0.01	0.77	0.77
M	0.85	0.770–0.913	0.01	0.90	0.65
TyG-NC	0.70	0.646–0.759	0.01	0.88	0.44
F	0.80	0.731–0.861	0.01	0.83	0.71
M	0.80	0.715–0.873	0.01	0.87	0.72
TyG-NHtR	0.77	0.720–0.824	0.01	0.78	0.68
F	0.78	0.717–0.850	0.01	0.68	0.81
M	0.82	0.737–0.890	0.01	0.85	0.68
METS-IR	0.80	0.751–0.850	0.01	0.71	0.77
F	0.82	0.761–0.884	0.01	0.80	0.75
M	0.81	0.726–0.882	0.22	0.70	0.80

metabolic syndrome.⁶ The effectiveness of IR markers has been compared in several investigations.^{7,11} TyG was found to have the greatest efficacy in diagnosis, succeeded by TG/HDLc and metabolic score for IR (METS-IR), in a comparison of TyG, METS-IR, and TG/HDLc for diagnosing metabolic syndrome that is consistent with our findings.¹²

Triglyceride (TG) glucose index (TyG)–WC, TyG–BMI, and finally, TyG index were listed in that order, which is contradictory with our study.⁷ Although it has already been noted that the markers' effectiveness varies among nations, it is plausible that ethnic heterogeneity can account for these variations.⁷ Correspondingly, our findings drew attention to the fact that TyG index is the finest predictor in identifying metabolic symptomatology in a sample of subjects of normally measured body weight. TyG–BMI appeared to be a better predictor of IR more accurately than TyG index, TyG–WC. TyG index and other indicators of obesity coherently accomplished better response in foreseeing IR than the TyG index alone.¹¹ Yet, this research demonstrates, in context to diagnose metabolic syndrome, that compared to its anthropometric index-based counterparts, TyG has a higher diagnostic value.

A recent and compelling biomarker of the metabolic syndrome, as well as cardiac risk, was suggested to be NC.^{13–15} Examination of the ROC curve NC has been demonstrated by et al., proving it to be the most likely measure for anticipation of metabolic syndrome.¹⁴ According to Yang et al.'s research, a higher NC raises the risk of coronary heart disease.¹⁵ Also, it appears that the neck and WCs have similar capacities to foresee cardiovascular chances and detect the appearance of metabolic syndrome.¹⁵ TG

to NC and TyG–NHtR might be a good portrayal of the hallmarks of the metabolic syndrome because NC and Ty–G seem to be promising markers of IR and the metabolic syndrome. The TyG–NHtR seems to have a supreme value as far as diagnosis is concerned, rather than TyG–NC, although the implementation of these double indicators clinically requires further research.

CONCLUSION

The metabolic score for IR, TyG index, and variants, which include the newly propounded TyG–NC and TyG–NHtR, lays an emphasis on the diagnostic value for indirect IR indicators' in the metabolic syndrome diagnosis and cardiovascular diseases. TyG–NC and TyG–NHtR are more helpful markers in Caucasians, although additional analysis is needed for deep understanding. It is important to note that TG/HDLc, which can be derived from just two biochemical parameters, has a diagnostic value comparable to that of other indicators and that its application in routine medical practice should be taken into consideration.

DISCLOSURES

Dr Antra Kumar is a postgraduate student in the Department of Internal Medicine at Acharya Shri Chander College of Medical Sciences and Hospital. She, along with other coauthors, worked together on this particular project and finally drafted the research article, keeping all the guidelines and necessary protocols under consideration.

AUTHORSHIP

The International Committee of Medical Journal Editors (ICMJE) has outlined the

criteria for authorship. All the writers have obeyed the constancy of these criteria, ensuring transparency in this scholarly publication.

ETHICAL APPROVAL

No human or animal life was put in danger during the study.

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Randomized, Double-blind, Phase III Trial of Lobeglitazone Add-on to Metformin in Type 2 Diabetes (SENSITIZE INDIA)



Shashank Joshi¹, Monika Tandon², Rahul Kodgule³, Wen Wu⁴, Vibhuti Jadhao^{5*}, Sachin Suryawanshi⁶, Hanmant Barkate⁷

Received: 04 January 2023; Accepted: 11 October 2023

ABSTRACT

Background: The efficacy and safety of lobeglitazone sulfate has been reported only in the Korean population, and no study has been conducted in India.

Materials and methods: In this 16-week randomized, double-blind, and multicenter study, the efficacy and safety of lobeglitazone sulfate 0.5 mg were evaluated with pioglitazone 15 mg. Type 2 diabetes mellitus (T2DM) patients with $\geq 7.5\%$ glycated hemoglobin (HbA1c) $\leq 10.5\%$ and on stable metformin dose were assigned to both treatment arms. The primary outcome was a mean change in HbA1c. Safety assessments included adverse events (AE), home-based glucose monitoring, vital parameters, electrocardiogram (ECG), and laboratory assessments.

Results: A total of 328 subjects were randomized equally in two groups. A statistically significant reduction in HbA1c at week 16 in the lobeglitazone group with the least square (LS) mean change: 1.01 [standard error (SE): 0.09] ($p < 0.0001$) was seen. The LS mean difference between the two groups was 0.05 (SE: 0.12) [95% confidence interval (CI): $-0.18, 0.27$], which was statistically significant ($p = 0.0013$). Statistically significant reductions were also observed in fasting and postprandial glucose. Treatment-emergent AEs (TEAE) were comparable between both groups.

Conclusion: Lobeglitazone 0.5 mg once daily was found to be efficacious and safe in the treatment of T2DM in the Indian population. Lobeglitazone significantly improved glycemic parameters and was noninferior to pioglitazone; hence, it could be a promising insulin sensitizer in T2DM management in India.

Journal of the Association of Physicians of India (2024): 10.59556/japi.71.0445

INTRODUCTION

Glycemic control is the central goal in the treatment of type 2 diabetes mellitus (T2DM). Several orally administered glucose-lowering agents have been developed for the treatment of diabetes. Metformin remains the first-line low-cost treatment option for the majority of patients, with good glucose-lowering efficacy and an acceptable safety profile. However, a large number of patients with type 2 diabetes have inadequately controlled diabetes despite treatment with metformin and need an additional glucose-lowering agent.

Most patients with impaired glucose tolerance or noninsulin-dependent DM and around 25% of nonobese people with normal oral glucose tolerance have resistance to insulin-stimulated glucose absorption.¹ When insulin secretion is insufficient to overcome insulin resistance, hyperglycemia arises due to decreased insulin action. Due to compensatory hyperinsulinemia, β -cell lipotoxicity, and increased islet inflammation, insulin resistance reduces pancreatic β -cell function.^{2,3} These factors result in increased β -cell apoptosis and progressive decreases in insulin secretory capacity. A rise in a number of cardiovascular risk

factors is linked to insulin resistance.^{4–8}

Dyslipidemia, which is caused by insulin resistance, lowers adiponectin, small dense low-density lipoprotein particles, and high-density lipoprotein cholesterol and increases triglycerides and plasma-free fatty acids.^{4,8–10} Steatohepatitis and hepatic steatosis are mostly caused by insulin resistance (nonalcoholic steatohepatitis).¹⁰ Thiazolidinediones (TZDs) primarily affect adipose tissue and reduce insulin resistance by lowering hepatic triglycerides, lowering visceral fat mass and activity, and raising subcutaneous fat mass through the activation of peroxisome proliferator-activated receptor (PPAR) γ .^{4,7,11,12} The main mechanism by which TZDs mitigate the negative consequences of insulin resistance is through the reduction of insulin resistance. TZDs reduce insulin resistance and increase the effectiveness of endogenous insulin, which lowers both fasting and postprandial hyperglycemia.

With an IC₅₀ of 20 and 18 nM, respectively, lobeglitazone sulfate is a TZD that works by activating PPAR- α/γ dual agonist. It was created in Korea by Chong Kun Dang Pharmaceutical to treat diabetes, and it differs significantly from the other two PPAR agonists, pioglitazone and rosiglitazone, in that it has PPAR- α activity. In South Korea

and India, the medication is authorized for the management of T2DM. In a 24-week randomized, double-blind, multicenter clinical trial, lobeglitazone sulfate 0.5 mg once daily was found to be safe and effective when compared to a placebo in treating naïve Korean people with T2D.¹³

Prior to the initiation of this study, no study on lobeglitazone in India was conducted. Hence, a study was conducted with the primary objective of evaluating the efficacy of lobeglitazone sulfate 0.5 mg once daily in comparison with pioglitazone 15 mg once daily in subjects with T2DM with inadequate glycemic control on metformin (≥ 1500 mg/day). The secondary objective was to evaluate the safety of lobeglitazone sulfate 0.5 mg once daily in comparison with pioglitazone 15 mg once daily in subjects with T2DM.

MATERIALS AND METHODS

Trial Design

This was a 16-week, multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-group trial to compare the safety and effectiveness of pioglitazone (15 mg) once daily vs lobeglitazone sulfate (0.5 mg) once a day. The study was conducted from December 2021 to September 2022 across 20 sites in India. The study was designed and monitored following the Sponsor procedures complying with the ethical principles of good clinical practice by following the declaration of Helsinki, as required by the regulatory authority of India. The study was reviewed by an Institutional Ethics Committee (EC) in India at each

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²Manager, Department of Global Medical Affairs (IF), Glenmark Pharmaceuticals Limited; ^{3,5–7}Glenmark Pharmaceuticals Limited, Mumbai, Maharashtra, India;

⁴Glenmark Pharmaceuticals Limited, Watford, Southern Hertfordshire, United Kingdom;

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How to cite this article: Joshi S, Tandon M, Kodgule R, et al. Randomized, Double-blind, Phase III Trial of Lobeglitazone Add-on to Metformin in Type 2 Diabetes (SENSITIZE INDIA). *J Assoc Physicians India* 2024;72(1): 32–42

investigator site. Proper approval from EC was obtained by each investigator before the initiation of the study. The trial was registered with the number CTRI/2021/12/038391. The study protocol is available from <http://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=63033&EncHid=&userName=lobeglitazone>

Participants

The trial comprised male and female T2DM patients who were at least 18 years old and no older than 65 years old, had a glycated hemoglobin (HbA1c) of at least 7.5% and $\leq 10.5\%$ at screening, and were on a stable dose of metformin (≥ 1500 mg/day) as monotherapy for at least 10 weeks previous to screening. Patients excluded were with a history of T1DM, metabolic acidosis or diabetic ketoacidosis, a history of more than one episode of hypoglycemia, body mass index of >45 kg/m², elevated thyroid stimulating hormone levels, abnormal liver function parameters, a significant history of cardiovascular events, ejection fraction of $<50\%$ on two-dimensional echocardiography and on antidiabetic medications other than metformin.

Randomization and Masking

The following therapies were randomly assigned to eligible individuals: arm 1—lobeglitazone sulfate 0.5 mg administered as one tablet once daily and a matching placebo of pioglitazone tablet for 16 weeks. Arm 2—pioglitazone 15 mg, one tablet once daily, and a matching placebo of lobeglitazone sulfate tablet for 16 weeks. Each randomized subject received two tablets in the morning. Treatments were administered for 16 weeks. Throughout the course of the trial, subjects received metformin at stable dosages of ≥ 1500 mg daily under open-label conditions. Metformin was dispensed in the form of 500 and 1000 mg sustained-release tablets and was taken along with the study medication. Based on the investigator's discretion, different numbers of tablets were taken in the morning and evening.

An interactive web response system was used to assign each eligible participant a unique randomization number [interactive web response system (IWRS)] progressively. A distinct material pack code that was connected to the computer-generated randomization method was used to identify each study medication. The pack of study materials was assigned at each visit through. Study drugs and their dummy placebo were identical and presented in the same packaging to ensure blinding of the medication. The randomization code of a withdrawn subject was not reused. The IWRS provided the investigator(s) or

pharmacists with the randomization codes allocated to the subjects, concealing the treatment allocation.

Procedures

Treatment started at visit 1, and subsequent visits two, three, four, and five were conducted after 4, 8, 12, and 16 weeks of treatment. At the time of the run-in visit, subjects received a glucometer and a diary to record information regarding the delivery of study drugs, adverse events (AEs), and self-monitored blood glucose levels. Assessment of efficacy parameters like HbA1c, fasting blood glucose (FBG), postprandial plasma glucose (PPG), and safety parameters like lipid profile, urine analysis, liver function tests, and hematology were performed in the centralized laboratory following standard procedures. Vital parameters and electrocardiogram were taken at the time of each visit as per standard protocols. Weighing scales of the same make were centrally provided to the sites. Subjects could discontinue the investigational product or comparator at the discretion of the investigator for valid reasons, as well as voluntarily discontinue study participation before the completion of the study.

Subjects meeting prespecified rescue criteria [fasting plasma glucose (FPG) >240 mg/dL at week 4; week 8; HbA1c $>8.5\%$ or FPG >200 mg/dL at week 12] were eligible for open-label rescue medication. Antidiabetic medications, except other TZDs or their combinations, were permitted as rescue medication. Change in dose of metformin was not permitted. Records of treatment compliance for each subject were kept during site visits till the completion of the study.

Efficacy and Safety Assessment

The mean difference in HbA1c levels between the pioglitazone and lobeglitazone sulfate groups from baseline to week 16 was the primary efficacy endpoint. Changes in fasting insulin, PPG, insulin resistance, fasting glucose, homeostasis model assessment-insulin resistance (HOMA-IR), and HOMA- β , as well as the percentage of subjects who achieved a therapeutic glycemic response and the percentage of subjects in need of rescue medication, were the secondary endpoints.

Treatment-emergent AEs (TEAE), laboratory testing (hematology, biochemistry, and urine analysis), vital signs, electrocardiogram (ECG), and physical examination were used to evaluate safety. Every AE that occurred throughout the study was documented, starting from the point of enrolment. Self-monitored blood glucose readings and hypoglycemic events were

collected in the subject diary and reviewed by the investigator at each visit.

Data Quality Assurance

The study monitor conducted on-site and remote monitoring visits, reviewing electronic case report forms (eCRFs) for accuracy and completeness. The investigator answered data questions as needed. Data generated during the completion of study-specific procedures were recorded in the subject's source documents or medical records. The eCRF was created by transcribing the data. The investigator was in charge of making sure all the data put in the eCRFs was adequate and accurate.

Statistical Analysis

With 164 participants in each treatment group (pioglitazone and lobeglitazone sulfate), a power of 90% was estimated at a one-sided significance level of 5%, an assumed standard deviation of 1.1% of HbA1c, and a 20% dropout rate to show that lobeglitazone sulfate was not inferior to pioglitazone in terms of HbA1c change from baseline at week 16, with a noninferiority (NI) margin of 0.40. The international guidelines for the development of antidiabetic agents (United States Food and Drug Administration guidance document 2008, Diabetes Mellitus: Developing drugs and biologics) are compliant with the NI margin of 0.40, which was chosen based on the effect size of the active comparator (pioglitazone 15 mg) in placebo-controlled studies. The continuous baseline variables (characteristics) of patients in two groups were summarized in terms of mean and standard deviation, while the categorical variable gender was expressed as frequency and percentage. Using the mixed model repeated measure (MMRM) technique, the difference in HbA1c between lobeglitazone sulfate 0.5 mg and pioglitazone 15 mg was compared from baseline to weeks 4, 8, 12, and 16 (end of treatment). Data of subjects while receiving rescue medication was considered missing. Imputation of missing data was performed only when analysis of covariance (ANCOVA) was used. For this investigation, the last observation carried forward (LOCF) was used. The MMRM approach was used to evaluate several secondary endpoints, such as mean change in FPG, PPG, HOMA- β , HOMA-IR, and fasting insulin, using the same variables. The primary analysis set was the per protocol analysis set, which comprised all randomized subjects who received at least one dosage of study medication, finished the study, and did not have any significant protocol deviations. Using Statistical Analysis System® software 9.4, all scheduled analyses were executed

following database lock, with a p -value of <0.05 deemed statistically significant.

RESULTS

A total of 438 patients were screened across 20 centers in India. Out of these, 110 did not meet one or more inclusion criteria, and 328 subjects were randomized in a 1:1 ratio to lobeglitazone sulfate 0.5 mg group (164) and pioglitazone 15 mg group (164). Eight patients from the lobeglitazone sulfate group and 12 subjects from the pioglitazone group were discontinued during the study due to reasons: loss to follow-up, noncompliance to procedures, or self-withdrawal (Fig. 1). The final per-protocol population was 156 and 152 in lobeglitazone sulfate and pioglitazone group, respectively. The study duration was December 2021 to September 2022.

The demographic and baseline characteristics were similar between the two therapy groups (Table 1). The participants in the pioglitazone 15 mg group had a mean age of 49.7 (9.35) years, whereas the lobeglitazone sulfate 0.5 mg group had a mean age of 51.1 (9.13) years. The difference in age between the two groups was not statistically significant. The gender distribution in the two groups was nearly identical, with 41.8% of the lobeglitazone

group and 43.4% of the pioglitazone group being female. There was no significant difference observed in the subjects' body weight, height, eGFR, HbA1c, FBG, PPG, HOMA- β , and Insulin between the two groups. Drug compliance was defined as utilizing at least 80% of the prescribed study medicines by the subjects. For the lobeglitazone sulfate 0.5 mg group, the mean [standard deviation (SD)] total drug compliance was 99.7% (1.17%), while for the pioglitazone 15 mg group, it was 99.6% (1.26%).

Primary Efficacy Endpoint

For the PP group, the MMRM approach was used to analyze the primary effectiveness objective, which is the change in HbA1c (%) values from baseline to week 16 (Table 2). Both therapy groups and all visits showed a decrease in the mean HbA1c values. The lobeglitazone sulfate 0.5 mg group's HbA1c levels decreased in the per-protocol population from baseline to week 16 in a statistically significant and clinically meaningful way, with a least squares (LS) mean change of -1.01 (SE 0.09) ($p < 0.0001$). Between the two groups, the LS mean difference was 0.05 (SE 0.12) [95% confidence interval (CI) $-0.18, 0.27$]. The 95% confidence interval's upper limit was less than the NI margin (0.40), indicating that lobeglitazone sulfate 0.5 mg was not inferior to pioglitazone

15 mg ($p = 0.0013$). Furthermore, in terms of lowering the mean change in HbA1c% levels from baseline to weeks 4, 8, and 12, the lobeglitazone sulfate 0.5 mg group was significantly noninferior to the pioglitazone 15 mg group ($p < 0.05$). The results were validated using LOCF-ANCOVA with the modified intent-to-treat (mITT) population.

Secondary Efficacy Endpoint

Using the MMRM approach, mean changes in plasma glucose levels during fasting and postprandial periods from baseline to week 16 were examined in the mITT population. In the lobeglitazone sulfate 0.5 mg group, there was a statistically significant decrease in FPG levels from baseline to week 16. At week 16, the lobeglitazone sulfate 0.5 mg group experienced an LS mean [standard error (SE)] change of -41.31 (3.25) mg/dL ($p < 0.0001$), while the pioglitazone 15 mg group experienced a decrease of -35.54 (3.09) mg/dL. Comparable improvement in FPG levels was suggested by the statistically not significant [-5.76 (95% CI $-14.27, 2.74$) mg/dL; $p = 0.183$] LS mean difference between the two groups in change from baseline to week 16. Within the treatment groups, the change in FPG levels from baseline at weeks 4, 8, and 12 was statistically significant ($p < 0.0001$), whereas the LS mean difference

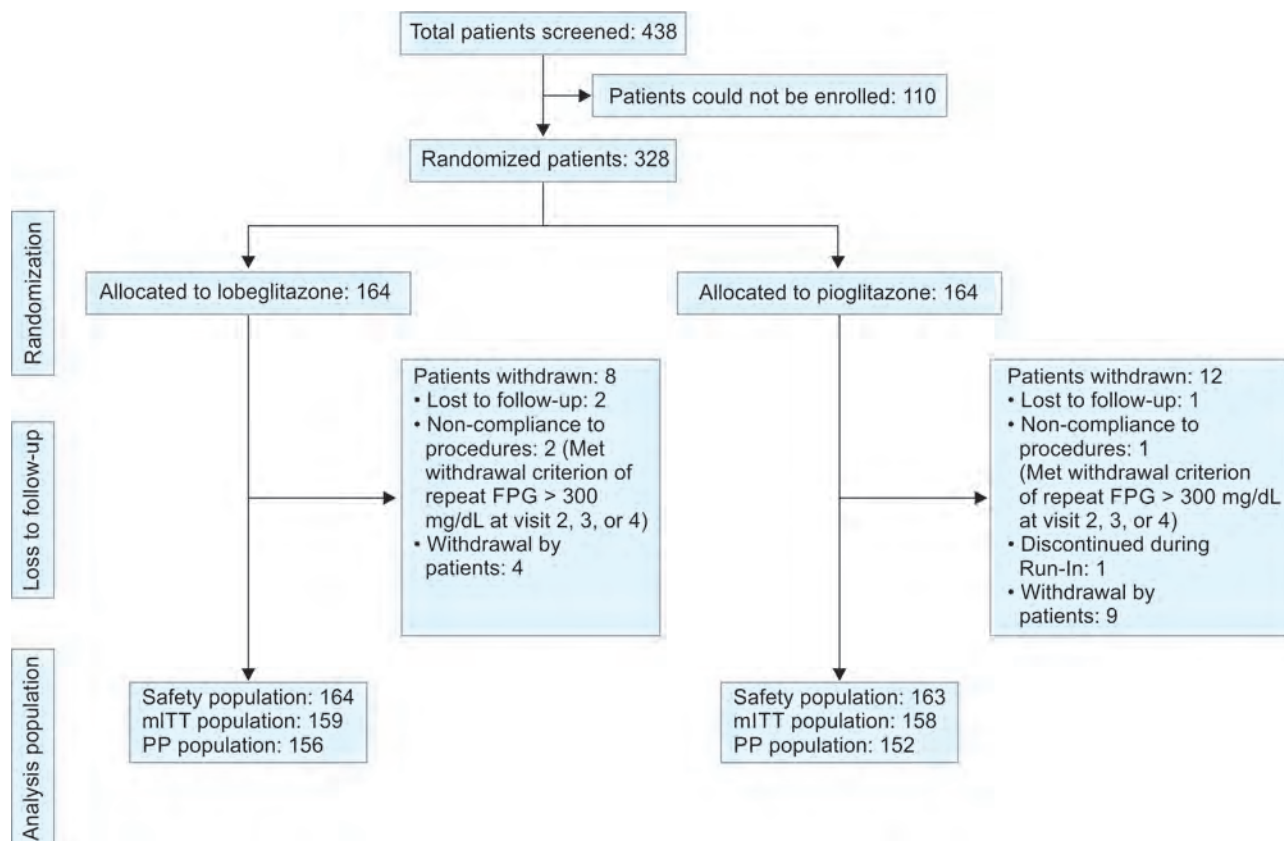


Fig. 1: Consolidated standards of reporting trials diagram

Table 1: Baseline characteristics of patients in two treatment groups (mITT population)

Parameter	Statistical parameter	Group	
		Pioglitazone N = 159	Lobeglitazone N = 158
Age (years)	<i>n</i>	159	158
	Mean (SD)	49.7 (9.35)	51.1 (9.13)
	Median	49.9	51.3
	Minimum, maximum	26.2, 65.1	26.8, 65.0
Gender, <i>n</i> (%)	Male	90 (56.6)	92 (58.2)
	Female	69 (43.4)	66 (41.8)
Body weight (kg)	Mean (SD)	70.7 (11.80)	71.1 (11.11)
	Median	68.5	70.6
	Minimum, maximum	49.4, 102.8	45.3, 98.0
Height (cm)	Mean (SD)	162.2 (8.31)	161.7 (8.87)
	Median	162.0	162.0
	Minimum, maximum	130.0, 181.0	142.0, 187.3
eGFR (mL/minute/1.73m ²)	Mean (SD)	100.9 (28.25)	95.6 (24.65)
	Median	97.0	90.0
	Minimum, maximum	47.0, 226.0	47.0, 193.0
FBG (mg/dL)	Mean (SD)	169.6 (54.94)	179.2 (61.95)
	Median	160.0	168.5
	Minimum, maximum	(81.0, 523.0)	(85.0, 435.0)
Postprandial blood glucose (mg/dL)	Mean (SD)	251.3 (70.37)	246.3 (67.52)
	Median	252.0	242.0
	Minimum, maximum	(75.0, 485.0)	(84.0, 472.0)
HOMA-β	Mean (SD)	67.7 (86.26)	79.8 (133.97)
	Median	42.4	47.3
	Minimum, maximum	(4.8, 813.9)	(1.8, 1435.7)
HOMA-IR	Mean (SD)	6.3 (6.0)	7.9 (7.08)
	Median	4.5	5.7
	Minimum, maximum	(0.6, 43.2)	(0.4, 33.0)
Insulin (mU/L)	Mean (SD)	15.3 (13.59)	18.3 (16.46)
	Median	11.3	12.5
	Minimum, maximum	(2.4, 100.6)	(0.8, 99.7)

eGFR: estimated glomerular filtration rate, HbA1c: glycosylated hemoglobin; HOMA: homeostasis model assessment

between the two groups was not significant ($p > 0.05$). The lobeglitazone sulfate 0.5 mg group showed a statistically significant decrease in PPG from baseline to week 16. At week 16, the lobeglitazone sulfate 0.5 mg group experienced an LS mean (SE) decrease of -41.24 (5.81) mg/dL ($p < 0.0001$), while the pioglitazone 15 mg group experienced a change of -32.87 (5.57) mg/dL ($p < 0.0001$). The two groups' LS mean difference in PPG levels from baseline to week 16 was statistically not significant [-8.37 (95% CI $-23.59, 6.84$) mg/dL; $p = 0.279$], indicating that the two groups' PPG levels had improved similarly. Additionally, the PPG levels in both treatment groups changed from baseline at weeks 4, 8, and 12 ($p < 0.05$), and the LS mean difference between the two groups was not significant ($p > 0.05$) (Table 3).

Similarly, the MMRM technique was applied to the mITT population to examine

changes in fasting insulin, HOMA-IR, and HOMA-β values from baseline week 16 (Table 4). In the lobeglitazone group, there was a statistically significant decrease in insulin resistance. The lobeglitazone sulfate 0.5 mg group experienced an LS mean (SE) change in HOMA-β levels of 13.47 (16.54) from baseline to week 16, while the pioglitazone 15 mg group experienced a change of -11.04 (16.13). The lobeglitazone sulfate 0.5 mg group experienced an LS mean (SE) change in HOMA-IR levels at week 16 of -2.41 (0.65) ($p = 0.0003$), while the pioglitazone 15 mg group experienced -2.57 (0.64). At week 16, the lobeglitazone sulfate 0.5 mg group experienced an LS mean (SE) change in fasting insulin levels of -2.77 (1.65) mU/L, while the pioglitazone 15 mg group experienced a change of -4.75 (1.60) mU/L. The statistical analysis revealed that there was no significant difference ($p > 0.05$) between

the two groups, indicating that the changes in HOMA-β, HOMA-IR, and fasting insulin levels were similar. At week 12, there was no statistically significant difference between the two groups' baseline values for any of these parameters, with the exception of HOMA-β in the lobeglitazone sulfate 0.5 mg group ($p = 0.027$). At week 12, there were no statistically significant differences between the two groups ($p > 0.05$).

Table S1 shows the percentage of cumulative participants that achieved response for FBG and HbA1c at various time points for the mITT population. For both measures, the proportions that differed between the two groups at different visits were not statistically significant. Additionally, there was a statistically insignificant difference in weight between the two therapy groups from baseline to week 12/16 (Table S2).

Table 2: Between and within-group comparison of glycosylated hemoglobin (HbA1c percentage) at different time points (PP, population): MMRM

Visit	Statistics	Pioglitazone (N = 156)	Lobeglitazone (N = 152)	p-value [‡]
Baseline	Mean (SD)	8.56 (0.94)	8.50 (0.89)	0.566
	Median	8.50	8.35	
	Minimum, maximum	(6.0, 11.6)	(6.9, 12.6)	
Baseline—week 4 (day 29)	LSM (SE); (95% CI)	−0.10 (0.09); (−0.27, 0.08)	−0.19 (0.09); (−0.36, −0.01)	0.037
	p-value [†]	0.277	0.037	
	Difference: LSM (SE); (95% CI)	−0.09 (0.12); (−0.33, 0.15)		
Baseline—week 8 (day 57)	LSM (SE); (95% CI)	−0.41 (0.09); (−0.60, −0.23)	−0.53 (0.09); (−0.71, −0.35)	<0.0001
	p-value [†]	<0.0001	<0.0001	
	Difference: LSM (SE); (95% CI)	−0.12 (0.13); (−0.37, 0.13)		
Baseline—week 12 (day 85)	LSM (SE); (95% CI)	−0.74 (0.09); (−0.92, −0.55)	−0.84 (0.09); (−1.02, −0.65)	<0.0001
	p-value [†]	<0.0001	<0.0001	
	Difference: LSM (SE); (95% CI)	−0.10 (0.13); (−0.35, 0.15)		
Baseline—week 16 (day 113)	LSM (SE); (95% CI)	−1.06 (0.08); (−1.22, −0.89)	−1.01 (0.09); (−1.19, −0.84)	<0.0001
	p-value [†]	<0.0001	<0.0001	
	Difference: LSM (SE); (95% CI)	0.05 (0.12); (−0.18, 0.27)		

LSM, least square mean; SE, standard error; difference obtained as lobeglitazone–pioglitazone, [†]obtained for within-group change from baseline; [‡]obtained for one-sided NI test with margin 0.4; MMRM, mixed model repeated measure

Safety Evaluation

In the safety population, 39 participants out of 327 (11.93%) suffered TEAEs. Table 5 provides an overview of all TEAEs by preferred word (PT) and organ class (SOC) in the Medical Dictionary for Regulatory Activities (MedDRA) system. The two groups' overall incidence of TEAEs was similar, with 19 (11.7%) in the group receiving lobeglitazone sulfate 0.5 mg and 20 (12.2%) in the group receiving pioglitazone 15 mg. No serious AE or death was reported during the study, and all the AEs were mild to moderate. In the lobeglitazone 0.5 mg group, 16 subjects (9.8%) had mild, and three subjects (1.8%) had moderate-intensity events. One patient (0.6%) who had a mild event was considered to be related to lobeglitazone sulfate, while 15 subjects (9.2%) with mild events and three subjects (1.8%) with moderate events were unrelated to the drug. In the pioglitazone 15 mg group, 17 subjects (10.4%) had mild, and three subjects (1.8%) had moderate-intensity events, and none were related to the drug.

Furthermore, at baseline, the hematological (Table S3) and biochemistry (Table S4) parameters were similar, and at the study's conclusion, there were no statistically significant variations in the mean values amongst treatment groups. Furthermore, no changes in the laboratory, ECG parameters, vital signs, or any other finding specific to the individual participant that would be clinically significant were observed (data not shown).

DISCUSSION

This is the first clinical trial assessing the safety and effectiveness of lobeglitazone sulfate 0.5 mg in individuals with T2DM from India who are not controlling their blood sugar levels adequately even after taking metformin. Lobeglitazone sulfate 0.5 mg once daily demonstrated a statistically significant and clinically relevant reduction in HbA1c levels at week 16 in this randomized, double-blind, and active comparator investigation. The decrease was comparable to 15 mg of pioglitazone. Over a 16-week period, lobeglitazone caused an HbA1c (%) level drop of −1.01. A similar effect size was reported with pioglitazone (HbA1c reduction of −0.8 to −1.3) in phase III studies.¹⁴ Interestingly, at weeks 4, 8, and 12, HbA1c (%) reductions were numerically larger in magnitude with lobeglitazone compared to pioglitazone with a treatment difference of −0.09, −0.12, and −0.10, respectively, suggesting its potential to cause an early reduction in glycemic parameters. NI of lobeglitazone with pioglitazone, as observed in this study, was also demonstrated in an earlier 24-week, randomized, double-blind clinical trial, providing replicate evidence of glucose-lowering efficacy of lobeglitazone.¹⁵ The HbA1c drop from baseline in the 24-week research was −0.74% in both groups and when added to metformin, lobeglitazone sulfate was determined to be noninferior in efficacy when compared to pioglitazone. The FPG, PPG, and insulin parameters significantly decreased, according to the results of the secondary

endpoint analysis. In our investigation, the decreases in FPG and PPG were similar for the two groups.

A major contributor to the pathophysiology of T2DM, insulin resistance is a powerful predictor of heart disease, myocardial infarction, and stroke.^{16–18} Insulin resistance was linked to a 64% increase in the risk of stroke (hazard ratio 1/64, 95% CI 1.29, 2.08) and a 28% increase in the risk of coronary heart disease (hazard ratio 1.28, 95% CI 1.10, 1.50) in a 22-year follow-up analysis.¹⁹ In this trial, the lobeglitazone group had a reduction in IR (HOMA-IR) of more than two units (−2.41 units). It has been demonstrated that the risk of cardiovascular events is significantly affected by a one-unit variation in HOMA-IR.¹⁸

In every pioglitazone registration clinical study, there was a dose-dependent increase in weight. In the United States placebo-controlled monotherapy trials, patients receiving pioglitazone experienced an average weight change of 0.5–2.8 kg, whereas those receiving placebo experienced an average weight change of −1.3 to −1.9 kg.¹⁴ However, in this study, the weight did not change significantly in the pioglitazone and lobeglitazone groups. This might be attributed to the diet and exercise counseling of patients during the study. There was a small, nonsignificant mean increase of 0.68% (SD: 5.149%) in hematocrit and a mean change of 0.3 mEq/L (SD: 4.52 mEq/L) in the sodium levels in the lobeglitazone group. This is inconsistent with the known fluid retention effect of the TZD class of drugs. Although the exact mechanism of fluid retention and

Table 3: Between and within-group comparison of FPG and PPG at different time points (mITT population): MMRM

Visit	Parameter	Statistics	Pioglitazone (N = 159)	Lobeglitazone (N = 158)	p-value [‡]
Baseline: week 4 (day 29)	FBG (mg/dL)	LSM (SE); (95% CI)	−20.09 (3.19); (−26.37, −13.81)	−19.59 (3.18); (−25.84, −13.34)	
		p-value [†]	<0.0001	<0.0001	
		Difference: LSM (SE); (95% CI)	0.50 (4.38); (−8.13, 9.13)		0.909
	Postprandial blood glucose (mg/dL)	LSM (SE); (95% CI)	−18.01 (6.11); (−30.03, −5.99)	−23.23 (6.06); (−35.16, −11.30)	
		p-value [†]	0.0034	0.0002	
		Difference: LSM (SE); (95% CI)	−5.21 (8.38); (−21.70, 11.27)		0.534
Baseline: week 8 (day 57)	FBG (mg/dL)	LSM (SE); (95% CI)	−21.66 (3.09); (−27.74, −15.59)	−29.41 (3.10); (−35.52, −23.30)	
		p-value [†]	<0.0001	<0.0001	
		Difference: LSM (SE); (95% CI)	−7.75 (4.25); (−16.12, 0.62)		0.069
	Postprandial blood glucose (mg/dL)	LSM (SE); (95% CI)	−18.85 (5.84); [−30.34, −7.35]	−25.64 (5.87); [−37.20, −14.09]	
		p-value [†]	0.0014	<0.0001	
		Difference: LSM (SE); (95% CI)	−6.80 (8.02); (−22.58, 8.99)		0.397
Baseline: week 12 (day 85)	FBG (mg/dL)	LSM (SE); (95% CI)	−36.60 (3.07); (−42.65, −30.56)	−33.69 (3.09); (−39.79, −27.60)	
		p-value [†]	<0.0001	<0.0001	
		Difference: LSM (SE); (95% CI)	2.91 (4.22); (−5.40, 11.21)		0.491
	Postprandial blood glucose (mg/dL)	LSM (SE); (95% CI)	−31.92 (5.54); (−42.82, −21.01)	−39.70 (5.58); (−50.67, −28.73)	
		p-value [†]	<0.0001	<0.0001	
		Difference: LSM (SE); (95% CI)	−7.78 (7.57); (−22.69, 7.12)		0.305
Baseline: week 16 (day 113)	FBG (mg/dL)	LSM (SE); (95% CI)	−35.54 (3.09); (−41.62, −29.46)	−41.31 (3.25); [−47.71, −34.90]	
		p-value [†]	<0.0001	<0.0001	
		Difference: LSM (SE); (95% CI)	−5.76 (4.32); (−14.27, 2.74)		0.183
	Postprandial blood glucose (mg/dL)	LSM (SE); (95% CI)	−32.87 (5.57); (−43.84, −21.90)	−41.24 (5.81); (−52.67, −29.81)	
		p-value [†]	<0.0001	<0.0001	
		Difference: LSM (SE); (95% CI)	−8.37 (7.72); (−23.59, 6.84)		0.279

LSM, least square mean; SE, standard error; difference obtained as lobeglitazone–pioglitazone; [†]obtained for within-group change from baseline; [‡]obtained for between-group change from baseline; MMRM, mixed model repeated measure

weight gain with TZDs is not known, the role of sodium uptake from renal tubules, potentially with the involvement of cotransporters, has been hypothesized.^{20,21} The higher affinity of lobeglitazone to PPAR-γ compared to other TZDs, resulting in a 30 times smaller dose of lobeglitazone (0.5 mg) compared to pioglitazone (15 mg), has the potential to retain antidiabetic effects with reduced side effects.²²

In this study, no serious AEs or deaths occurred in the study population. No subject

reported severe hypoglycemia or an event of cardiac failure. AEs of hypoglycemia are known with the administration of glucose-lowering agents; however, TZD have a relatively lower risk of hypoglycemia. In this study, three subjects (1.8%) reported mild (level 1) hypoglycemia in the lobeglitazone group. This incidence is similar to a 2% incidence of hypoglycemia reported with pioglitazone.¹⁴ An important AE associated with the use of TZDs is cardiac failure;

however, no such event was reported during the study. In similar studies, TZD usage has been linked to mild-to-moderate edema AEs. In a pioglitazone clinical trial, edema was reported by 4.8% of pioglitazone-treated patients vs 1.2% of placebo-treated patients.¹⁴ Edema incidence of 1–2.5% has been reported in the placebo arm in different studies.²³ In this study, two subjects (1.2%) in the lobeglitazone group reported mild peripheral edema, which resolved during the study. One of the

Table 4: Between and within-group comparison of mean change in HOMA-B, HOMA-IR, and fasting insulin from baseline (mITT population)—MMRM

Visit	Parameter	Statistics	Pioglitazone (N = 159)	Lobeglitazone (N = 158)	p-value [‡]
Baseline—week 12 (day 85)	HOMA-β	LSM (SE); (95% CI)	21.81 (32.09); (−41.39, 85.01)	71.51 (32.19); (8.12, 134.91)	
		p-value [†]	0.497	0.027	
		Difference: LSM (SE); (95% CI)	49.70 (44.55); (−38.06, 137.47)		0.266
	HOMA-IR	LSM (SE); (95% CI)	−1.63 (0.89); (−3.38, 0.12)	−0.97 (0.89); (−2.71, 0.78)	
		p-value [†]	0.068	0.278	
		Difference: LSM (SE); (95% CI)	0.66 (1.21); (−1.72, 3.05)		0.586
	Insulin (mU/L)	LSM (SE); (95% CI)	−1.60 (2.14); (−5.81, 2.62)	0.66 (2.15); (−3.57, 4.89)	
		p-value [†]	0.456	0.758	
		Difference: LSM (SE); (95% CI)	2.26 (2.92); (−3.48, 8.00)		0.439
Baseline—week 16 (day 113)	HOMA-β	LSM (SE); (95% CI)	−11.04 (16.13); (−42.82, 20.74)	13.47 (16.54); (−19.12, 46.06)	
		p-value [†]	0.494	0.416	
		Difference: LSM (SE); (95% CI)	24.51 (20.19); (−15.32, 64.35)		0.226
	HOMA-IR	LSM (SE); (95% CI)	−2.57 (0.64); (−3.82, −1.32)	−2.41 (0.65); (−3.70, −1.13)	
		p-value [†]	<0.0001	0.0003	
		Difference: LSM (SE); (95% CI)	0.15 (0.82); (−1.46, 1.77)		0.852
	Insulin (mU/L)	LSM (SE); (95% CI)	−4.75 (1.60); (−7.90, −1.60)	−2.77 (1.65); (−6.02, 0.48)	
		p-value [†]	0.003	0.095	
		Difference: LSM (SE); (95% CI)	1.98 (2.08); (−2.11, 6.07)		0.341

LSM, least square mean; SE, standard error; difference obtained as lobeglitazone–pioglitazone; [†]obtained for within-group change from baseline; [‡]obtained for between-group change from baseline; HOMA-β, homeostatic model assessment–percentage β-cell; HOMA-IR, homeostatic model assessment–insulin resistance; MMRM, mixed model repeated measure

limitations of the study is the duration of follow-up, which could have been longer to establish long-term safety.

CONCLUSION

To sum up, the primary pathophysiological flaw in type 2 diabetes is insulin resistance, and the only class of antidiabetic medications that address insulin resistance exclusively is TZD. Lobeglitazone (0.5 mg) is a new dual PPAR agonist that was recently approved in India. This trial, the first on lobeglitazone in Indian patients, showed that lobeglitazone was just as effective as pioglitazone (15 mg) in treating metformin-uncontrolled type 2 diabetes in Indian patients without posing a significant risk to safety. In the study, lobeglitazone significantly improved glycemic parameters and was well tolerated. Lobeglitazone was found to be noninferior to pioglitazone in terms of change in fasting insulin, HOMA-IR, and HOMA-β; hence, it may be a promising insulin sensitizer for the management of type 2 diabetes in India.

Evidence before Study

We did a PubMed search in September 2022 for publications in English, using the

term “lobeglitazone,” and got 42 hits with pharmacokinetic studies, randomized trials, and review articles. Lobeglitazone has been approved in Korea since 2013, and all the Korean studies showed clinically meaningful improvements in HbA1c, other glycemic parameters, insulin resistance, and lipid parameters with lobeglitazone either as a monotherapy or in combination with one or more anti-hyperglycemic medications. Pharmacokinetic studies of lobeglitazone with other classes of antidiabetic medications like sitagliptin, dapagliflozin, warfarin, amlodipine, and ketoconazole have not shown any major drug–drug interactions or tolerability issues. We found only one article evaluating the efficacy and safety of lobeglitazone added to metformin in patients with T2DM in the Korean population.

Added Value of This Study

This is the first study of lobeglitazone conducted in the non-Korean population (Indian study). In this randomized, double-blind, active control, and add-on to the metformin study, there was a statistically significant reduction in glycemic parameters. The mean change from baseline in HbA1c percentage in the lobeglitazone 0.5 mg group

was noninferior to that in the pioglitazone 15 mg group. There were no major safety concerns reported in the study. Lobeglitazone was safe and well tolerated. This study confirmed the efficacy and safety of lobeglitazone 0.5 mg in the non-Korean (Indian) population.

Implications of All the Available Evidence

Thiazolidinediones (TZD) act on insulin resistance, the core defect of diabetes, and have been used for treating diabetes for more than three decades. Lobeglitazone, a novel dual PPAR agonist, is a favorable alternative to the existing glitazones for treating type 2 diabetes with good efficacy and tolerability.

CONTRIBUTORS

The collection, interpretation, and analysis of the data, as well as the manuscript's revision, were all done by the authors. All authors agreed to be held accountable for all aspects of the work, including making sure that any concerns about the accuracy or integrity of any part of the work are duly investigated and resolved. They also had complete access to all of the study's data and final say over whether

Table 5: Summary of subjects with TEAE (safety population)

System organ class preferred term	Pioglitazone (N = 164)	Lobeglitazone (N = 163)
	n (%)	
Any event	20 (12.2)	19 (11.7)
Blood and lymphatic system disorder	3 (1.8)	0
Lymphopenia	1 (0.6)	0
Thrombocytopenia	2 (1.2)	1 (0.6)
Gastrointestinal disorders	2 (1.2)	3 (1.8)
Diarrhea	2 (1.2)	2 (1.2)
Dyspepsia	0	1 (0.6)
General disorders and administration site conditions	2 (1.2)	3 (1.8)
Asthenia	1 (0.6)	0
Edema peripheral (mild)	0	2 (1.2)
Pyrexia	1 (0.6)	1 (0.6)
Infections and infestations	1 (0.6)	1 (0.6)
Urinary tract infection	1 (0.6)	1 (0.6)
Injury, poisoning, and procedural complications	0	1 (0.6)
Clavicle fracture	0	1 (0.6)
Investigations	0	1 (0.6)
Liver function tests increased	0	1 (0.6)
Metabolism and nutrition disorders	8 (4.9)	7 (4.3)
Dyslipidemia	4 (2.4)	3 (1.8)
Hyperglycemia	1 (0.6)	0
Hypertriglyceridemia	0	1 (0.6)
Hypoglycemia	3 (1.8)	3 (1.8)
Nervous system disorders	3 (1.8)	3 (1.8)
Diabetic neuropathy	1 (0.6)	0
Dizziness	0	1 (0.6)
Headache	2 (1.2)	2 (1.2)
Psychiatric disorders	1 (0.6)	1 (0.6)
Insomnia	1 (0.6)	1 (0.6)
Respiratory, thoracic, and mediastinal disorders	2 (1.2)	0
Cough	1 (0.6)	0
Oropharyngeal pain	1 (0.6)	0

Percentages were based on the number of subjects in the safety population in the respective treatment group; system organ class and preferred terms were coded using the MedDRA version 24.0 or the latest available dictionary; if a subject experienced more than one episode of an AE, the subject was counted once for that event

to submit the work for publication. Verifying study data and designing the study were tasks completed by MT, RK, and WW.

DECLARATION OF INTERESTS

SJ received consulting fees from Glenmark. The rest of the authors do not have any competing interests.

DATA SHARING

Any questions or concerns related to clinical trial data mentioned in this manuscript can be addressed to Glenmark's clinicaltrialsdisclosedesk@glenmarkpharma.com mail.

ROLE OF FUNDING SOURCE

The study was funded by Glenmark Pharmaceuticals Ltd. Mumbai. The study protocol was designed by Glenmark's clinical development team.

ACKNOWLEDGMENTS

This study was funded by Glenmark. We thank all the participants and study personnel. We thank Ardent Clinical Research, Pune, India, for medical writing assistance funded by Glenmark.

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Table S1: Proportion of cumulated subjects achieving response for glycemic parameters (mITT population)

Parameter	Visit	Statistical parameter	Group	
			Pioglitazone N = 159	Lobeglitazone N = 158
HbA1c (mg/dL)	Week 4	n (%)	55 (34.6)	46 (29.1)
		Difference (%)		−5.4
		95% CI		(−15.7, 5.0)
	Week 8	p-value		0.312
		n (%)	91 (57.2)	84 (53.2)
		Difference (%)		−4.1
	Week 12	95% CI		(−15.0, 6.9)
		p-value		0.466
		n (%)	117 (73.6)	103 (65.2)
	Week 16	Difference (%)		−8.4
		95% CI		(−18.5, 1.7)
		p-value		0.105
FBG (mg/dL)	Week 4	n (%)	124 (78.0)	111 (70.3)
		Difference (%)		−7.7
		95% CI		(−17.3, 1.9)
	Week 8	p-value		0.116
		n (%)	73 (45.9)	83 (52.5)
		Difference (%)		6.6
	Week 12	95% CI		(−4.4, 17.6)
		p-value		0.239
		n (%)	106 (66.7)	117 (74.1)
	Week 16	Difference (%)		7.4
		95% CI		(−2.6, 17.4)
		p-value		0.150
	Week 4	n (%)	127 (79.9)	127 (80.4)
		Difference (%)		0.5
		95% CI		(−8.3, 9.3)
	Week 8	p-value		0.910
		n (%)	138 (86.8)	137 (86.7)
	Difference (%)		−0.1	
	95% CI		(−7.5, 7.4)	
	p-value		0.982	

p-value obtained using Pearson's Chi-squared test; 95% confidence interval of the difference%; HbA1c responders, $\geq 0.7\%$ reduction from baseline in HbA1c or a target HbA1c of $< 7\%$; FPG responders, ≥ 30 mg/dL reduction from baseline in FPG or a target FPG of < 126 mg/dL

Table S2: Between and within-group comparison of mean change in weight from baseline (mITT population): MMRM

Visit	Parameter	Statistics	Pioglitazone (N = 159)	Lobeglitazone (N = 158)	p-value [‡]
Baseline—week 12 (day 85)	Weight (kg)	LSM (SE); (95% CI)	−0.06 (0.09); (−0.25, 0.14)	−0.02 (0.09); (−0.22, 0.17)	
		p-value [†]	0.551	0.817	
		Difference: LSM (SE); (95% CI)	0.04 (0.14); (−0.23, 0.30)		0.790
Baseline—week 16 (day 113)	Weight (kg)	LSM (SE); (95% CI)	−0.15 (0.12); (−0.39, 0.08)	−0.17 (0.12); [−0.41, 0.07]	
		p-value [†]	0.189	0.155	
		Difference: LSM (SE); (95% CI)	−0.02 (0.17); (−0.34, 0.31)		0.923

LSM, least square mean; SE, standard error; difference obtained as lobeglitazone–pioglitazone; [†]obtained for within-group change from baseline; [‡]obtained for between-group change from baseline; MMRM, mixed model repeated measure

Table S3: Clinical laboratory assessment: hematology–safety population

Parameter	Visit	Statistical parameter	Group	
			Pioglitazone N = 164	Lobeglitazone N = 163
		<i>n</i>	156	149
Absolute basophils ($\times 10^3/\mu\text{L}$)	Baseline—week 16	Mean (SD)	−0.02 (0.07)	−0.002 (0.07)
		Minimum, maximum	−0.22, 0.15	−0.16, 0.19
Absolute eosinophils ($\times 10^3/\mu\text{L}$)	Baseline—week 16	Mean (SD)	0.01 (0.29)	0.01 (0.14)
		Minimum, maximum	−0.51, 3.15	−0.61, 0.63
Absolute lymphocytes ($\times 10^3/\mu\text{L}$)	Baseline—week 16	Mean (SD)	−0.03 (0.70)	−0.09 (0.69)
		Minimum, maximum	−2.61, 2.94	−1.90, 2.31
Absolute monocytes ($\times 10^3/\mu\text{L}$)	Baseline—week 16	Mean (SD)	0.002 (0.25)	0.01 (0.21)
		Minimum, maximum	−1.45, 0.84	−0.52, 0.75
Absolute neutrophils ($\times 10^3/\mu\text{L}$)	Baseline—week 16	Mean (SD)	−0.25 (1.47)	−0.16 (1.59)
		Minimum, maximum	−4.59, 4.29	−5.57, 6.18
Basophils (%)	Baseline—week 16	Mean (SD)	−0.25 (1.01)	−0.02 (0.92)
		Minimum, maximum	−2.5, 2.5	−2.5, 2.4
Eosinophils (%)	Baseline—week 16	Mean (SD)	0.02 (3.54)	0.24 (1.86)
		Minimum, maximum	−19.5, 26.0	−8.2, 5.8
Ery. mean corpuscular hemoglobin (pg)	Baseline—week 16	Mean (SD)	−0.34 (3.47)	−0.35 (2.61)
		Minimum, maximum	−12.1, 9.9	−11.0, 8.9
Ery. mean corpuscular volume (fl)	Baseline—week 16	Mean (SD)	4.92 (10.44)	4.22 (8.51)
		Minimum, maximum	−28.1, 35.5	−20.4, 36.8
Erythrocytes ($\times 10^6/\mu\text{L}$)	Baseline—week 16	Mean (SD)	−0.09 (0.69)	−0.13 (0.54)
		Minimum, maximum	−2.63, 2.18	−1.84, 1.27
Hematocrit (%)	Baseline—week 16	Mean (SD)	1.20 (7.58)	0.68 (5.15)
		Minimum, maximum	−35.0, 21.5	−20.9, 14.9
Hemoglobin (gm/dL)	Baseline—week 16	Mean (SD)	−0.45 (2.38)	−0.55 (1.57)
		Minimum, maximum	−12.3, 7.6	−6.3, 3.8
Leukocytes ($\times 10^3/\mu\text{L}$)	Baseline—week 16	Mean (SD)	−0.29 (1.89)	−0.24 (2.09)
		Minimum, maximum	−5.94, 5.73	−7.87, 7.40
Lymphocytes (%)	Baseline—week 16	Mean (SD)	0.66 (8.51)	−0.44 (7.65)
		Minimum, maximum	−19.3, 53.8	−26.4, 19.9
Monocytes (%)	Baseline—week 16	Mean (SD)	0.41 (3.13)	0.42 (2.74)
		Minimum, maximum	−14.4, 10.5	−6.7, 10.0
Neutrophils (%)	Baseline—week 16	Mean (SD)	−0.82 (10.07)	−0.19 (8.64)
		Minimum, maximum	−40.4, 29.7	−21.5, 24.8
Platelets ($\times 10^3/\mu\text{L}$)	Baseline—week 16	Mean (SD)	−6.3 (75.32)	−8.8 (67.08)
		Minimum, maximum	−264, 245	−274, 215

Ery., erythrocytes

Table S4: Clinical laboratory assessment: kidney function test–safety population

Parameter	Visit	Statistical parameter	Group	
			Pioglitazone N = 164	Lobeglitazone N = 163
Creatinine (mg/dL)	Baseline—week 16	<i>n</i>	154	151
		Mean (SD)	0.02 (0.20)	0.01 (0.19)
		Minimum, maximum	−0.50, 0.90	−0.60, 1.10
Potassium (mEq/L)	Baseline—week 16	Mean (SD)	0.06 (0.66)	−0.03 (0.59)
		Minimum, maximum	−2.5, 3.0	−2.4, 1.3
Sodium (mEq/L)	Baseline—week 16	Mean (SD)	0.2 (4.45)	0.3 (4.52)
		Minimum, maximum	−13, 11	−27, 11



Insights and Opinions of Critical Care Healthcare Professionals in the Management of Carbapenem-resistant Enterobacteriaceae Cases and Antibiotic-Resistant Infections in the Intensive Care Unit Setting: A Survey-Based Approach

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Received: 20 July 2023; Accepted: 24 November 2023

ABSTRACT

Introduction: A survey-based approach to managing antibiotic-resistant infections in the intensive care unit (ICU) setting, with a focus on carbapenem-resistant Enterobacteriaceae (CRE) cases, was conducted. Among CRE, New Delhi metallo- β -lactamase 1 (NDM-1) is a carbapenemase that is resistant to β -lactam antibiotics and has a broader spectrum of antimicrobial resistance than other carbapenemase types. The article explains that healthcare-associated infections (HAIs) are a significant problem, particularly in low- and middle-income countries, and that carbapenem in combination with other antibiotics are the most potent class of antimicrobial agents effective in treating life-threatening bacterial infections, including those caused by resistant strains.

Aim: The survey aimed to gather critical care healthcare professionals (HCPs') opinions on their current practices in managing infections acquired in the hospital and ICU settings, with a focus on CRE cases, specifically NDM-1 and other antibiotic-resistant infections.

Methods: Responses from critical care healthcare professionals, including online surveys and in-person interviews, to gain insights into the management of infections caused by multidrug-resistant bacteria. The findings related to the insights on the prevalence of bacterial flora, clinical experiences on efficacy and safety of meropenem sulbactam ethylenediaminetetraacetic acid (EDTA) (MSE) in CRE cases, and various combination therapies of antibiotics used to treat antibiotic-resistant infections in ICU setting were evaluated.

Results: *Klebsiella pneumoniae* bacteria were the most common bacteria in cultures, followed by *Escherichia coli*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. NDM-1 was the type of carbapenemase found in around 50% of CRE patients. MSE is among the most preferred antibiotics besides colistin, polymyxin B, and ceftazidime avibactam for CRE cases and specifically for NDM-1 cases due to its high rate of efficacy and safety.

Conclusion: The article concludes with a discussion on the antibiotics used in response to CRE cases, reporting that critical care HCP considers MSE with high efficacy and safe antibiotic combination and was used as both monotherapy and in combination with other antibiotics. The survey highlights the need for exploring and better understanding the role of MSE in the management of CRE infections, especially in NDM-1.

Journal of the Association of Physicians of India (2024); 10.59556/japi.71.0442

INTRODUCTION

The emergence of novel β -lactamases in gram-negative bacteria has led to resistance to β -lactam antibiotics, including carbapenems. Carbapenemases are particularly concerning as they can hydrolyze a broad range of β -lactams and exhibit resistance to β -lactamase inhibitors, making them challenging to treat. One such carbapenemase, New Delhi metallo- β -lactamase 1 (NDM-1), has rapidly spread globally and has a broader spectrum of antimicrobial resistance than other carbapenemase types. Various studies have shown the prevalence of 40–50% NDM-1 in overall carbapenem-resistant Enterobacteriaceae (CRE) cases. As a result,

there is an urgent need to understand treatment options for NDM cases, especially in the intensive care unit (ICU) setting.

Healthcare-associated infections (HAIs) are a significant problem, particularly in low- and middle-income countries where the risk is up to 20 times higher than in high-income ones. HAIs are frequently caused by multidrug-resistant microorganisms due to antibiotic overuse, resulting in increased morbidity and mortality rates, longer hospital stays, and higher healthcare costs. Carbapenem antibiotics are the most potent class of antimicrobial agents and are effective in treating life-threatening bacterial infections, including those caused by resistant strains.

However, antibiotic combination therapy is increasingly used due to the emergence of resistance and the inadequate efficacy of monotherapies. The market research survey aimed to gather critical care healthcare professionals' (HCPs') opinions and recent scientific updates on managing infections acquired in the hospital and ICU settings.

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How to cite this article: Pandit RA, Vijayakumar PC, Shah M, *et al.* Insights and Opinions of Critical Care Healthcare Professionals in the Management of Carbapenem-resistant Enterobacteriaceae Cases and Antibiotic-Resistant Infections in the Intensive Care Unit Setting: A Survey-Based Approach. *J Assoc Physicians India* 2024;72(1):43–46.

The two series of the survey were conducted in the month of January 2023 and covered a wide range of opinions from experts with key findings drawn from the survey. The objectives of the survey were:

- To gather the opinions of critical care HCPs on the efficacy and safety of meropenem sulbactam ethylenediaminetetraacetic acid (MSE) against CRE cases in the ICU setting.
- To gather insights on the prevalence of bacterial flora, especially resistant bacteria, in their respective institute.
- To discuss various combination therapies of antibiotics that can be used to treat antibiotic-resistant infections, including NDM cases.

METHODS

The surveys involved gathering responses from critical care healthcare professionals from 18 centers across the country through various means, such as online surveys or in-person interviews. The survey has involved a literature review of recent studies and scientific updates related to managing infections in the ICU setting. Additionally, the survey included a review of clinical experiences and case studies shared by critical care HCPs to gain insights into the management of infections caused by multidrug-resistant bacteria. The opinion collected through this survey has been

analyzed to draw conclusions and identify key findings related to the objectives of the survey.

Findings of the Survey

- All (100%) of the responders reported that gram-negative bacteria are more prevalent in the hospital setting.
- About 40% of responders reported that *Klebsiella pneumoniae* was the most prevalent bacteria in the ICU in their clinical practice, while 30% reported that *Escherichia coli* was the most prevalent bacteria in the ICU (Fig. 1).

About 80% of responders observe 30% of CRE in their clinical practice, while 13% observe 20% of CRE (Fig. 2).

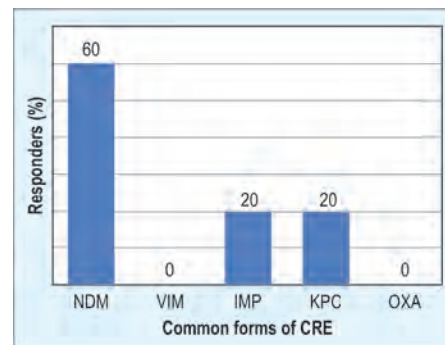


Fig. 3: Response to the most common form of CRE observed in clinical practice

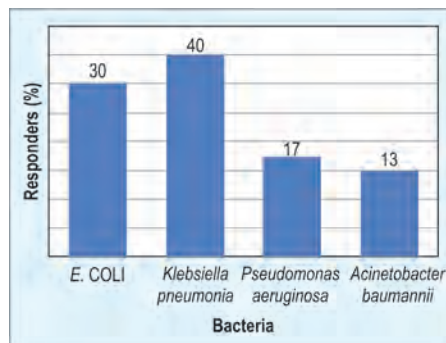


Fig. 1: Response to the most prevalent bacteria in the ICU

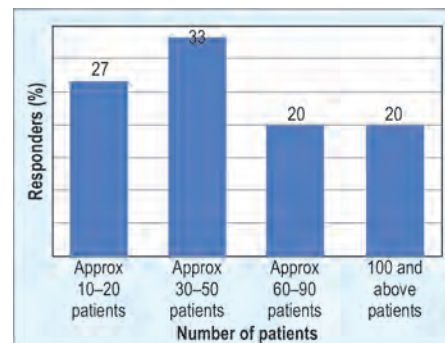


Fig. 4: Opinion based on using MSE in approximately how many patients

- About 60% of the responders reported that they observe NDM as the most common form of CRE in their clinical practice (Fig. 3).
- Below responses of critical care HCP in this survey were basis their experience of using MSE collectively on >750 patients (Fig. 4).
- After having experienced MSE in CRE infection in >750 patients in their ICU, 27% considered colistin, polymyxin B, MSE, and CA as the preferred antibiotics. About 20% considered MSE alone in hemodynamically stable patients, colistin and MSE, and colistin, polymyxin B and MSE, respectively, as their preferred antibiotic choices, while 7% considered polymyxin B, MSE and colistin and amikacin, and MSE and colistin and amikacin, respectively as their preferred antibiotics (Fig. 5).
- Additionally, all responders (100%) reported no adverse effects associated with the MSE combination (Fig. 6).
- In the survey, 60% of responders ranked efficacy and safety as the most preferred characteristics (grade I) of the MSE combination (Fig. 7).
- About 53% prefer MSE monotherapy for moderate cases if the patient is hemodynamically stable, while 47% combine MSE with other antibiotics in these cases (Fig. 8).

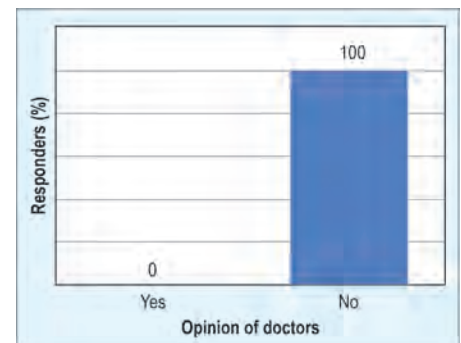


Fig. 6: Response to adverse effects associated with the MSE combination

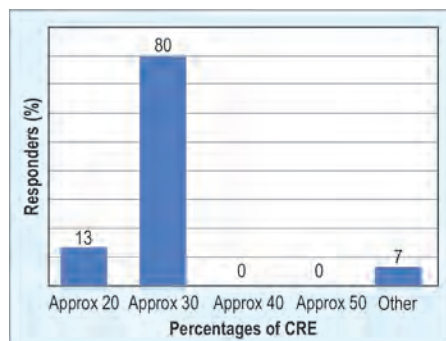


Fig. 2: Response to percentage of CRE observed in clinical practice

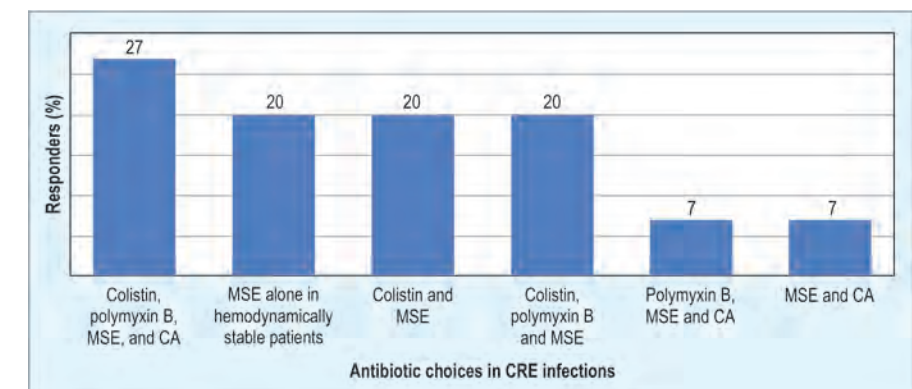


Fig. 5: Response to preferred antibiotic choices after having experience of using MSE in CRE infection

Most critical care providers (CCPs) combine MSE with colistin, followed by polymyxin B, tigecycline, ceftazidime-avibactam, and others (teicoplanin, targocid, antifungals). About 67% of the responders reported that they commonly combine colistin with MSE. While 53% of responders reported combining polymyxin B, 47% with tigecycline, 13% with ceftazidime avibactam, and 13% reported combining other drugs (teicoplanin, targocid, linid, or antifungals) with MSE (Fig. 9).

In severe cases of infection, 40% of the responders continue with MSE, whereas 60% consider replacing MSE with other antibiotic options. About 44% of survey responders consider ceftazidime avibactam, 33% consider colistin, and 22% consider polymyxin B as an option to replace the MSE combination (Fig. 10).

DISCUSSION

The inappropriate prescription and administration of antibiotics have led to a global public health threat of antibiotic resistance.¹ CRE is a type of bacteria that belongs to the Enterobacteriaceae family and can survive and grow even in the presence of clinically relevant carbapenem concentrations. The Centers for Disease Control and Prevention (CDC) defines CRE as enterobacteria that are either known to

produce carbapenemases or are resistant to any carbapenem.¹

Carbapenemases are enzymes that belong to different Ambler classes (A, B, D) and act as β -lactamases. These enzymes can be encoded by both chromosomal and plasmid-mediated genes and are known to hydrolyze a wide range of β -lactams, including carbapenems, cephalosporins, penicillin, and aztreonam.² NDM-1 is the most predominant carbapenemase-producing resistance in countries such as India, Pakistan, and Sri Lanka.¹

The overuse of antibiotics has led to the emergence of antibiotic resistance, making CRE a major public health threat.

Meropenem sulbactam ethylenediaminetetraacetic acid (MSE) is a broad-spectrum antibacterial combination available in hospitals across the country. MSE is being used across tertiary care hospitals in the country as empirical therapy before identifying the causative organisms or for serious infections caused by susceptible bacteria in adults.³ There is an encouraging response from the critical care HCP on the role of MSE in managing CRE infection. HAIs are infections that patients contract while receiving medical or surgical care. The prevalence of HAIs varies between nations and is dependent on economic conditions. Low- and

middle-income countries have up to 20 times higher risk of acquiring HAIs.⁴

In a study by Alhumaid et al., gram-negative pathogens were found to be 2.3 times more likely to cause HAIs than gram-positive bacteria (71.9 vs 28.1%). Additionally, the authors conducted a retrospective analysis and observed that HAI events were more frequent in ICU settings than in non-ICU locations.⁵

Gram-negative organisms were the most common isolates causing HAIs, including *Escherichia coli*, *Klebsiella* species, *Staphylococcus aureus*, and *Pseudomonas* species.⁵

Carbapenem antibiotics are effective in treating severe bacterial infections, including antimicrobial-resistant strains.⁶ The rise of CRE rates among healthcare-associated species, particularly *Klebsiella pneumoniae*, is concerning.⁶

Three groups of carbapenemases, *Klebsiella pneumoniae* carbapenemase (KPC), NDM, and oxacillinase-48 (OXA-48), are considered the main β -lactamases of epidemiological and clinical significance. KPC is the most frequently observed carbapenemase in Enterobacteriaceae worldwide, with KPC-2 and KPC-3 being the most prevalent alleles.⁶ NDM is the most prevalent carbapenemase in the Indian subcontinent, including India, Pakistan, and Bangladesh, as well as in some Balkan nations.⁶

Outbreaks of OXA-48-producing *Enterobacteriaceae* are common in European and Mediterranean countries, including North Africa, while sporadic cases have been identified in the United States, frequently associated with recent travel to India.⁶

Marie et al. demonstrated a notable bactericidal effect when using the combination of sulbactam with either meropenem or colistin. This combination could be a potential alternative treatment option for multiple and extremely resistant bacteria.⁷

Therapy for CRE depends on several factors, including the infection site, identified pathogen, resistance profile, and species-specific resistances.⁸

Second-line treatments are necessary due to the high resistance of CRE to most antibiotics.⁸

Some antibiotics that may be effective against CRE include MSE, polymyxins, aminoglycosides, tigecycline, fosfomycin, and beta-lactam/beta-lactamase inhibitors (BLBLI).⁸

Combinations of medications that show synergy or partial synergy may improve treatment for patients with infections caused by resistant pathogens.⁹

Kiffer et al. demonstrated synergism or partial synergism for most *Acinetobacter*

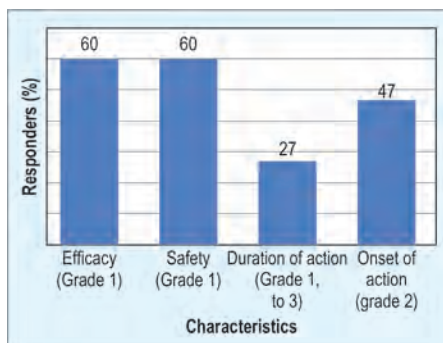


Fig. 7: Response to the characteristics of MSE

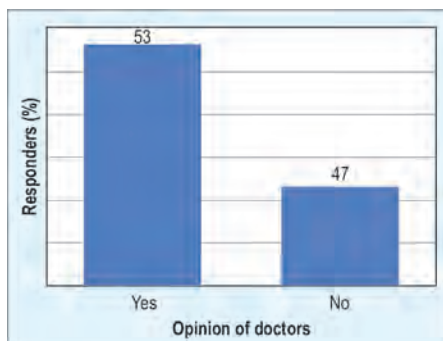


Fig. 8: Response to preference of MSE combination alone in the clinical practice

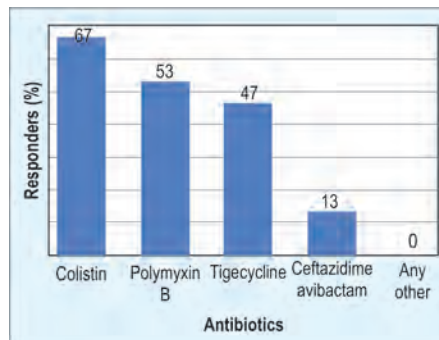


Fig. 9: Response to which of the following antibiotics commonly combined with MSE during severe cases of infection

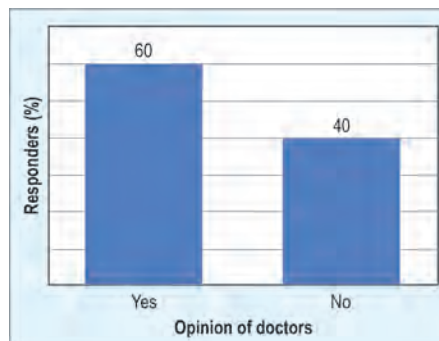


Fig. 10: Response to replacing MSE combination with other antibiotic options during severe cases of infection in clinical practice

baumannii isolates with the combination of meropenem and sulbactam.⁹

There is less documentation on the potential adverse effects of combination antibiotics exhibiting synergistic effects compared to their effectiveness.¹⁰

As resistance to antibiotics continues to grow, there is increasing use of various combination therapy to improve treatment efficacy. Meropenem in various combinations has demonstrated effectiveness in enhancing the therapeutic effects of antibiotics for *Acinetobacter baumannii* strains with NDM-1-related multidrug resistant infections.¹¹ It has also been found to be well-tolerated, with acceptable CNS and gastrointestinal tolerability in adult and pediatric patients with serious bacterial infections.¹² Combination therapy with synergistic drugs may be an option for treating infections caused by resistant organisms.⁹

The triple combination of meropenem, sulbactam, and colistin showed synergy against 96.7% of multidrug resistant *Acinetobacter baumannii*.¹³ The double combinations of either meropenem and sulbactam, meropenem and colistin, or sulbactam and colistin demonstrated synergy effects of 70, 73.3, and 53.3, respectively.¹³ The triple combination had a better killing impact than any of the double combinations in a time-kill assay with ten isolates.¹³

Overuse of carbapenems has led to an increase in carbapenem resistance. It is necessary to reduce the selection pressure on carbapenems by using combination medications.¹⁴ The rise of antimicrobial resistance is a significant threat to public health, particularly with the increase in carbapenem resistance, as alternative treatments are limited. Fortunately, new combination agents

with activity against carbapenem-resistant bacteria are in development or have recently been introduced for clinical use.¹⁵

CONCLUSION

The survey provided valuable insights into the prevalence of resistant bacteria and management through various combination therapies of antibiotics that can be used to treat antibiotic-resistant infections, including NDM cases. The survey also provided valuable insights into the effectiveness and safety of MSE for treating CRE cases in the ICU setting. This information can be utilized to enhance treatment outcomes and patient experiences.

CONFLICT OF INTEREST

All the participants have disclosed their affiliation or involvement in an organization or entity with a financial or nonfinancial interest in the subject matter or materials discussed in this manuscript. The survey was conducted by DocMode Health Technologies Ltd with an academic grant from Lifecare Biosciences Pvt Ltd, Mumbai.

ACKNOWLEDGMENT

We thank Dr Rahul Pandit for his assistance in conducting this survey. We also thank other participants for sharing their observations and opinions.

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Effect of Disease-related Variables on Bone Mineral Density in Patients with Rheumatoid Arthritis

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Received: 14 May 2023; Accepted: 08 September 2023

ABSTRACT

Objective: Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects the bony architecture. Nevertheless, it remains uncertain whether these effects are due to disease progression, limited mobility, or medication. We conducted this study to analyze changes in bone mineral density (BMD) in patients with RA and its relationship with various disease parameters, such as demographic factors, disease activity, functional disability, duration since onset of symptoms, cumulative steroid dose, and titers of rheumatoid factor (RF).

Materials and methods: This cross-sectional study was conducted at the Rheumatology Clinic of the Tertiary Care Hospital of Mumbai. We included 96 consecutive patients diagnosed with RA using the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria. Demographic, clinical, and biochemical data were also collected. Disease severity was assessed using the Disease Activity Score 28 with Erythrocyte Sedimentation Rate (DAS28-ESR) score, and physical disability was assessed using the Health Assessment Questionnaire (HAQ) score. BMD was calculated using dual-energy X-ray absorptiometry (DEXA). Significant variations among continuous variables were examined using the *t*-test, while disparities between categorical variables were evaluated using the Chi-squared test. Statistical significance was set at $p < 0.05$ within the 95% confidence interval (CI) range.

Results: Of the 96 patients, 77 were female, and 19 were male. The mean age of the study population was 45.28 ± 10.15 years. As the age of patients increased, BMD was found to decrease in the total lumbar spine, neck of the femur, and total hip region ($p < 0.05$). Sex did not seem to affect BMD. In all three regions, a decrease in BMD with increasing duration since the onset of RA symptoms was observed. Disease severity, measured using the DAS28-ESR score, did not decrease BMD. There was an increase in functional disability, calculated using the HAQ score, with a decrease in BMD at all sites. RF positivity was associated with decreased BMD at the neck of the femur and total hip region but not the total lumbar spine. Long-term use of steroids (≥ 30 days) decreased BMD at all three sites.

Conclusion: Our study reiterates the effect of RA on the BMD of patients. Advanced age, duration since symptom onset, physical disability, RF positivity, and long-term corticosteroid use are disease-related factors affecting BMD in patients with RA.

Journal of the Association of Physicians of India (2024): 10.59556/japi.71.0404

INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory disorder that primarily affects the joints. It is characterized by asymmetric peripheral polyarthritis, mainly involving small and large joints of the hands. RA is the most common type of long-term inflammatory arthritis.¹ It can also cause joint damage and severe disabilities. RA affects the mechanical characteristics of bones and causes changes in bone composition, either through the heightened release of pro-inflammatory cytokines or through hormone-related processes.²⁻⁴ Multiple studies have shown that individuals with RA experience reduced bone mineral density (BMD) in both hip and vertebral fractures compared to those without RA. However, it remains uncertain whether osteoporosis in the context of established RA is the result of treatment, immobility, or disease activity.

Previous research has explored the link between demographic and disease-related factors and BMD in patients.^{5,6} Some studies that examined the variables associated with BMD have reported inconsistencies, potentially stemming from methodological differences, such as sample size and patient selection.⁷⁻⁹ Furthermore, the intricate interplay between inflammation, immobility, and corticosteroid use may contribute to these inconsistent findings.

Nevertheless, it is often suggested that the duration of the disease, extent of functional impairment, and severity of inflammation have an impact on BMD in patients with RA.¹⁰ Beyond conventional osteoporosis risk factors, factors such as physical disability, inadequate treatment, and disease activity also play a role in bone loss and osteoporosis in RA.¹¹ Additionally, disease duration and presence of rheumatoid

factors (RF) have been linked to bone loss in RA.

Our study aimed to confirm or refute these proposed factors within an Indian population, marking the first study of its kind in this context.

Bone mineral density (BMD) measurement is useful only if it can be followed up with effective anti-osteoporotic therapy. Although the relationship between low BMD and fracture rate has not yet been established in patients with RA, low BMD can be helpful in prescribing anti-osteoporotic drugs to RA patients. In patients with RA, data on the relationship between fracture rate and BMD are limited, indicating that further research is needed on the relationship between low BMD and fracture rate in patients with RA.¹⁰

Our study aimed to determine the correlation between BMD and RA severity and disease activity using the Disease Activity Score 28 with Erythrocyte Sedimentation Rate (DAS28-ESR) score, 14 functional disabilities using the Health Assessment Questionnaire (HAQ) score, 15 duration since onset of symptoms, steroid usage, and titers of RF. To further correlate BMD with age and sex, we studied the effects of the standard of care provided to patients with RA on BMD.

MATERIALS AND METHODS

Study Design

This cross-sectional study took place in Mumbai, India, in a tertiary care hospital. The research spanned 3 months and enrolled a total of 96 patients.

Inclusion Criteria

Patients of age >18 years who fulfilled the criteria for diagnosis of RA by the American

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How to cite this article: Naik S, Sonawale A, Sonawale K, et al. Effect of Disease-related Variables on Bone Mineral Density in Patients with Rheumatoid Arthritis. *J Assoc Physicians India* 2024;72(1):47-50

College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria.¹² Both previously diagnosed and newly diagnosed cases of RA were enrolled.

Exclusion Criteria

Patients on drugs causing loss of BMD except corticosteroids that have been used for the treatment of RA. Some examples of drugs causing bone loss are phenytoin, carbamazepine, tamsulosin, pregnant patients, and the presence of other factors affecting BMD like malignancy, chronic kidney disease, and alcoholism.

Methodology

The details of the patients were noted, including their demographic data, history, and physical and clinical examination findings. Investigations, as done by the treating physician, were also noted down. BMD at lumbar spine, neck of femur, and total hip were measured by dual-energy X-ray absorptiometry (DEXA) scan done at the time of enrolment in the study, and no follow-up scans were performed. T score of <1 was considered osteopenia, and T score of <2.5 was considered osteoporosis. The disease activity of RA was measured using DAS28-ESR score, which includes examination of 28 joints (wrists, elbows, shoulders, and knees, metacarpophalangeal and proximal interphalangeal joints of the hands), ESR, and global assessment of health (the activity of disease in the last 7 days indicated by scores from 0 to 100 that is from very good to very bad). A score of ≤ 2.6 indicates disease remission, whereas a score of 2.7–3.2, 3.3–5, and ≥ 5.1 indicates mild, moderate, and severe disease activity, respectively. Physical function assessment was done by HAQ scoring. The score of 0–1 was classified as having mild to moderate disability, 2–3 score having moderate to severe disability, and >3 HAQ score indicating severe to very severe disability.

Ethics

Approval was granted by the Institutional Ethics Committee (IEC). All participants were only selected after taking their written informed consent.

Statistical Analysis

Significant variations among continuous variables were examined using the *t*-test, while disparities between categorical variables were evaluated using the Chi-squared test. Statistical significance was set at $p < 0.05$, within the 95% confidence interval (CI) range. Statistical analyses were carried out using IBM

SPSS software, specifically version 27 of the Statistical Package for Social Sciences (SPSS).¹³

RESULTS

Demographic Variables

Of the 96 patients, 77 (80%) were female and 19 (20%) were male. A total of 36 (46.75%) female patients were premenopausal, and the remaining 41 (53.25%) were postmenopausal. The mean age of the study population was 45.28 ± 10.15 years. Mean age of the female population was 44.14 ± 10.38 years, whereas the mean age of the male population was 49.89 ± 7.85 years.

The mean duration since patients experienced symptoms of RA was 50.38 ± 47.05 months. The demographic data and disease-related variables such as severity of disease measured using the DAS28-ESR score, functional disability using HAQ score, RF, vitamin D levels, global score, ESR, anti-citrullinated protein antibodies (ACPA) positivity, and other bone-related variables

including BMD and T score at all sites are summarized in Table 1.

Relation between Age and Gender to the BMD

As the age of the patients increased, a decrease in BMD was found at all three sites studied, namely the total lumbar spine, femoral neck, and total hip region. The *p*-values were 0.00004, <0.00001, and <0.01, respectively.

Mean BMD was lower in females by 4.5% (*p*-value = 0.19), 9% (*p*-value = 0.09), and 7.5% (*p*-value = 0.07) at the lumbar spine, the neck of the femur and total hip region respectively, which were not statistically significant (Table 1).

Relationship between the Duration since Onset of Symptoms of RA and BMD at All Sites

We divided the patients into groups depending on the duration since the onset of symptoms of RA—<1 year, 1–5 years,

Table 1: Demographic, disease-related, and bone-related variables in RA

	Sample size or mean $\pm$ standard deviation	Percentage
<i>Demographic variables</i>		
Age in years	45.28 ± 10.15	
Gender		
Female	77	80%
Male	19	20%
Menopausal status		
Premenopause	36	46.75%
Postmenopause	41	53.25%
<i>Disease-related variables</i>		
Duration since onset of symptoms of RA (in months)	50.38 ± 47.05	
HAQ score	1.15 ± 0.624	
Hemoglobin (gm%)	10.82 ± 1.31	
ESR (mm at the end of 1 hour)	44.01 ± 13.39	
Vitamin D levels (ng/mL)	26.25 ± 13.54	
DAS28-ESR score	5.36 ± 1.63	
RF		
Positive	64	66.66%
Negative	32	33.34%
ACPA factor		
Positive	79	82.29%
Negative	17	17.70%
<i>Bone-related variables</i>		
BMD at total lumbar spine (gm/cm ²)	0.8182 ± 0.1252	
BMD at neck of femur (gm/cm ²)	0.6401 ± 0.1317	
BMD at total hip region (gm/cm ²)	0.7966 ± 0.1388	
T score at total lumbar spine	-2.165 ± 1.130	
T score at neck of femur	-1.868 ± 1.060	
T score at total hip	-1.27 ± 1.087	

5–10 years, and >10 years. Most patients (36.45%) had symptoms for 1–5 years. BMD decreased with increasing duration since the onset of symptoms at all three sites. The *p*-values were <0.00001, <0.00001, and <0.00001, respectively (Table 2).

Relationship between Disease Severity by DAS28-ESR Score and BMD at All Sites

The disease severity was calculated using the DAS28-ESR score. Most of the patients (61.45%) in the study had severe disease activity, that is, DAS28-ESR score of >5, and only nine patients (9.3%) were in remission with a DAS28-ESR score of <2.6. As severity of disease increased, the BMD was found to decrease, but this was not a significant finding (*p*-values were 0.502, 0.32, and 0.11, respectively) (Table 2).

Relationship between Functional Disability Calculated by HAQ Score and BMD at All Sites

Functional disability was assessed using the HAQ score. The mean HAQ score in this study was 1.15 (± 0.62). Patients were classified based on the HAQ score, score 0–1 having mild to moderate disability, score 2–3 having moderate to severe disability, and >2 HAQ score indicating severe to very severe disability. There was an increase in functional disability with decreasing BMD at all sites. The *p*-values were

0.006, 0.02, and 0.03, respectively, at these sites, which were significant. Therefore, functional disability, calculated using the HAQ score, was a significant factor that affected BMD in RA patients (Table 2).

Relationship between RF Positivity and BMD at All Sites

Of the 96 patients, 64 (66.66%) were RF-positive, and 32 (33.34%) were negative. BMD was lower by 4% in RF-positive patients in the lumbar spine, whereas in the neck of the femur and total hip region, it was lower by 7.1 and 7%, respectively. In RF-positive patients, BMD was significantly lower at the neck of the femur (*p* = 0.04) and total hip (*p* = 0.02); however, such a relationship was not observed at the lumbar spine (*p* = 0.06) (Table 2).

Relationship between Corticosteroid Use and BMD at All Sites

Of the 96 patients, 50 had taken steroids during their disease course at some time, whereas 46 patients had not used oral steroids. BMD was lower in patients who had used steroids by 7.6% in the lumbar spine (*p* = 0.014), 13.3% in the neck of the femur (*p* = 0.0005), and 14.8% in the total hip region (*p* = 0.0001) (Table 2).

DISCUSSION AND CONCLUSION

We found that the BMD was lower in patients with RA compared to the reference

population.¹⁴ There was also no statistical difference in BMD between males and females in our study. A study conducted by Arain et al.¹⁵ also suggested this finding.

We furthermore found that the duration since onset of symptoms of RA was a significant factor that affected BMD, with decreasing BMD observed with increasing duration. These findings were like the study conducted by Laan et al.,⁹ however, the study conducted by Hafez et al.¹⁶ did not find this correlation to be significant.

Previous studies showed an independent association between the presence of RF positivity and reduced BMD in previously established and recent onset RA.¹⁷ In our study, there was no significant decrease in BMD at total lumbar region, but these findings were significant at total hip region and neck of femur. However, the study conducted by Lodder et al.¹⁸ and Hafez et al.¹⁶ did not find any correlation between RF positivity and BMD. A review of literature on this specific finding may provide further clarity.

Glucocorticoid-induced osteoporosis remains a prevalent and significant concern among RA patients, and there's an ongoing debate about the safety of low-dose corticosteroid treatment concerning its impact on bone health. This should be balanced against the positive effects of managing arthritis and reducing functional limitations.^{7,8,19} In our study, we observed a notable decrease in BMD at the neck of the

Table 2: Relation of duration since onset of symptoms, HAQ score, RF positivity, and steroid use to BMD

	Duration in months	Sample size	<i>p</i> -value at total lumbar spine	<i>p</i> -value at neck of femur	<i>p</i> -value at total hip region
<i>p</i> -values for decrease in BMD with increasing duration since onset of symptoms					
Duration since onset of symptoms	0–12	31	<0.00001	<0.00001	<0.00001
	13–60	35			
	61–120	24			
	>120	6			
Total		96			
<i>p</i> -values for increase in functional disability with decreasing BMD					
HAQ score	0–1 (mild to moderate)	42	0.006	0.02	0.03
	1–2 (moderate to severe)	43			
	>2 (severe to very severe)	11			
	Total	96			
<i>p</i> -values for decrease in BMD observed with RF positivity					
RF	Positive	64	0.06	0.04	0.02
	Negative	32			
	Total	96			
<i>p</i> -values for decrease in BMD observed with use of corticosteroids					
Corticosteroid usage	Yes	50	0.014	0.0005	0.0001
	No	46			
	Total	96			

femur, the total hip area, and the lumbar spine associated with corticosteroid use. However, a study conducted by Lodder et al. did not identify any connection between corticosteroid use and a decline in BMD.¹⁸ This difference could be attributed to the fact that the average prednisolone dose in their study was <10 mg/day and approximately half of the patients on steroid therapy were also receiving bone-protective treatments.

Our study demonstrated the effect of RA on BMD. Advanced age, duration since onset of symptoms, physical disability, RF positivity, and long-term corticosteroid use were disease-related factors affecting BMD in patients with RA in our study. A decrease in BMD over time can lead to osteopenia or osteoporosis, which increases the risk of fracture. This makes it an important parameter for monitoring patients with RA.

Our study had some limitations. First, as previously mentioned, the majority of patients in our study were females. Second, all patients included in this study were recruited from a single tertiary care hospital, which may not accurately represent the entire population. Finally, a larger sample size may be required to increase the generalizability of the results.

The associations derived in our study provide a broader and more in-depth picture of the clinical profile and prognostic markers present in RA and how each factor individually affects BMD in patients, which is paramount for developing broader treatment options, to, in turn, prevent long-term morbidity

from reduction in BMD, which is frequently encountered among patients with RA.^{20–22}

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To Access Knowledge Regarding Organ Donation among Healthcare Workers and Their Willingness toward Organ Donation



Kapil Zirpe¹, Sushma Gurav², Subhal Dixit^{3*}, Prajakta Pote⁴, Abhijeet Deshmukh⁵, Anand Tiwari⁶, Prasad Suryawanshi⁷, Surekha Joshi⁸, Khalid Khatib⁹, Lochana Jadhav¹⁰, Manasi Gole¹¹, Sinu Mathew¹², Raveena L Shaikh¹³

Received: 05 May 2023; Accepted: 08 September 2023

ABSTRACT

Background: In India, critical shortage of organ donations, particularly deceased donations, has led to a dire situation in India, with thousands of patients waiting for transplants and a significant number of them succumbing. One of the reasons for the shortage of organs for transplantation is unawareness and prejudiced information about organ donation. Being direct or indirect stakeholders, the knowledge regarding organ donation among healthcare workers may play an important role in the donation process.

Aim: To assess the knowledge regarding cadaver organ donation among healthcare workers and their willingness toward organ donation.

Materials and methods: It is a cross-sectional offline self-administered questionnaire-based survey conducted among healthcare professionals at tertiary care teaching institutes. Survey was carried out between the months of August to December 2019. A structured questionnaire was used to assess knowledge and willingness toward organ donation. Statistical analysis was done by using statistical package for social sciences (SPSS) 20.0. All *p*-values were considered significant at <0.05 .

Results: A total of 1,039 healthcare professionals participated in the survey. Out of them, 362 (34.8%) were males and 675 (65%) were females. Average age of the healthcare workers participating in survey was 30.81 years, and age ranged from 18 to 60 years. Awareness regarding corneal donation after brain death was found to be maximum (89.7%) and was comparable to that of kidney (86.6%) and heart (83.7%). Participants were unaware of donation of lungs, pancreas, hands and unaware of heart valve donation. About 45% respondents considered that age affected the donors. About 40% respondents considered younger patients as ideal recipients, while 18.7% respondents considered waiting list patients as ideal recipients.

Doctors had highest willingness (78.3%) for organ donation, followed by nurses (69.9%) and support staff (59.3%) ($p < 0.001$). Only 119 (11.5%) participants received organ donation cards as against 68.7% willingness toward organ donation ($p < 0.01$).

Conclusion: We have observed fair awareness regarding overall cadaver organ donation concept among healthcare workers. There is a need to improve knowledge of extended age criteria and which organs can be retrieved from deceased donor. Authorities have to work hard on delivery of organ donation pledging card to promote donation program.

Journal of the Association of Physicians of India (2024): 10.59556/japi.71.0418

INTRODUCTION

There is a continued disparity between the supply and demand for organs across the globe, but when it comes to India, the numbers narrate a disheartening story. India's rate of 0.8 donors per million population is very dismal compared with Croatia's 36.5, Spain's 43.6, and America's 30.3 per million.¹

Organ donation following brain stem death is very infrequent in India, leading to huge shortage of organs in India, and majority of organ failure patients die while on the waiting list for lack of timely availability of organs. Only 5% of all patients with end-stage kidney disease undergo kidney transplantation in India.²

According to an official United States Government website, an average of 17 people

die each day because the organs they need are not donated on time, whereas at least 60% of United States adults are registered as donors.³

Compared to this situation, the plight of organ-waiting patients becomes more painful in India, where awareness about organ donation and official registration as donors is very scarce.

Awareness, positive attitude, and consent by relatives for organ donation in brain death patient are the prerequisites for organ donation.⁴ Horton and Horton's model of factors related to organ donation indicates that knowledge and attitudes were the strongest predictors of organ donation, with personal values playing a much weaker role.⁵ Therefore, better knowledge

about organ donation and possessing a positive attitude may incrementally help in enhancing the donations. Being direct or indirect stakeholders, the knowledge and attitude of medical staff may play a very important role in the donation process. A recent study from Chennai conducted among student population reported very low awareness of organ transplant legislations in India, which prompted us to test the knowledge among medical and paramedical staff.⁶

All over the world, many studies were conducted to evaluate knowledge and attitude toward organ donation among medical students and nurses. Very few studies are carried out among support staff working in hospital in different departments. Support staff, including class IV workers, coordinators, persons working in billing department, human resources (HR), etc., might come in contact with process of organ donation directly or indirectly. The purpose of this study was to assess knowledge, attitude, and practices about organ donation and to study the association of sociodemographic factors with knowledge, attitude, and practice of organ donation among healthcare professionals including support staff.

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How to cite this article: Zirpe K, Gurav S, Dixit S. *et al.* To Access Knowledge Regarding Organ Donation among Healthcare Workers and Their Willingness toward Organ Donation. *J Assoc Physicians India* 2024;72(1):56-62

MATERIALS AND METHODS

Study Design

It is cross-sectional, self-administered, questionnaire-based survey conducted among healthcare professionals working in two hospitals. Survey was carried out between the months of August to December 2019. A structured questionnaire was used to assess knowledge and willingness toward organ donation.

Sample Size and Data Collection and Analysis

Convenience sampling technique was used to recruit participants from healthcare professionals working in the hospital. A total of 1,039 participants could be recruited and answered the questionnaire regarding organ donation after signing informed consent. Data collected from the structured questionnaire was divided to assess sociodemographic variables, knowledge and willingness, and behavior toward organ donation. The questionnaire contained the questions in the form of multiple-choice questions. Data collected was entered into an Excel sheet and analyzed by using statistical package for social sciences (SPSS) 20.0. All *p*-values were considered significant at <0.05 .

Ethics Committee Approval

Ethics committee approval was taken from both sites. Participation in the study was voluntary and without any form of compensation.

RESULTS

We have interpreted the survey data under the following headings.

Sociodemographic Variables

A total of 1,039 healthcare professionals participated in the survey (Table 1). Out of them, 362 (34.8%) were males and 675 (65%) were females. More number of female participants may be attributed to the most nursing staff being females. Average age of the participants was 30.81 years, and age ranged from 18 to 60 years. About 106 (10.2%) participants were educated <10 th standard, 119 (11.5%) studied 10th–12th standard, 677 (65.2%) had graduate degree, and 137 (13.2%) had postgraduate degree. Most of the participants [594 (51.17%)] had experience of <5 years, 335 (32.24%) had experience of 5–15 years, and 110 (10.6%) participants were working for >15 years. Out of 1,039, 286 (27.5%) were doctors, 420 (40.4%) were nurses, and 333 (32.1%) were support staff. We included class IV workers, billing personnel, coordinators, and security guards as support staff for survey assessment.

Knowledge Regarding Organ Donation

A set of questions was asked to assess knowledge of the participants regarding organ donation. Questions were related to declaration of brain death, organs that can be donated after brain and cardiac death, knowledge about the transplant waiting lists, and sources of information about organ donation (Table 2).

A total of 760 (73%) participants knew correctly that brain dead person is an ideal organ donor and most of the participants 739 (71%) were aware that brain death is declared at intensive care unit (ICU). Awareness regarding corneal donation after brain death was found to be maximum (89.7%) and was comparable to that of kidney (86.6%) and heart (83.7%). Knowledge about eye donation was also maximum (61%) when participants were asked about organs that can be donated after death at home. Almost half the participants [468 (45%)] thought that age does affect organ donation, while 82.2% (854) participants thought that cancer patients cannot donate organs.

A total of 659 participants (63.61%) were aware of waiting list for organ recipients and agreed to the fact that patient on waiting list should get the priority for getting the organs. About 40.3% (419) participants thought that young patients would be ideal organ recipients, while another 28.3% thought that patients on waiting list for longer time would be ideal recipients. About 56.5% (587) participants thought that organ donation is not supported by all religions, while rest of them thought that it is supported by all religions.

Effect of Age and Experience upon Knowledge of Organ Transplant

When knowledge about organ donation is correlated with the age, education, and experience of the participants, it was observed that age, education as well as experience did affect the knowledge parameters of the participants significantly. Higher education was directly proportional to better knowledge levels.

Sources of Information

Internet seems to be the most common (39.7%) source of information for organ donation among all the participants, followed by information from doctor, television, newspaper, and friends and colleagues (Fig. 1). When this information is cross tabulated with medicos (doctors and nurses) and nonmedicos within the participants, most common source among medicos was internet (44.9%) while that among nonmedicos was friends and

colleagues (30.9%). Significant amount of medicos (42.1%) got information from doctors compared to nonmedicos (25.8%) ($p < 0.05$) (Table 3).

Willingness and Behavior toward Organ Donation

Among all participants, 714 (68.7%) were willing to organ donation (Fig. 2). When willingness is compared with age, education, and experience, there was no significant difference between willingness and organ donation and age or education or experience of participants. When willingness is compared to the profession of participants as doctors vs nurses vs support staff, there was significant difference in willingness toward organ donation ($p < 0.05$).

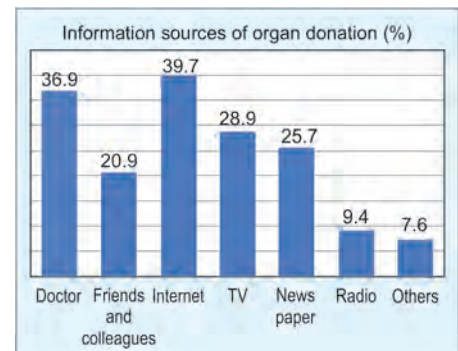
Participants were asked if they had taken a pledge for organ donation or had they received an organ donor card; it was found that only 119 (11.5%) participants had received organ donation card as against 68.7% showed

Table 1: Sociodemographic characteristics of study population

Variables	Frequency	Percentage
Age group		
18– $\leq$ 25 years	347	33.4
26– $\leq$ 35 years	396	38.1
36– $\leq$ 45 years	184	17.7
46– $\leq$ 55 years	85	8.2
>55 years	27	2.6
Gender		
Male	362	34.8
Female	675	65
Nonresponders	2	0.2
Education group		
<10 th	106	10.2
10th–12th	119	11.5
Graduate	677	65.2
Postgraduate	137	13.2
Experience group		
≤ 1 years	243	23.4
2– ≤ 5 years	341	32.8
6– ≤ 10 years	207	19.9
11– ≤ 15 years	128	12.3
16– ≤ 20 years	61	5.9
>20	49	4.7
No experience	10	1.0
Profession group		
Doctors	286	27.5
Nurses	420	40.4
Support staff	333	32.1
Marital status		
Married	572	55.1
Single	467	44.9

Table 2: Knowledge regarding brain death and organ donation—overall

Variables	Frequency	Percentage
Where can a patient be declared brain dead?		
Home	21	2.0
Hospital	248	23.9
ICU	739	71.1
Ward	30	2.9
Nonresponders	1	0.1
Who will be the ideal organ donor?		
Brain dead patient	760	73.1
Brought dead patient	114	11.0
Handicapped	12	1.2
Postcardiac arrest patient	44	4.2
Terminally ill patient	109	10.5
Which organs can be donated after brain death?		
Kidney	900	86.6
Cornea	932	89.7
Heart	870	83.7
Liver	816	78.5
Lungs	672	64.7
Pancreas	638	61.4
Hands	565	54.4
All of the above	397	38.2
Which organs can be donated if death occurs at home?		
Eyes		
Yes	634	61.0
No	405	39.0
Skin		
Yes	291	28.0
No	748	72.0
Bones		
Yes	236	22.7
No	809	77.3
Heart valves		
Yes	216	20.8
No	823	79.2
Does age affect organ donation?		
Yes	468	45.0
No	568	54.7
Nonresponders	3	0.3
Can cancer patient donate organ?		
Yes	182	17.5
No	854	82.2
Nonresponders	3	0.3
Who should be given priority for getting the organ?		
Donors near relative	246	23.74
Hospital's own patient	659	63.61
Rich patients	118	11.38
Patients who are in waiting list	13	1.25
Nonresponders	3	0.3
Ideal organ recipient as per you will be?		
Chronically ill patient	196	18.9
Long waiting time on registry	294	28.3
Low-income patients	71	6.8
Patient with history of transplant	59	5.7
Young patients	419	40.3
Does all religions support organ donation?		
Yes	452	43.5
No	587	56.5

**Fig. 1:** Distribution of information sources

willingness toward organ donation. When willingness is compared to organ donation card receivers, it is found that significant amount ($p < 0.05$) of participants who are willing to organ donation have not received organ donor card, and few participants who are not willing for organ donation have received organ donor card.

Participants were asked whether they know any organ donor. Only 30.8% (320) participants knew organ donors, while 719 (69.2%) did not know any organ donor. It was found that significant ($p < 0.05$) number of participants who know organ donor were willing for organ donation.

When asked about willingness toward eye and blood donation, it was found that willingness to eye (64.6%) and blood (68.6%) donation is similar to willingness for organ donation among all participants. Similarly, willingness toward eye and blood donation in doctors' group was comparable to willingness toward organ donation in that group. When willingness toward organ donation is compared to willingness toward eye and blood donation, it is found that those who do not want to donate organs are significantly not willing for blood or eye donation either.

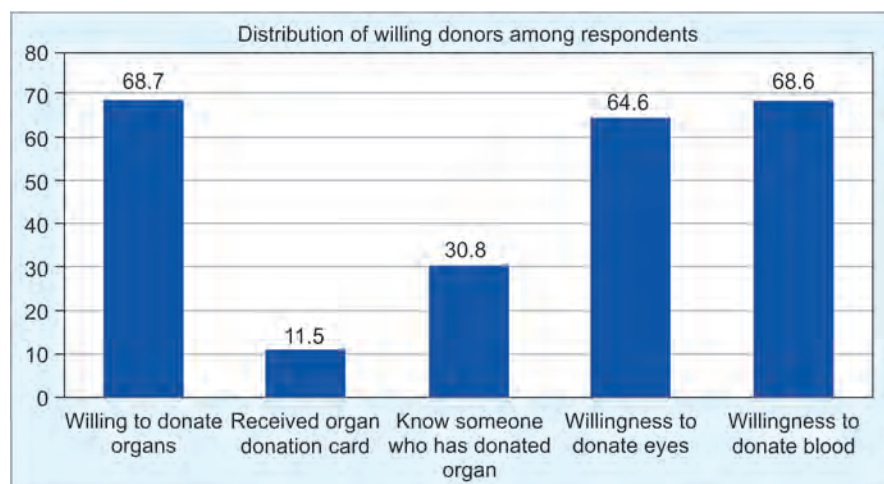
DISCUSSION

Taking into account the worldwide gap in demand of donated organs for the patients on the waiting list for transplantation, knowledge and attitude of healthcare professionals cannot only affect the willingness and rate of organ donation among healthcare professionals but also the general population.

This self-administered survey was conducted in two hospitals in Pune city, where organ procurement and transplantation rates are among the highest in the country. Contrary to previous studies, we have included support staff, that is, class IV workers, coordinators, billing personnel, and security personnel from the hospital in our survey. Support staff, although not coming in direct contact with brain dead patient, need to deal with different

Table 3: Distribution of information sources stratified between medicos and nonmedicos

Information source	Medicos		Nonmedicos		p-value
	Frequency	Percentage	Frequency	Percentage	
Doctor	297	42.1	86	25.8	<0.001
Friends and colleagues	114	16.1	103	30.9	<0.001
Internet	317	44.9	95	28.5	<0.001
Television	208	29.5	92	27.6	0.543
News paper	177	25.1	90	27.0	0.501
Radio	62	8.8	36	10.8	0.296
Others	36	5.1	43	12.9	<0.001

**Fig. 2:** Willingness and behavior toward organ donation

aspects of the procedure of declaration of brain death and organ donation process. Their knowledge and attitude can affect their willingness toward organ donation.

In this survey, we assessed sociodemographic parameters, knowledge, and willingness of total 1,039 participants through self-administered questionnaire. About 65% of participants were female. This finding is comparable to two Indian studies by Sah et al. and Alex et al., where the respondents had female predominance.^{7,8} Overall willingness to organ donation was found to be 68.7%, which is equivalent to previous studies conducted on medical students or staff,^{8,9} however, it was higher than the general urban population.¹⁰ In a study on medical students in South India, 53.5% of participants of expressed willingness to pledge their organs for donation after death.¹¹ Another study of medical students reported that about one out of two students was willing to donate own organs, and 61% of the students were positive about their family member's postmortem organ donation.¹²

The willingness rate shown in our survey was exactly similar to a newspaper survey where 69% participants showed inclination to potential organ donation.¹³ Studies conducted in Muslim-majority countries like Saudi Arabia¹⁴ and Pakistan¹⁵ reported large numbers of participants, that is, 73.5

and 62.3%, respectively, displayed positive intent to becoming an organ donor. About 57.9% of study population of Egypt-based study was also willing to donate their organs.¹⁶ However, few studies, like Sahu et al., reported willingness among only 44.1% of participants.¹⁷ Also, a Nigerian study showed a poor response, with meager 30% respondents willing to donate their organs.¹⁸ A study involving participants from Germany and Spain observed that only 17.71% of participants were seriously thinking (much thought), and 54.5% were somewhat thinking to donate organs.¹⁹ An astounding finding was reported by studies from Ohio²⁰ to Brazil.²¹ with 96 and 87% participants, respectively, showing willingness to donate.

We found that profession does affect the willingness for organ donation as doctors (78.32%) and nurses (69.93%) are significantly more willing for organ donation than support staff (59.34%) (Table 4). Amaliyar et al.⁹ reported a similar observation where the willingness for organ donation among science students (92.0%) was very high compared to commerce (86.0%) and arts students (57.0%). This can be associated with their knowledge as nurses and doctors are more closely involved in the process of organ donation.

In our study, although there was significant difference in the knowledge about brain dead patients among different classes of education group, this did not affect the willingness toward organ donation. The results were in tandem with Tamuli et al.'s study, which showed significant differences in knowledge between undergraduates and postgraduate students.²² Thus education might add to the knowledge of people regarding organ donation but might not affect the willingness. Thus, imparting knowledge about brain death needs to be backed with sustainable efforts in generating positive opinions on donation (Table 5).

Most of the medicos, that is, doctors and nurses, get information from internet to senior doctors, while support staff receive most information from friends and colleagues, and few among them receive information from internet, doctor, and other social communication sources such as television, radio, newspaper, etc. Similar sources were quoted by previous studies^{9,10} with growing trend toward internet and electronic media. Easy availability and accessibility of internet can be harnessed more effectively to provide information and increase awareness toward brain death and orientation toward organ donation. As many support staff got information from their friends and colleagues who might be more closely related to organ donation procedure. Thus, sensitizing the medical staff to spread awareness and enhancing their own knowledge about organ donation seems to be of paramount importance.

Although total of 68.7% participants expressed willingness to donate organs, only 11.5% have taken pledge or received organ donor card, which explains sheer lack of behavior even after willingness. Knowledge about donor card was also reported low in different studies from South India, where the rate of transplantation is highest in the country (42.0%, 35.0%).^{8,23} Compared to the other Indian studies,^{11,12} the rate of pledging the organs was found strikingly low in our study. While most of the Indian campaigns are dedicated to enhancing awareness, this survey

Table 4: Willingness to organ donation stratified by age, experience, education, and role

	Willingness to organ donation		p-value
	Yes	No	
Age group	Frequency (percentage)	Frequency (percentage)	
<25 years	226 (65.3)	120 (34.7)	0.22
26–45 years	409 (70.6)	170 (29.4)	
>45 years	79 (70.5)	33 (29.5)	
Experience group			
No experience	6 (60)	4 (40)	0.533
≤5 years	399 (68.4)	184 (31.6)	
6–15 years	227 (68)	107 (32)	
>15 years	82 (75)	28 (25)	
Education group			
<12th	159 (70.7)	66 (29.3)	0.445
Graduate	456 (67.6)	219 (32.4)	
Postgraduate	99 (72.3)	38 (27.7)	
Role			
Doctors	224 (78.32)	62 (21.68)	<0.001
Nurses	293 (69.93)	126 (30.07)	
Support staff	197 (59.34)	135 (40.66)	

Table 5: Knowledge parameters stratified by education group

	Education group			p-value
	<12th	Graduate	Postgraduate	
Where can a patient be declared brain dead?				
Home	6 (2.7)	13 (1.9)	2 (1.5)	0.696
Hospital	24 (10.7)	205 (30.3)	19 (13.9)	<0.001
ICU	179 (79.6)	447 (66.1)	113 (82.5)	<0.001
Ward	16 (7.1)	11 (1.6)	3 (2.2)	<0.001
Who will be the ideal organ donor?				
Brain dead patient	111 (49.3)	533 (78.7)	116 (84.7)	<0.001
Brought dead patient	68 (30.2)	38 (5.6)	8 (5.8)	<0.001
Handicapped	5 (2.2)	4 (0.6)	3 (2.2)	0.067
Postcardiac arrest patient	12 (5.3)	32 (4.7)	0 (0)	0.028
Terminally ill patient	29 (12.9)	70 (10.3)	10 (7.3)	0.237
Priority for getting the organ should be given to?				
Donors near relative	74 (33.18)	148 (21.89)	24 (17.52)	0.001
Hospital's own patient	47 (28.07)	65 (9.61)	6 (4.38)	<0.001
Patient in waiting list	99 (44.39)	453 (67.01)	107 (78.1)	<0.001
Rich patient	3 (1.34)	10 (1.47)	0 (0)	0.362
Ideal organ recipient should be?				
Chronically ill patient	35 (15.6)	139 (20.5)	22 (16.1)	0.17
Long waiting list on registry	42 (18.7)	212 (31.3)	40 (29.2)	0.001
Low-income patient	52 (23.1)	16 (2.4)	3 (2.2)	<0.001
Patient who had transplant	5 (2.2)	52 (7.7)	2 (1.5)	0.001
Young patient	91 (40.4)	258 (38.1)	70 (51.1)	0.018

has emphasized the need for more effective campaigns that could positively influence the behavior of willing donors. The finding on donor cards asks for meticulous follow-up of willing donors and implementation of strategy at the policy level. If a brain-dead patient in the hospital carries an organ donor card, it might be helpful to convey

and counsel the family regarding patient's wish. Thus, focus on the issuance of donor card can play substantial role in the organ donation drive. Also, the overall awareness on legality regarding organ donation in India was reported very low even among the urban population,^{24,25} which prompts need for spreading awareness on transplant laws.

It is found that awareness about eye donation is the maximum among all other organs. Many participants were willing for blood donation. When willingness to organ donation is compared with willingness to eye and blood donation, it is found that 50% of the participants not willing for organ donation are also not willing for blood or eye donation,

Table 6: Knowledge parameters stratified by age-group

	Age group			p-value
	<25 years	26–45 years	>45 years	
Where can a patient be declared brain dead?				
Home	2 (2.6)	11 (1.9)	1 (0.9)	0.509
Hospital	38 (11)	181 (31.2)	29 (25.9)	<0.001
ICU	290 (83.8)	380 (65.5)	69 (61.6)	<0.001
Ward	9 (2.6)	8 (1.4)	13 (11.6)	<0.001
Who will be the ideal organ donor?				
Brain dead patient	278 (80.1)	417 (71.9)	65 (58.0)	<0.001
Brought dead patient	37 (10.7)	61 (10.5)	16 (14.3)	0.493
Handicapped	5 (1.4)	6 (1.0)	1 (0.9)	0.823
Postcardiac arrest patient	10 (2.9)	31 (5.3)	3 (2.7)	0.136
Terminally ill patient	17 (4.9)	65 (11.2)	27 (24.1)	<0.001
Priority for getting the organ should be given to?				
Donors near relative	101 (29.19)	126 (21.79)	19 (16.96)	0.008
Hospital's own patient	20 (5.78)	79 (13.67)	19 (16.96)	<0.001
Patient in waiting list	218 (63.00)	367 (63.49)	74 (66.07)	0.839
Rich patient	7 (2.02)	6 (1.04)	0 (0)	0.193
Ideal organ recipient should be?				
Chronically ill patient	49 (14.1)	115 (19.8)	32 (28.6)	<0.001
Long waiting list on registry	113 (32.6)	164 (28.3)	17 (15.2)	0.002
Low-income patient	32 (9.2)	25 (4.3)	14 (12.5)	0.001
Patient who had transplant	21 (6.1)	37 (6.4)	1 (0.9)	0.067
Young patient	132 (38.0)	239 (41.2)	48 (42.9)	0.538

Table 7: Knowledge parameters stratified by experience group

	Experience group				p-value
	NA	0–≤5 years	6– year	>15 years	
Where can a patient be declared brain dead?					
Home	1 (10)	7 (1.20)	10 (2.98)	3 (2.73)	0.509
Hospital	1 (10)	158 (27.05)	77 (22.98)	12 (10.91)	<0.001
ICU	8 (80)	405 (69.35)	236 (70.45)	90 (81.82)	<0.001
Ward	0 (0)	13 (2.22)	12 (3.58)	5 (4.55)	<0.001
Who will be the ideal organ donor?					
Brain dead patient	9 (90)	448 (76.71)	227 (67.76)	76 (69.09)	<0.001
Brought dead patient	1 (10)	61 (10.45)	37 (11.04)	15 (13.63)	0.493
Handicapped	0	7 (1.20)	4 (1.19)	1 (0.90)	0.823
Postcardiac arrest patient	0	27 (4.62)	12 (3.58)	5 (4.54)	0.136
Terminally ill patient	0	41(7.02)	55 (16.42)	13 (11.82)	<0.001
Priority for getting the organ should be given to?					
Donors near relative	3 (30)	162 (27.74)	66 (19.88)	15 (13.63)	0.008
Hospital's own patient	1 (10)	49 (8.39)	49 (14.76)	19 (17.27)	<0.001
Patient in waiting list	6 (60)	362 (61.98)	215 (64.76)	76 (69.09)	0.839
Rich patient	0	11 (1.88)	2 (0.60)	0	0.193
Ideal organ recipient should be?					
Chronically ill patient	3 (30)	108 (18.49)	71 (21.19)	14 (12.72)	<0.001
Long waiting list on registry	2 (20)	197 (33.73)	66 (19.70)	29 (26.36)	0.002
Low-income patient	1 (10)	41 (7.02)	12 (3.58)	17 (15.45)	0.001
Patient who had transplant	2 (20)	35 (5.99)	20 (5.97)	2 (1.81)	0.067
Young patient	2(20)	203 (34.76)	166 (49.55)	48 (43.63)	0.538

while >70% of participants who are willing for organ donation are also willing for blood and eye donation. This indicates that there is significant need of promotion eye and blood donation, and through this, organ donation can also be promoted.

One of the striking observations in this survey revealed that knowledge about heart valves donation was only 20.8% among the participants. The finding highlights the need of more focused campaigns aimed at imparting specific knowledge and inclusion of the information in academic curriculum.

The misconception about donorage among the participants is also a big concern (Table 6). About 45% consider that age can affect the donation, while the institutional experience of the authors suggests that successful organ retrievals were done from donors of age up to 75 years (Table 7). When enquired about ideal donor, around 40% respondents opined that younger patients were ideal donor. Regarding the recipient, 18.7% participants believed that waiting list patients are ideal recipients. Studies evaluating the preferences for medical professionals regarding organ allocation are often asking either for agreement/disagreement toward specific statements^{26,27} or for an opinion of whether a hypothetical patient is eligible for transplantation.²⁸ The data on reasoning behind the bias toward specific recipients is lacking. This survey also could not probe further on the reasoning for respondents' preferences to organ allocation. We estimate that their choices are mostly emotionally driven.

Participants who knew organ donor or their families were significantly more in favor of organ donation. Thus, organ donor families or relatives can help in promotion of organ donation through social programs and social media and help people solve queries regarding organ donation.

CONCLUSION

We have observed fair awareness regarding overall organ donation among healthcare

workers. There is a need to improve extended age criteria concept for organ donation and which organs can be retrieved from deceased donors. Authorities have to work hard on delivery of organ donation pledging cards to promote donation program.

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Current Place of SGLT2i in the Management of Heart Failure: An Expert Opinion from India

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Received: 28 November 2023; Accepted: 02 December 2023

ABSTRACT

Heart failure (HF) is a global health concern that is prevalent in India as well. HF is reported at a younger age in Indian patients with comorbidity of type 2 diabetes (T2DM) in approximately 50% of patients. Sodium-glucose cotransporter-2 inhibitors (SGLT2i), originally approved for T2DM, are new guideline-recommended and approved treatment strategies for HF. Extensive evidence highlights that SGLT2i exhibits profound cardiovascular (CV) benefits beyond glycemic control. SGLT2i, in conjunction with other guideline-directed medical therapies (GMDT), has additive effects in improving heart function and reducing adverse HF outcomes. The benefits of SGLT2i are across a spectrum of patients, with and without diabetes, suggesting their potential place in broader HF populations irrespective of ejection fraction (EF). This consensus builds on the updated evidence of the efficacy and safety of SGLT2i in HF and recommends its place in therapy with a focus on Indian patients with HF.

Journal of the Association of Physicians of India (2024): 10.59556/japi.71.0440

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How to cite this article: Chopra HK, Nair T, Wander GS, *et al.* Current Place of SGLT2i in the Management of Heart Failure: An Expert Opinion from India. *J Assoc Physicians India* 2024;72(1):63–73.

INTRODUCTION

Heart failure prevalence in India is estimated to be 1%, but its annual incidence is expected to increase by 18% by 2025.^{1,2} Unfortunately, HF affects the younger population in India compared to the Western world.^{1–4} High treatment costs, poor quality of life (QoL), and high mortality rates (23%) are noticed in India.^{1–4} Moreover, the management and prognosis of HF are complicated by the high prevalence of comorbidities viz type 2 diabetes mellitus (T2DM), coronary artery disease (CAD), and chronic kidney disease (CKD).^{2,3}

Heart failure with reduced EF (HFrEF) is common in India, with a prevalence of 67.5% of total HF patients, followed by HF with mildly reduced EF (HFmrEF) in 17.6% and HF with preserved EF (HFpEF) in 14.9% of patients.⁵

Half the patients with HF have coexisting T2DM and are therefore complicated by its microvascular and macrovascular disease.² The incidence of HF per 1000-person years increased from 2.3 to 11.9, with an increase in glycated hemoglobin (HbA1c) from <6 to >11.9%.⁶

Four guideline-directed medical therapies (GDMTs) are recommended for HF in view of their potential benefits for reducing cardiovascular mortality and HF hospitalization (HHF). These include angiotensin receptor-neprilysin inhibitor (ARNi)/angiotensin-converting

enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), β -blocker (BB), mineralocorticoid receptor antagonist (MRA), and sodium-glucose cotransporter-2 inhibitors (SGLT2i).^{7–9}

Substantial evidence highlights that SGLT2i exhibits profound CV effects beyond glycemic control.^{10–14} SGLT2i in conjunction with other GDMTs lead to additive or synergistic effects in improving heart function and reducing adverse HF outcomes.¹⁵

Sodium-glucose cotransporter-2 inhibitors have been recently added to the treatment milieu of HF in India.^{16,17} This consensus was drafted to highlight the clinical place of SGLT2i in the management of HF with a focus on Indian patients.

Possible Mechanisms of SGLT2i Benefits in Heart Failure

The beneficial effects of SGLT2i in HF are due to an intricate interplay between glucose homeostasis, metabolic readjustments, inflammation reduction, oxidative stress reduction, and improvement in CV physiology (Fig. 1).¹⁸

Cardiac and Vascular Effects of SGLT2i in Heart Failure

Current clinical evidence has shown that the CV benefit of SGLT2i is apparent within the first week of initiation, thereby indicating an underlying hemodynamic mechanism

of action and not an anti-atherosclerotic effect.^{19,20} Factors contributing to the cardioprotective effects of SGLT2i are poorly understood but thought to be beyond that of ventricular loading and cardiac remodeling effects.¹⁹ SGLT2i may positively impact the heart and vasculature in HF through several mechanisms, as listed in Table 1.

METHODOLOGY

The national consensus meeting was organized on 6th August 2023, to discuss the current evidence-based place of SGLT2i in the management of HF. A total of 77 experts from India in the fields of cardiology, nephrology, endocrinology, and intensive care specialty attended this meeting. One senior cardiologist presented the comprehensive and most updated evidence of SGLT2i in HF. The experts discussed the literary and guideline-based evidence on the rationale, benefits, and role of SGLT2i in the management of HF. They also shared their clinical experience in managing HF with SGLT2i. The panel discussion was moderated by leading cardiologists, nephrologists, and diabetologists. With focused discussion and deliberation, the expert opinion was formulated and accepted by all the participating faculty. This consensus was further discussed individually with three United States experts by the moderator.

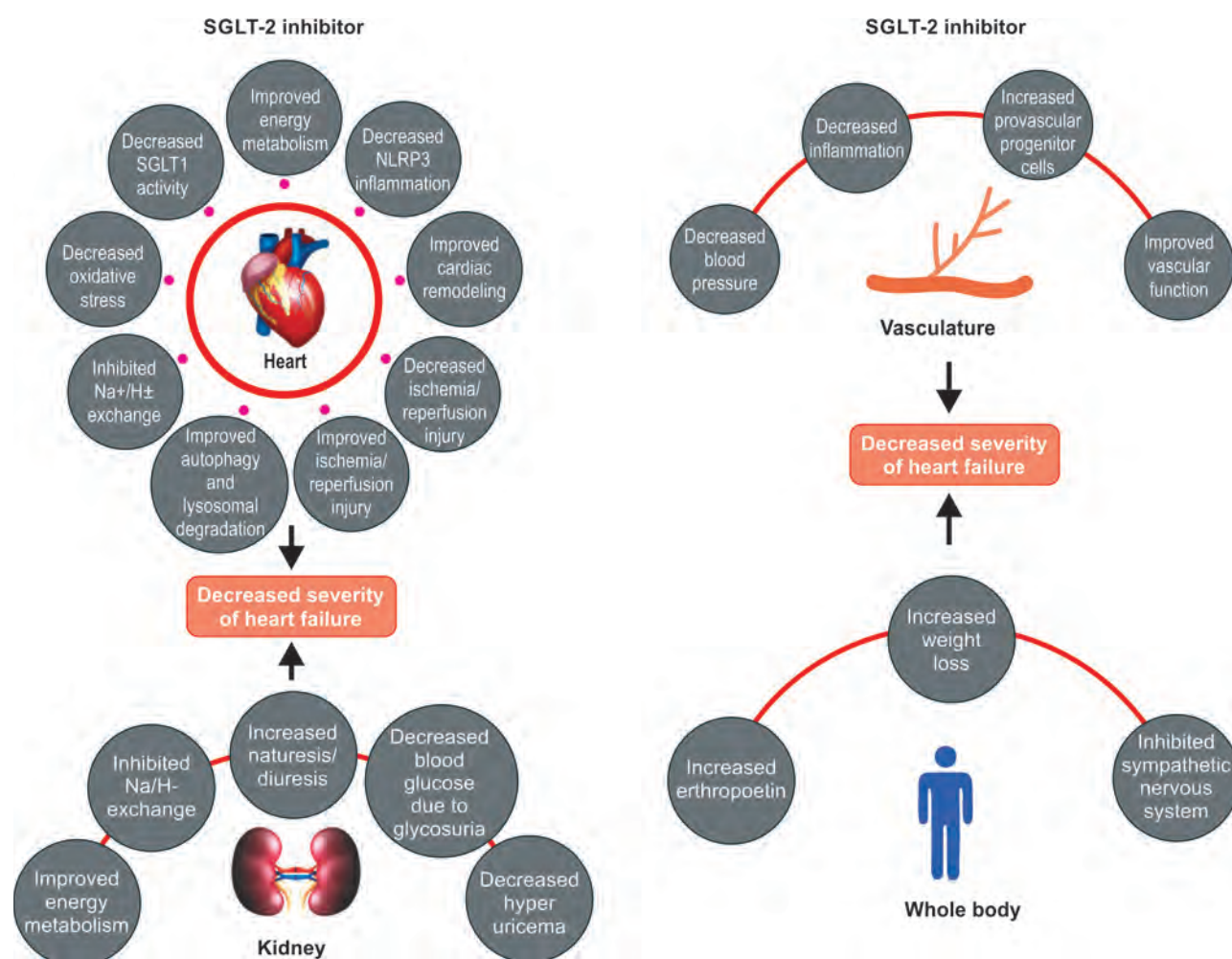


Fig. 1: Overview of the beneficial effect of SGLT2i in HF^{11,12,18,75}, CV, cardiovascular; EPO, erythropoietin; HF, heart failure; Na⁺/H⁺, sodium-hydrogen exchanger; SGLT2i, SGLT2i, sodium-glucose cotransporter 2 inhibitor

Table 1: Protective effects of SGLT2i on heart and vasculature in HF^{12,18,19,75}

1. Improving ionic homeostasis: by inhibiting the overexpressed cardiac Na⁺/H⁺ exchanger, thereby normalizing sodium and calcium imbalance>>net effect: enhanced myocardial contractility.
2. Optimizing myocardial energy production through autophagy of dysfunctional mitochondria.
3. Improving the failing heart's dysfunctional metabolism by augmenting ketone metabolism.
4. Neutralizing proinflammatory cytokines and reducing macrophage infiltration, thereby reducing CV inflammation. Restoration of provascular progenitor cells: proinflammatory M1 cells decrease, and M2 polarized, anti-inflammatory cells increase in blood vessels of type 2 diabetes patients; effect on patients without diabetes not known.
5. Mild antihypertensive effect due to improved endothelial function, reduced arterial stiffness, increased vasodilation, and reduction in sympathetic nervous activity.
6. Reducing apoptosis mainly through anti-caspase activity.
7. Exerting antifibrotic and anti-remodeling effects by decreasing inflammation, oxidative stress, and apoptosis.
8. Enhancing nitric oxide (NO)—soluble guanylyl cyclase (sGC)—cGMP-dependent protein kinase (PKG) signaling pathway, which reduces myocardial passive stiffness, improves myocardial contractility and diastolic function(via phosphorylation of myofilament regulatory proteins).
9. Reducing epicardial fat by improving altered adipokine (cytokines like leptin and adiponectin) regulation (effects could also be secondary to systemic effects of weight loss and lipolysis).
10. Increases in renal erythropoietin production increase red blood cell mass and hematocrit, thereby improving oxygen delivery to myocardial cells.

SGLT2i Approved in India

Of the five SGLT2i (dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, and sotagliflozin) extensively researched and indicated for the management of T2DM, only dapagliflozin,

empagliflozin, and canagliflozin are approved in India for both T2DM and HF.^{16,17,21–25} Dapagliflozin and empagliflozin are strongly recommended by several guidelines (including Indian guideline) in HF.^{7,9,26,27}

Hence, this consensus primarily focuses on the role of dapagliflozin and empagliflozin in HF. Both dapagliflozin and empagliflozin are started at 10 mg daily, and this is also their target dose.⁹

Panel Discussion: Role of SGLT2i in Different Types of HF

Based on robust evidence (Table 2), various guidelines have recommended using SGLT2i, in conjunction with other GDMTs, in HFrEF, HFmrEF, and HFpEF with a class I or 2a recommendation (Table 3).^{8,26–28}

A meta-analysis of five randomized controlled trials (RCTs; $N = 21,947$) in HFmrEF or HFpEF (DELIVER and EMPEROR-preserved), HFrEF (DAPA-HF and EMPEROR-reduced), and patients hospitalized with worsening HF, irrespective of EF (SOLOIST-WHF) demonstrated a reduction in the risk of composite CV death or HHF, CV death, first hospitalization for HF, and all-cause mortality.²⁹ These beneficial effects of SGLT2i were seen irrespective of EF and care setting, thereby highlighting the role of SGLT2i as the foundational therapy in a broad spectrum of HF patient profiles.²⁹

High-quality evidence from a systematic review and meta-analysis showed that SGLT2i reduces HHF by 37, 32, and 26% at 6 months, 1 year, and 2 years, respectively, and reduces

CV death by 14% at 1 year.³⁰ Maximum benefit was seen at 1 year, irrespective of the diabetes status, thereby highlighting the inclusion of SGLT2i as the foundational therapy in patients with HF who did not have diabetes.³⁰

SGLT2i in Heart Failure with Reduced Ejection Fraction

Sodium-glucose cotransporter-2 inhibitor are one of the four GDMTs strongly recommended in conjunction with background GDMT for treating New York Heart Association (NYHA) classes II–IV HFrEF, regardless of diabetes status.^{7–9,26} This quadruple therapy (ACEi/ARB/ARNi, BB, MRA, SGLT2i) now forms the backbone of GDMT in chronic HF.²⁶

The recommendations for the use of SGLT2i as foundation therapy in HFrEF were based on the results of the DAPA-HF³¹ and EMPEROR-reduced³² trials, which demonstrated a similar and significant reduction in HHF/CV death in HFrEF patients with or without diabetes.³³ Dapagliflozin in the DAPA-HF study also alleviated HF

symptoms and improved physical function and QoL in symptomatic patients with HFrEF.³¹

A subsequent meta-analysis of DAPA-HF and EMPEROR-reduced ($N = 8,474$) suggested that dapagliflozin and empagliflozin consistently and significantly reduced HHF (by 26%; $p < 0.0001$), CV mortality (by 14%; $p = 0.027$) and all-cause mortality (by 13%; $p = 0.018$), and significantly improved renal outcomes ($p = 0.013$) in HFrEF patients.³⁴ The use of SGLT2i on a backdrop of other GDMTs was safe and well tolerated and did not result in an increased risk of hypovolemia, hypoglycemia, renal insufficiency, or hyperkalemia as compared with placebo.^{7,33}

Sodium-glucose cotransporter-2 inhibitor (dapagliflozin and empagliflozin) are recommended for all patients with HFrEF already treated with GDMTs (ARNi, BB, and MRA), regardless of diabetes status.³⁵ This inclusion of SGLT2i as a part of quadruple therapy at the population level is expected to reduce the absolute and relative risk of all-cause mortality by 26 and 73%, respectively.³⁶

Table 2: SGLT2i—literary evidence of benefits of different types of HF

Trial	SGLT2i/N	MACE outcome	CV death	HHFs
HFrEF in patients with or without diabetes				
DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) ³¹	Dapagliflozin vs placebo ($N = 4,744$)	Reduced risk of HF exacerbation and all-cause mortality when compared to placebo	Significant reduction of 18%	Significant reduction by 30% in HHF/urgent HF visit (first episode of worsening HF)
DEFINE-HF (Dapagliflozin Effect on Symptoms and Biomarkers in Patients with HF) ⁷⁶	Dapagliflozin vs placebo ($N = 263$)	Higher proportion of patients with clinically meaningful improvements in HF-related health status or natriuretic peptide concentrations, irrespective of diabetes status		
EMPEROR-Reduced ³²	Empagliflozin vs placebo ($N = 3,730$)	Significantly lower composite of CV death or HHF ($p < 0.001$) Annual rate of eGFR decline was significantly slower in the empagliflozin group ($p < 0.001$)		Significantly lower HHF ($p < 0.001$)
HFmrEF and HFpEF: LVEF was >40 , and NYHA class II–IV EMPEROR-Preserved ⁴¹	Empagliflozin vs placebo ($N = 5,988$)	Significantly reduced a composite of CV death or HHF ($p < 0.001$), mainly driven by HHF reduction; no reduction in CV death The effect is seen irrespective of T2DM status		
DELIVER ^{42,77}	Dapagliflozin vs placebo ($N = 6,263$)	Significantly reduced a composite of CV death or HHF ($p < 0.001$), mainly driven by HHF reduction; no reduction in CV death Significantly reduced risk of death from CV causes ($p = 0.01$) The effect is seen irrespective of T2DM and LVEF status Symptomatic patients continued to receive benefit despite improved LVEF		
PRESERVED-HF ⁷⁸	Empagliflozin vs placebo	Significantly improved patient-reported symptoms ($p = 0.001$), physical limitations ($p = 0.026$) and exercise function ($p = 0.007$)		
T2D was recently hospitalized for worsening HF and receiving intravenous diuretics; sotagliflozin initiated before or shortly after discharge SOLOIST-WHF ⁷⁹	Sotagliflozin vs placebo ($N = 1,222$)	Significantly reduced primary endpoint of total number of CV deaths and HHF and urgent visits for HF (first and subsequent) ($p < 0.001$)		

*Composite of end-stage kidney disease, (dialysis, transplantation, or a sustained estimated GFR of <15 mL/minute/1.73 m²); CV, cardiovascular; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; EMPEROR-reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction; GFR, glomerular filtration rate; HF, heart failure; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction; PRESERVED-HF, Effects of Dapagliflozin on Biomarkers, Symptoms and Functional Status in Patients with Preserved Ejection Fraction Heart Failure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SOLOIST-WHF, Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure; T2DM, type 2 diabetes mellitus

Table 3: Guideline recommendations for SGLT2i in HF

Guideline	Type of HF	Recommendation	Class of recommendation	Level of evidence
ESC 2021 ³⁵ and 2023 ESC update ²⁶	HFrEF	Dapagliflozin or empagliflozin are recommended to reduce the risk of HHF and death	I	A
	HFmrEF	An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HHF or CV death	I	A
	HFpEF	An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of HHF or CV death	I	A
AHA/ACC/HFSA 2022 ⁸	Stage A, at risk of HF	To prevent HHF in patients with T2D who have CVD or at high risk of CVD	I	
		Stage C, symptomatic HF		
	HFrEF	To prevent HHF and CV mortality in patients with symptomatic chronic HFrEF, regardless of the presence of T2DM	I	
	HFmrEF	To reduce HHF and CV mortality	II	a
	HFpEF	To reduce HHF and CV mortality	II	a
Canadian Cardiovascular Society (CCS) Heart Failure Guidelines ⁷	HFrEF	Recommend dapagliflozin or empagliflozin, irrespective of T2DM status, to improve symptoms and QoL and to reduce the risk of HHF and/or CV mortality	Strong	High quality
HFpEF Guidelines (Heart Failure Association of India, Endorsed by Association of Physicians of India) 2022 ²⁷	HFpEF	SGLT2i—empagliflozin, dapagliflozin, and probably sotagliflozin have shown benefits, mostly by reducing HHF in both diabetic and nondiabetic patients		
ACC 2021 update ⁹	HFrEF (EF ≤ 40%) with or without diabetes	NYHA class II–IV HF administered in conjunction with a background of GDMT for HF; eGFR of ≥30 mL/minute/1.73 m ² (dapagliflozin) and ≥20 mL/minute/1.73 m ² (empagliflozin)		
ACC consensus 2023 ²⁸	HFpEF	Barring contraindication, all individuals with a diagnosis of HFpEF should be treated with an SGLT2i, with the goal of reducing CV death/HHF and improving health status		

CV, cardiovascular; GDMT, guideline directed medical therapy; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; NYHA, New York Heart Association; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus

SGLT2i Sequencing in Heart Failure with Reduced Ejection Fraction

The optimal sequencing of SGLT2 inhibitors in HF treatment is unclear. Previously, GDMTs were added sequentially, with each drug titrated to its target dose before introducing the next class. However, the independent efficacy of one GDMT does not seem to impact another.^{37,38}

Current evidence supports the early initiation of SGLT2i in the treatment paradigm of HF.³⁸ In a *post hoc* analysis of the DAPA-HF trial, dapagliflozin reduced the risk of worsening HF and CV death in HFrEF patients, regardless of background GDMT type or achieved target dose (<50 or ≥50%).³⁹

DAPA-HF and EMPEROR-reduced trials found no difference in SGLT2 inhibitor efficacy with or without an MRA, suggesting the potential benefits of initiating SGLT2 inhibitors before MRAs.^{31,32,40} The diuretic and natriuretic properties of SGLT2i may confer additional benefits in reducing congestion, thereby decreasing the need for a loop diuretic.³⁵

Interestingly, the DAPA-HF and EMPEROR-Reduced trials showed an early separation of the curves between the placebo and intervention arms, reinforcing the evidence for early initiation of SGLT2i in the treatment paradigm of HFrEF.³³ In the DAPA-HF trial, the primary endpoints reached a nominal statistical significance as early as day 28.³³

Since BBs are one of the most effective GDMTs in HFrEF with the added advantage of reducing the risk of sudden death, and since SGLT2i significantly reduces HHF risk and mitigates the risk of worsening of HF seen with BB, the two classes of drugs can be initiated together as first-line treatment of HFrEF. Further, ARNI and MRA can be initiated sequentially, and the doses of all drugs can be titrated as needed.³⁷

SGLT2i in Heart Failure with Mildly Reduced/Preserved Ejection Fraction

New recommendations from the 2022 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) HF Guideline (class

2a recommendation) and the 2023 European Society of Cardiology (ESC) updates (class I recommendation) include the use of SGLT2 inhibitors for the treatment of HFpEF.^{8,26} Other GDMTs (ARNi, ACEi, ARB, MRA, and BB) have a weaker (class 2b) recommendation in this setting.

The recommendations were based on the EMPEROR-Preserved⁴¹ and the DELIVER⁴² trials demonstrating significantly reduced composite of CV death or HHF; >80% of patients were already on ACE-I/ARB/ARNi; BBs and MRA were the other commonly prescribed GDMTs.

A subsequent meta-analysis of the two trials confirmed a significant reduction in the composite endpoint of CV death or first HHF (by 20%; $p < 0.001$) and HHF (by 26%; $p < 0.001$) in patients with HFmrEF/HFpEF across all left ventricular EF (LVEF) studied (trials included LVEF >40%; mean LVEF was approximately 54%); however, there was no significant reduction in CV death.²⁹

Another individual patient data meta-analysis of DAPA-HF in HFrEF with DELIVER in

HFmrEF/HFpEF confirmed that the beneficial effects of dapagliflozin in reducing CV death ($p = 0.01$) and HHF were seen irrespective of EF.⁴³

Recent evidence supports the use of SGLT2i upfront in all patients with HFpEF, except patients with T1DM, estimated glomerular filtration rate (eGFR) <20 mL/minute/1.73 m², and history of diabetic ketoacidosis (DKA).⁴⁴

SGLT2i in Ambulatory Patients with Heart Failure

Sodium-glucose cotransporter-2 inhibitor can be given to ambulatory patients of HF across the entire EF spectrum. The DAPA-HF and the EMPEROR-Reduced trials enrolled patients with chronic HFrEF being treated in the outpatient setting.^{31,32} Both trials recruited ambulatory patients with HFrEF if they had HF of NYHA classes II–IV and LVEF $\leq 40\%$ despite optimal background GDMTs.^{31,32} The DAPA-HF trial population was ambulatory, with as many in NYHA class II HF as in class III and IV, while the EMPEROR-Reduced trial included outpatients with predominantly class II HF.

Similarly, the EMPEROR-Preserved and DELIVER trials recruited outpatients with HF of NYHA class II–IV (predominantly class II) and LVEF $>40\%$ despite optimal background GDMT.^{41,42} However, the DAPA-HF and EMPEROR-Reduced trials and their meta-analysis highlight that though the benefits of SGLT2i were seen across NYHA classes II–IV, the effects were more prominent in patients with NYHA class II.^{31–34}

SGLT2i in Acute Heart Failure (AHF)/Hospitalized Patients

Though not yet approved for AHF/hospitalized patients, SGLT2i may be beneficial in these patients. A recent analysis of the DELIVER trial in patients with HFmrEF or HFpEF enrolled during or following hospitalization demonstrated that dapagliflozin reduced composite of CV death or HHF by 22% in recently hospitalized patients vs 18% in not hospitalized [hazards ratio (HR): 0.78 vs 0.82; $p_{\text{interaction}} = 0.71$].⁴⁵

Empagliflozin also provided clinical benefit in 530 clinically stable patients hospitalized with acute de novo or decompensated chronic HF regardless of LVEF and was well tolerated.⁴⁶ The EMPULSE trial highlighted a significant clinical benefit ($p = 0.0054$) defined as a hierarchical composite of death from any cause, number of HF events, and time to first HF event or a 5-point or greater change from baseline in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score at

90 days.⁴⁶ The clinical benefit was seen regardless of the LVEF and T2DM status.⁴⁶ However, larger empagliflozin trials are required to confirm the benefit of AHF.

Rationale for Combining SGLT2i with Other GDMTs in HF

The DAPA-HF^{31,47} and EMPEROR-Reduced³² trials and their meta-analysis³⁴ confirmed the additive beneficial effects of SGLT2i in HFrEF on a background of GDMT of ARNI/ACEi/ARB, BB, or MRA.^{7,33,34,47–49} These GDMTs have complementary mechanisms of action in HF, thus providing a rationale for a multidrug approach.^{7,15,40} Despite similarities to neurohormonal antagonists, this multidrug approach offers independent benefits, supporting the combination for improved outcomes.

Sodium-glucose cotransporter-2 inhibitors improves adverse cardiac remodeling (including reduction of fibrosis, inflammation, and oxidative stress, and improvement in endothelial function) and improves global longitudinal strain (surrogate of LV systolic function).^{15,50–52} In the DAPA-MODA trial at 180 days, dapagliflozin added to HF patients on GDMTs significantly improved cardiac remodeling, reducing left atrial volumes ($p = 0.008$), LV mass index (by 13.9%; $p < 0.001$), end-diastolic volume (by 8.0%, $p < 0.001$), and end-systolic volume (by 11.9%, $p < 0.001$). N-terminal prohormone of brain natriuretic peptide (NT pro-BNP) decreased significantly by 18.2% ($p < 0.001$), while filling Doppler measures showed no changes.⁵³ Together, these beneficial effects will likely improve cardiac morbidity and mortality outcomes.⁵⁰

Hyperkalemia in HF is associated with an increased risk of HHF and CV death.⁵⁴ SGLT2i reduces the risk of hyperkalemia seen with ACEi/ARB/ARNi and MRA, especially in patients with T2DM and CKD.⁵⁴ Additionally, the combination of MRA with empagliflozin did not reduce the HF and renal outcomes provided by the SGLT2 inhibition.⁵⁵

Sodium-glucose cotransporter-2 inhibitor-induced diuresis and volume reduction can complement the anti-RAAS effects of ACEi/ARB and BB, potentially leading to enhanced fluid and pressure control.^{51,52,56} Further, SGLT2i mechanisms of cardiac remodeling could complement the sympathetic overdrive reduction capacity of BBs, thereby attenuating cardiac stress and enhancing cardiac remodeling by reducing heart rate, contractility, and oxygen demand.^{57,58}

Moreover, in patients with HFpEF, dapagliflozin significantly reduced the composite of CV death and HHF, irrespective

of the presence or absence of atrial fibrillation (AF) and the type of AF.⁵⁹ Thus, when combined with BBs, which are usually prescribed for AF in HF, SGLT2i and BB can exert their individual benefits in improving HF outcomes.

Panel Discussion: Literary Evidence for SGLT2i in Heart Failure with Comorbidities

Heart failure is a complex syndrome in which patients are often already on multiple medications due to associated comorbidities.⁹ Table 4 captures guideline recommendations for SGLT2i in HF with comorbidities.

Primary Prevention of Heart Failure in Patients with Diabetes

Sodium-glucose cotransporter-2 inhibitor are recommended in T2DM patients for the primary prevention of HF in established CVD or high CVD risk patients (2022 AHA/ACC/HFSA)⁸ and for CVD and kidney failure risk reduction in CKD (eGFR ≥ 20 mL/minute/1.73 m²) (ESC 2023).⁶⁰

These recommendations are based on the significant reduction in HHF, and CV mortality demonstrated in the randomized EMPA-REG OUTCOME,⁶¹ CANVAS program,⁶² and DECLARE-TIMI 58⁶³ clinical trials in patients at high risk of HF.^{61–63}

Sodium-glucose cotransporter-2 inhibitor confers renal protection in T2DM and delays the transition to end-stage renal disease (ESRD), which indirectly improves HF outcomes.⁴⁸

Treatment of Heart Failure in Patients with Diabetes

Sodium-glucose cotransporter-2 inhibitor significantly reduces HHF risk and renal disease progression across a broad spectrum of T2DM patients regardless of their HF history or the presence of atherosclerotic CV disease (ASCVD).

Systematic reviews and meta-analyses of (EMPA-REG OUTCOME, CANVAS program, CREDENCE, VERTIS CV, and DECLARE-TIMI 58 trials demonstrated that empagliflozin, canagliflozin, and dapagliflozin significantly reduced the risk of CV death or HHF and the risk of progression of renal disease.^{64,65}

The advantage was seen irrespective of the ASCVD status, baseline HbA1c, albuminuria, eGFR, and history of HF.^{64,65} However, ertugliflozin failed to show any statistical significance for renal outcomes.⁶⁵

Thus, empagliflozin, dapagliflozin, and canagliflozin are recommended in T2DM patients with HF.⁶⁰

Table 4: Guideline recommendations for SGLT2i in heart failure with other comorbidities

Guideline	Type of HF	Recommendation	Class of recommendation	Level of evidence
ESC 2021 ³⁵	HF prevention	SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with T2DM at risk of CV events to reduce hospitalizations for HF, major CV events, end-stage renal dysfunction, and CV death.	I	
	HF prevention	SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HHFs.	I	A
	HFrEF	SGLT2 inhibitors (dapagliflozin, empagliflozin, and sotagliflozin) are recommended in patients with T2DM and HFrEF to reduce hospitalizations for HF and CV death.	I	A
	HF prevention	Empagliflozin should be considered in patients with T2DM in order to prevent or delay the onset of HF and prolong life.	IIa	
AHA/ACC/HFSA 2022 ⁸	Primary prevention in patients at risk of HF	In patients with type 2 diabetes and either established CVD or at high CV risk, SGLT2i should be used to prevent hospitalizations for HF.	I	A
Canadian Cardiovascular Society (CCS) Heart Failure Guidelines ⁷	HFrEF	We recommend an SGLT2 inhibitor, such as empagliflozin, canagliflozin, or dapagliflozin, be used for the treatment of patients with type 2 diabetes and ASCVD to reduce the risk of HHF and death.	Strong	High quality
		We recommend an SGLT2 inhibitor, such as dapagliflozin, be used in patients with type 2 diabetes who are older than 50 years with additional risk factors for ASCVD to reduce the risk of HHF.	Strong	High quality
		We recommend SGLT2 inhibitors such as canagliflozin or dapagliflozin be used in patients with albuminuric renal disease, with or without type 2 diabetes, to reduce the risk of HHF and progression of renal disease.	Strong	High quality
ESC 2023 guidelines for the management of CVD in patients with T2D ⁶⁰	HFrEF (NYHA class II–IV) and diabetes	SGLT2 inhibitors (dapagliflozin, empagliflozin, or sotagliflozin) are recommended in all patients with HFrEF and T2DM to reduce the risk of HHF and CV death.	I	A
		An intensive strategy of early initiation of evidence-based treatment (SGLT2 inhibitors, ARNI/ACE-Is, BBs, and MRAs), with rapid up-titration to trial-defined target doses starting before discharge and with frequent follow-up visits in the first 6 weeks following an HHF is recommended to reduce re-admissions or mortality.	I	B
	Diabetes and LVEF >40% (HFpEF)	Empagliflozin or dapagliflozin are recommended in patients with T2DM and LVEF >40% (HFmrEF and HFpEF) to reduce the risk of HHF or CV death.	I	A

ACEi, angiotensin converting enzyme inhibitor; ARNI, angiotensin receptor-neprilysin inhibitor; CV, cardiovascular; GDMT, guideline directed medical therapy; HF, heart failure; HFmrHF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus

Treatment of Heart Failure in Patients with Established CVD or ASCVD

Robust literary evidence shows that SGLT2i reduces the risk of CV and all-cause mortality and HHF in patients with CVD and ASCVD. The magnitude of CV benefit conferred by SGLT2i is similar in patients with HFrEF and HFpEF.⁶⁶ The SGLT2i have demonstrated their efficacy and safety in patients with established CV disease (EMPA-REG OUTCOME⁶¹), established CV disease or CV risk factors (CANVAS⁶² and DECLARE-TIMI 58⁶³), and CKD and CV risk (SCORED trial⁶⁷).

A systematic review and meta-analysis ($N = 34,322$ T2DM patients) of the EMPA-REG OUTCOME, CANVAS program, and DECLARE-TIMI 58 trial demonstrated that dapagliflozin, empagliflozin, and canagliflozin produced significant reductions in major adverse CV events by 11% ($p = 0.0014$), only in patients with ASCVD.⁶⁴

Evidence shows that SGLT2i reduced the risk of myocardial infarction or stroke and CV mortality compared with dipeptidyl peptidase-4 inhibitors (DPP4i), especially in HFrEF^{66,68}; risk for HHF as compared to DPP4i and glucagon-like peptide 1 receptor

agonists (GLP1RA) (by 21%; p for effect size <0.01),^{66–69} and risk of composite of eGFR 50% reduction or <60 mL/minute/1.73 m², micro- or macroalbuminuria, renal failure, dialysis, renal transplantation, or renal death (by 17%; p for effect size = 0.04).⁶⁹

Thus, SGLT2i fare better than DPP4i and GLP1RA for reducing CVD mortality, all-cause mortality, and risk for HHF in patients with established CVD.⁶⁸

In patients with T2DM and CAD, SGLT2i protects against adverse cardiac remodeling by significantly reducing LV mass ($p = 0.01$) without compromising the LVEF and end-

diastolic/systolic volume and by significantly improving LV volumes/mass, EF, and systolic function ($p < 0.001$ for all), and functional capacity ($p = 0.017$).^{70,71} Thus, SGLT2i should be used in HFrEF patients independent of their glycemic status.

Primary Prevention/Delay of Renal Disease in Patients with Heart Failure

Patients with HFrEF are prone to worsening renal function, and this affects the ability to optimize HF treatment with diuretics or neurohormonal antagonists and worsens HF prognosis.³³ A meta-analysis of DAPA-HF and EMPEROR-reduced ($N = 8,474$) suggested that dapagliflozin and empagliflozin significantly improved renal outcomes (composite of $\geq 50\%$ sustained 167 declines in eGFR, (ESRD) or renal death) (pooled HR 0.62, 95% confidence interval [CI] 0.43–0.90, $p = 0.013$) in HFrEF patients.³⁴

Treatment of Heart Failure in Patients with Renal Disease

Improving HF outcomes in patients with CKD remains an unmet need.³³ The DAPA-HF³¹ and EMPEROR-reduced³² trials demonstrated a reduction in the composite of CV death and HHF, even in patients with eGFR ≥ 30 mL/minute/1.73 m² but < 60 mL/minute/1.73 m² in DAPA-HF and eGFR ≥ 20 mL/minute/1.73

m² but < 60 mL/minute/1.73 m² in EMPEROR-Reduced trial.³³ The DAPA-HF and EMPEROR-reduced trials did not include participants with eGFR < 30 mL/minute/1.73 m² and < 20 mL/minute/1.73 m², respectively.^{9,72} Moreover, clinical trial data at eGFRs below those included in these trials is not available.

The DAPA-CKD trial demonstrated a significant reduction in the primary composite outcome of a sustained decline in eGFR of $\geq 50\%$, ESRD, or death from renal or CV causes by 44% ($p < 0.001$), composite of CV death or HHF ($p = 0.009$), and all-cause mortality ($p = 0.004$). All the benefits provided by dapagliflozin were irrespective of the diabetes status.⁷²

Though DAPA-CKD⁷² trial included participants with eGFR > 25 mL/minute/1.73 m², dapagliflozin is usually considered safe at eGFR ≥ 30 mL/minute/1.73 m² and empagliflozin at ≥ 20 mL/minute/1.73 m².⁷⁹

Sodium-glucose cotransporter-2 inhibitor-induced renoprotection and natriuresis could be particularly beneficial in patients with lower baseline eGFR.⁶⁴ However, it should be noted that the renal hemodynamic changes and the initial reduction in plasma volume seen with SGLT2i result in a small initial decrease in the eGFR by 4–5 mL/minute/1.73 m². This soon corrects itself and results in either a moderately increased or a stabilized

eGFR.²⁰ This transient decrease in renal function should not prompt the interruption of SGLT2i, which should be continued as long as the increase in serum creatinine is $< 50\%$ above baseline and < 266 mol/L (3 mg/dL) or the decrease in eGFR is $< 10\%$ from baseline and > 25 mL/minute/1.73 m².³⁵

Safety Profile of SGLT2i

Evidence shows that SGLT2i available in India for the management of HF have similar safety profiles across chronic HF, T2DM, and CKD patients.⁷³

The safety profile of four SGLT2i (dapagliflozin, empagliflozin, ertugliflozin, and canagliflozin) versus placebo were analyzed and compared via a meta-analysis across nine safety parameters and across three chronic conditions (chronic HF, T2D and CKD (Fig. 2).⁷³ SGLT2i significantly increased the risks of genital infection [relative risk (RR) 3.75], DKA (RR 2.57), and volume depletion (RR 1.14). There was a trend toward increased risks of amputation (RR 1.21), fracture, and urinary tract infection (RR 1.07 for both). SGLT2i significantly reduced the risk of acute kidney injury (RR 0.75) vs placebo and demonstrated a trend toward reducing the risk of severe hypoglycemia (RR 0.86). These effects were consistent across three chronic diseases (chronic HF, T2DM, and CKD) and across four SGLT2i (dapagliflozin,

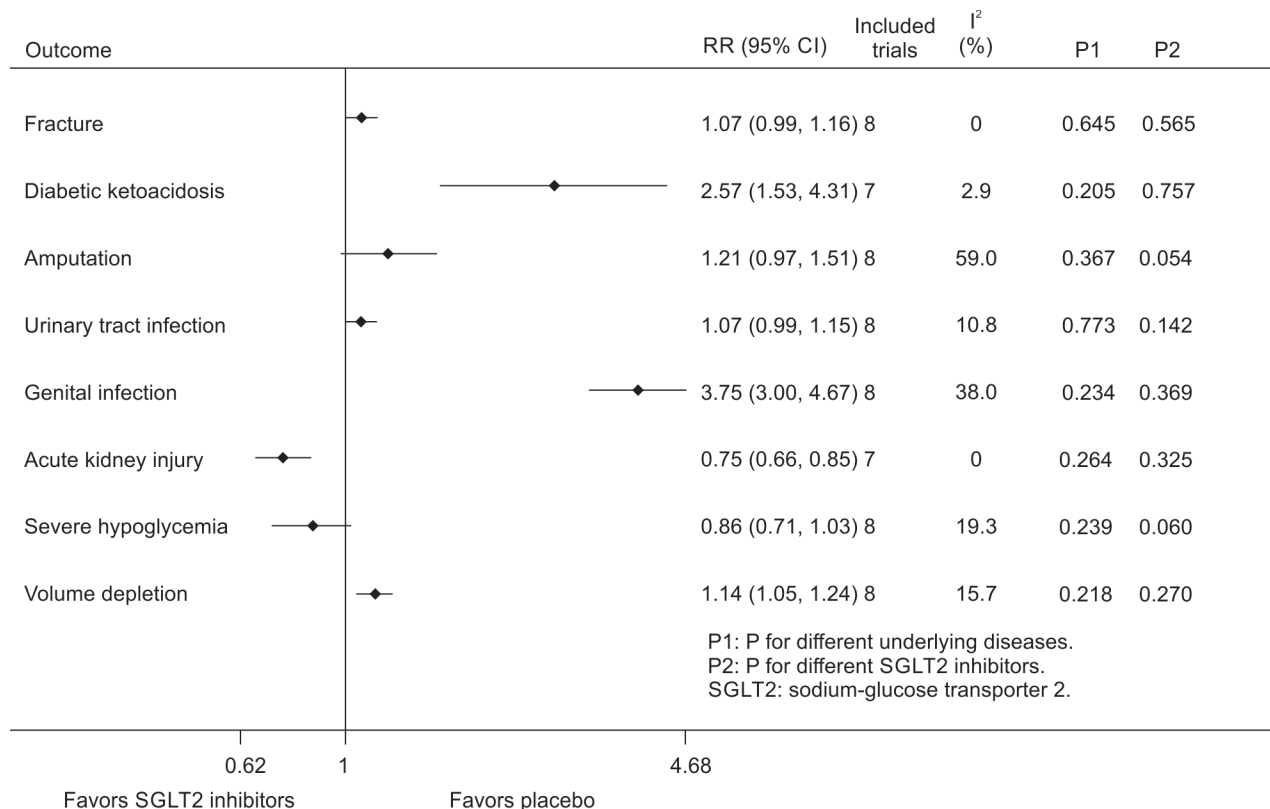


Fig. 2: Meta-analysis of the safety profile of four SGLT2i (dapagliflozin, empagliflozin, ertugliflozin, and canagliflozin) across nine safety parameters and across three chronic conditions (chronic HF, T2DM, and CKD)⁷³; CKD, chronic kidney disease; HF, heart failure; T2DM, type 2 diabetes mellitus; RR, relative risk; SGLT2i, SGLT2i, sodium-glucose cotransporter 2 inhibitor

empagliflozin, canagliflozin, and ertugliflozin) (all $p_{\text{subgroup}} > 0.05$).⁷³

Mycotic genital infections are a concern with all SGLT2is. A systematic review and meta-analysis of 86 RCTs showed that SGLT2is had a significantly higher risk of mycotic genital infections compared to placebo (RR 3.37; I^2 : 0%) and compared to other GLDs (RR 3.89; I^2 : 0.3%).⁷⁴ However, there were no significant differences between the SGLT2is: canagliflozin (RR 3.91; I^2 : 0%), dapagliflozin (RR 3.45; I^2 : 0%); empagliflozin (RR 3.11; I^2 : 9%).

There was no evidence that SGLT2i increased the risk of respiratory tract infections. However, there was a significant decrease in gastritis (RR 0.38; I^2 : 0%). In general, SGLT2i are safe to use in HF, and though mycotic genital infections are a concern, they are usually easily managed.

CONCLUSION

Heart failure treatment in India is complicated by the presence of comorbidities, predominantly T2DM, CAD, and CKD. SGLT2i, a glucose-lowering class of drugs, has recently been approved for HF and included in HF guidelines due to its tremendous positive effect in lowering CV deaths HHF and delaying renal outcomes.

The experts recommended that SGLT2i (dapagliflozin and empagliflozin) should be used in HFrEF, HFmrEF, and HFpEF of NYHA classes II–IV unless contraindicated. SGLT2i should be considered an important treatment option in a wide spectrum of HF patients, viz in patients with or without diabetes, with CKD or CAD, and in both ambulatory and hospitalized patients with HF. The experts proposed that SGLT2i should be incorporated into the HF treatment paradigm as per the recommendations of the panel outlined herewith.

ETHICS COMPLIANCE

This is a consensus statement and, hence, does not require Ethical Compliance approval.

FUNDING

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

MEDICAL WRITING ASSISTANCE

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

CONFLICT OF INTEREST

Dr Onkar Swami, Dr Sanjay Jain, and Dr Priyank Shah are full-time employees of Alembic Pharmaceuticals Limited, which actively markets SGLT2i.

CONSENSUS STATEMENTS

No.	Consensus statements
1	HF is usually associated with comorbidities such as hypertension, diabetes, micro and macrovascular CAD, dyslipidemia, obesity, CKD, etc.
2	Clinical evaluation, echocardiography, NT Pro BNP, and eGFR navigation are cornerstones in the management of HF.
3	GDMT has shown mortality and morbidity benefits along with HHF reduction.
4	SGLT2i are useful in all spectrums of HF irrespective of EF. SGLT2i have a rapid onset of action (<30 days) and remarkably consistent benefits in major RCTs. They are safe, effective, and promising.
5	SGLT2i has enormous mortality and morbidity benefits such as CV mortality, all-cause mortality, sudden cardiac death, reduced HHF, HF severity, and worsening of HF.
6	SGLT2i are cardio, vaso, and renoprotective.
7	SGLT2i available in India for HF are dapagliflozin, canagliflozin, and empagliflozin, Approved in HF with diabetes or without diabetes, with or without hypertension, with or without AF, with or without congestion, and with or without stroke.
8	SGLT2i are osmotic diuretics, anti-diabetic, anti-inflammatory, antifibrotic, anti-aldosterone, anti-atherosclerotic, anti-oxidant, decrease renal glomerulosclerosis, decrease proteinuria, and decrease the need for insulin. They enhance atrioventricular and vascular, thereby helping to improve the structural and functional parameters that affect hemodynamics, reduce NT pro-BNP, enhance cellular reprogramming, and improve mitochondrial function.
9	SGLT2i uniqueness: once daily dose, no dose titration, no hypotension, no hyperkalemia, improves eGFR decline, controls diabetes hypertension, enhances weight loss, can be used in all spectrum of HF.
10	SGLT2i are indicated in HFpEF, HFrEF, HFmrEF, HFimpEF, AHF, and the prevention of HF in patients with DM and established CVD and CKD.
11	Earlier SGLT2i sequencing is preferred in HFrEF.
12	HFpEF seems to be distinct from HFrEF, and the therapeutic options of HFpEF are beginning to emerge in the form of SGLT2i, which is the first drug of choice with morbidity and mortality benefits.
13	SGLT2i are recommended for primary prevention of HF in patients with diabetes.
14	SGLT2i in HF also reduces the risk of CVD and delays the progress of renal disease.
15	SGLT2i has enormous CV, renal, and metabolic benefits by CV remodeling reversal, thereby improving the prognosis in HF patients.
16	SGLT2i can be combined with ARNI, BB, MRA and loop diuretic.

ACKNOWLEDGMENTS

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

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Drug-induced Kidney Disease: Revisited

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Received: 06 August 2023; Accepted: 19 August 2023



ABSTRACT

Drug-induced kidney disease (DIKD) is a frequent cause of acute and chronic kidney disease (CKD) that leads to high morbidity, hospitalization, and increased healthcare costs. There is a need to constantly update our knowledge in this field, given the ever-burgeoning list of newer treatments that are emerging, especially in the field of cancer immunotherapy. Generalizing the complex pathways causing DIKD from different agents, the common mechanisms include direct toxicity, immune-mediated injury, and drug-induced alterations in renal blood flow. Proper management of this condition involves risk minimization, early detection of renal damage, and timely discontinuation of potential agents to avoid irreversible renal damage.

Journal of the Association of Physicians of India (2024): 10.59556/japi.71.0417

INTRODUCTION

Drug-induced kidney disease (DIKD) is a significant contributor to acute kidney injury (AKI), comprising 19–26% of cases among hospitalized patients and, if not mitigated, can result in severe consequences such as chronic kidney disease (CKD), dialysis dependence, prolonged hospital stays, and escalated healthcare expenses.¹ Around 2 decades ago, we published a narrative review in this journal, compiling the state-of-the-art knowledge on various clinical syndromes and the complex pathogenesis of drug-associated nephrotoxicity as well as evidence-based measures to treat this form of kidney disease.² Since the last review, newer forms of treatment for malignancies, such as biologic agents that target molecular mechanisms of cancer, have become widely available, leading to improved patient survival but also unraveling unique renal adverse effects that internists and specialists need to be aware of. Additionally, the establishment of international evidence-based guidelines through the aegis of the Kidney Disease Improving Global Outcomes (KDIGO) group led to the formulation of a consensus definition of AKI in 2012, which has streamlined the process of timely identification of drug-induced renal toxicities in cases which are acute in onset.³ This general review encompasses a variety of developments in the field regarding diagnosing renal diseases from known agents, as well as establishes a framework for diagnosing similar issues with emerging agents that are gaining broader acceptance in clinical practice.

CLINICAL MANIFESTATIONS OF DIKD

Timely identification of DIKD necessitates careful attention to the patient's clinical

history, particularly their drug history, potential risk factors, urine output, and relevant biochemical tests such as serum creatinine (Scr), blood urea nitrogen, urine microscopy, and proteinuria. It is important to note that Scr levels may not always accurately reflect renal disease, as elevated levels can be caused by drugs that inhibit renal tubular creatinine secretion (e.g., trimethoprim, tyrosine kinase inhibitors, and fenofibrate) and are known as "pseudo AKI."¹ In such cases, more specific glomerular filtration rate (GFR) biomarkers like serum cystatin C can be utilized to determine actual renal function deterioration. To facilitate the recognition of DIKD, four phenotypes have recently been established based on guidelines from the International Serious Adverse Event Consortium (Table 1).⁴ These phenotypes categorize DIKD into AKI, glomerular disorder, tubular disorder, and nephrolithiasis/crystalluria, considering the known mechanisms of nephrotoxicity, disease progression timeline, and clinical setting. The progression of DIKD can vary depending on the mechanism of drug injury, duration of drug exposure, the temporal profile of serum biomarkers (such as Scr), and the timeliness in identifying the culprit agent. DIKD can generally be classified into three timeframes: acute (<7 days), subacute (injury occurring beyond 7, but <90 days), and chronic (>90 days).⁴

Identification of causality of drug-induced renal disease is a key issue for medication recently adopted for clinical practice, even though safety data for the drug has been published in pivotal clinical trials. This is especially so for drugs with idiosyncratic adverse effects with no consistent renal safety data, either because the adverse effect was too rare or occurred at time points beyond the trial observation period. In this setting,

the Naranjo criteria have been widely used in pharmacovigilance and clinical research to assess the causality of adverse drug reactions (ADR) of any organ.⁵ It is a set of 10 questions that evaluate various aspects of the patient's clinical history and the specific adverse event in question, including its temporal relationship with drug administration, the presence of alternative explanations for the reaction, and the patient's response to discontinuation or readministration of the drug. The responses are quantified, and a total score is given, which varies from –4 to +13 with an assumption of causality considered as "definite" if the score is 9 or higher, "probable" if 5–8, "possible" if 1–4, and "doubtful" if 0 or less (Table 2).

MECHANISMS OF DIKD

Mechanisms causing DIKD can be broadly classified into two types: type A and type B reactions (Table 3).⁴ Type A reactions are dose-dependent and predictable based on the pharmacological properties of the drug. They can be managed by reducing drug exposure through dose reduction or withdrawal. Examples include aminoglycosides or colistin nephrotoxicity. Type B reactions are immune-mediated, idiosyncratic, and unpredictable. Acute interstitial nephritis (AIN) from proton-pump inhibitors (PPI) or crescentic glomerulonephritis from hydralazine use are typical examples. The specific risk factors for developing a particular drug reaction are unknown, but genetic factors may influence drug metabolism and elimination, predisposing individuals to type A reactions. Type B reactions involve complex immunological sensitization to drugs acting as haptens or antigens. Additionally, prerenal AKI can be seen with the use of diuretics due

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How to cite this article: Ganguli A, Singh NP. Drug-induced Kidney Disease: Revisited. *J Assoc Physicians India* 2024;72(1):74–80

Table 1: Standardized clinical syndromes associated with DIKD (adapted from Mehta et al. Kid Int 2015)

	<i>AKI</i>	<i>Glomerular disorder</i>	<i>Nephrolithiasis</i>	<i>Tubular dysfunction</i>
Clinical terminology	ATN and AIN	Hematuria Proteinuria	Crystalluria Ultrasound findings of stone with or without obstruction	Renal tubular acidosis (RTA), Fanconi syndrome, syndrome of inappropriate antidiuretic hormone (SIADH), DI, hypophosphatemia
Primary criteria	Rise in Scr that presents or progresses to stage 2 (KDIGO), which is 2–2.9× higher than reference Scr OR Decline by at least 50% from peak Scr over 7 days in relationship to changes in drug dosing adjustment or discontinuation within 2 weeks	Biopsy-proven drug-induced glomerular disease (done within 4 weeks of stopping the drug) AND Proteinuria is defined by 24-hour urine collection >1 gm protein or urine dipstick >2+ protein or urine: protein creatinine ratio (UPCR) > 0.8 gm/gm Hematuria is defined by >50 redblood cell (RBC) per HPF	Must be new onset following drug exposure with no prior history of nephrolithiasis No congenital etiology for nephrolithiasis If obstructive, rise in Scr that presents or progresses to stage 2 (KDIGO) or higher If nonobstructive, then urinalysis with crystals and ultrasound with stone	Renal phosphate loss or tubular hypophosphatemia OR/AND Renal glucosuria, that is, urinalysis with 3+ glucose without hyperglycemia (Fanconi's syndrome) OR/AND Hyperchloremic metabolic acidosis (RTA) OR/AND Euvolemic hyponatremia (SIADH) OR/AND Hypernatremia on multiple occasions and/or polyuria >3 L/day (DI)
Secondary criteria	Oliguric or urine output <0.5 mL/kg/hour for 12 hours at least (KDIGO-2012) Urinalysis findings: Granular and muddy casts consistent with ATN Urinary eosinophils (possible AIN) Proteinuria <1 gm/day Fractional excretion of sodium (FeNa) >1% AND/OR Clinical symptoms for AIN: fever, rash, and joint pains	RBC casts, dysmorphic RBCs in urine microscopy Absence of secondary disorders that can cause glomerulonephritis, such as diabetes mellitus, systemic lupus nephritis, postinfectious causes, and hepatitis Microangiopathic changes in blood smear, elevated serum LDH, low serum haptoglobin (TMA)	Crystals on urine microscopy: Sheaves of wheat: sulfa drugs Yellow or golden brown annular: methotrexate Needle and fan-shaped: indinavir Thin needles: acyclovir Calcium oxalate: IV ascorbate or orlistat Plate or geometric shapes: foscarnet Flat or wedge prisms with rosette formation: sodium phosphate	Tubular hypophosphatemia: fractional excretion of phosphate (FePO ₄) >5% Hypomagnesemia: serum magnesium <1.2 mg/dL Hypouricemia: serum uric acid <2 mg/dL Tubular proteinuria: 24 hour urine <1 gm protein or UPCR <0.8 or dipstick <2+ protein DI Serum osmolality >300 mOsm/kg Urine osmolality <100 mOsm/kg Urine sodium <10 mEq/L

Table 2: The Naranjo ADR probability scale

Question	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	–1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was readministered?	+2	–1	0	
5. Are there alternative causes (other than the drug) that could, on their own, have caused the reaction?	–1	+2	0	
6. Did the reaction reappear when a placebo was given?	–1	+1	0	
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
Total score				

Modified from: Naranjo CA et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239–245

to hypovolemia or from renin–angiotensin–aldosterone system (RAAS) blockade due to a drop in GFR from efferent arteriolar dilation, especially in the backdrop of reduced renal blood flow from shock or hypovolemia.²

RISK FACTORS FOR DIKD

Various factors, such as modifiable and nonmodifiable risk factors, influence DIKD beyond individual drug characteristics. Modifiable risks include volume depletion,

hypotension, exposure to other nephrotoxic substances, high drug doses, and incorrect dosing.^{1,2} Nonmodifiable risks include age, preexisting kidney disease, liver disease, diabetes, heart failure, postsurgery,

Table 3: Common drugs associated with DIKD and their mechanisms

Drug	Time course	Genetic mechanisms	AKI		Glomerular disease		Tubular disease		Nephrolithiasis	
			Type A	Type B	Type A	Type B	Type A	Type B	Type A	Type B
Abacavir	Acute/SA	HLA								
Acyclovir	SA	OAT								
Aminoglycosides	Ac/SA	Megalin/cathepsin/caspase								
Ampicillin	SA	HLA								
Amphotericin	Ac/SA	–								
Anabolic steroids	SA/chronic	–								
Atazanavir	SA	–								
Bevacizumab	SA	VEGF								
Ceftazidime	SA	HLA								
Cidofovir	Acute	OAT								
Cisplatin	SA/chronic	OAT								
Ceftazidime	SA	HLA								
Colistin	SA	OCT								
Didanosine	SA	OAT/mitochondria								
Flouroquinolones	SA	HLA								
Foscarnet	SA	NaPO ₄ transport								
Hydralazine	SA/chronic	HLA								
Ifosfamide	SA/chronic	OAT								
Indinavir	SA	OCT								
Li	SA/chronic	VA receptors								
Methotrexate	Acute/chronic	–								
Nafcillin/methicillin	SA	HLA								
Pamidronate (IV)	SA	–								
Piperacillin/tazobactam	Acute/SA	HLA								
Propylthiouracil	SA/chronic	HLA								
Rifampicin	SA	HLA								
Ritonavir	SA	MRP-2,4, PGP								
Sodium phosphate (oral)	Acute/chronic									
Sulfadiazine, sulphamethoxazole	Acute/SA	HLA								
Tacrolimus/CNI	Acute/SA	CYP 3A								
Tenofovir	SA	OAT								
Vancomycin	Acute/SA	Oxidative stress, HLA								
Zolindronate (IV)	Acute/SA	–								

CYP, cytochrome P450; HLA, human leukocyte antigen; IV, intravenous; MRP, multidrug resistance-associated protein; NSAIDs, nonsteroidal anti-inflammatory drugs; OAT, organic anion transporter; OCT, organic cation transporter; PGP, p-glycoprotein; SA, subacute

critical illness, burns, and immune compromise.^{1,2} Unfortunately, prediction tools for nephrotoxicity risk are not widely available except the Mehran score, which has been recently validated in predicting contrast-associated AKI after percutaneous interventions.⁶ This score considers several clinical factors present at the time of intervention along with the volume of intravenous (IV) contrast in determining the risk of AKI and dialysis post-AKI.⁶

Some selective drugs cause kidney disease (Fig. 1).

CONTRAST-INDUCED OR CONTRAST-ASSOCIATED AKI

Contrast-induced AKI as defined by the KDIGO working group in 2012, is an elevation in plasma creatinine greater than 1.5 times or >0.3 mg/dL from baseline within 48 hours to 7 days and/or oliguria, defined as a urinary volume of <0.5 mL/kg/hour persisting for at least 6 hours after exposure to intravascular iodinated radiocontrast agents.⁶ These agents can cause nephrotoxicity by direct tubular epithelial cell toxicity or through

indirect mechanisms like vasoconstriction due to renin–angiotensin activation, release of endothelins, and increased blood viscosity that lead to microcirculation damage and ischemic injury. Recently, the role of extraneous factors like concomitant medications, hypotension, and/or atheroemboli has been emphasized as promoters of AKI in this setting, leading to the use of the term “contrast-associated AKI.” Preexisting CKD is considered the most significant risk factor among comorbidities. Specific characteristics of the contrast agent associated with AKI include the type of

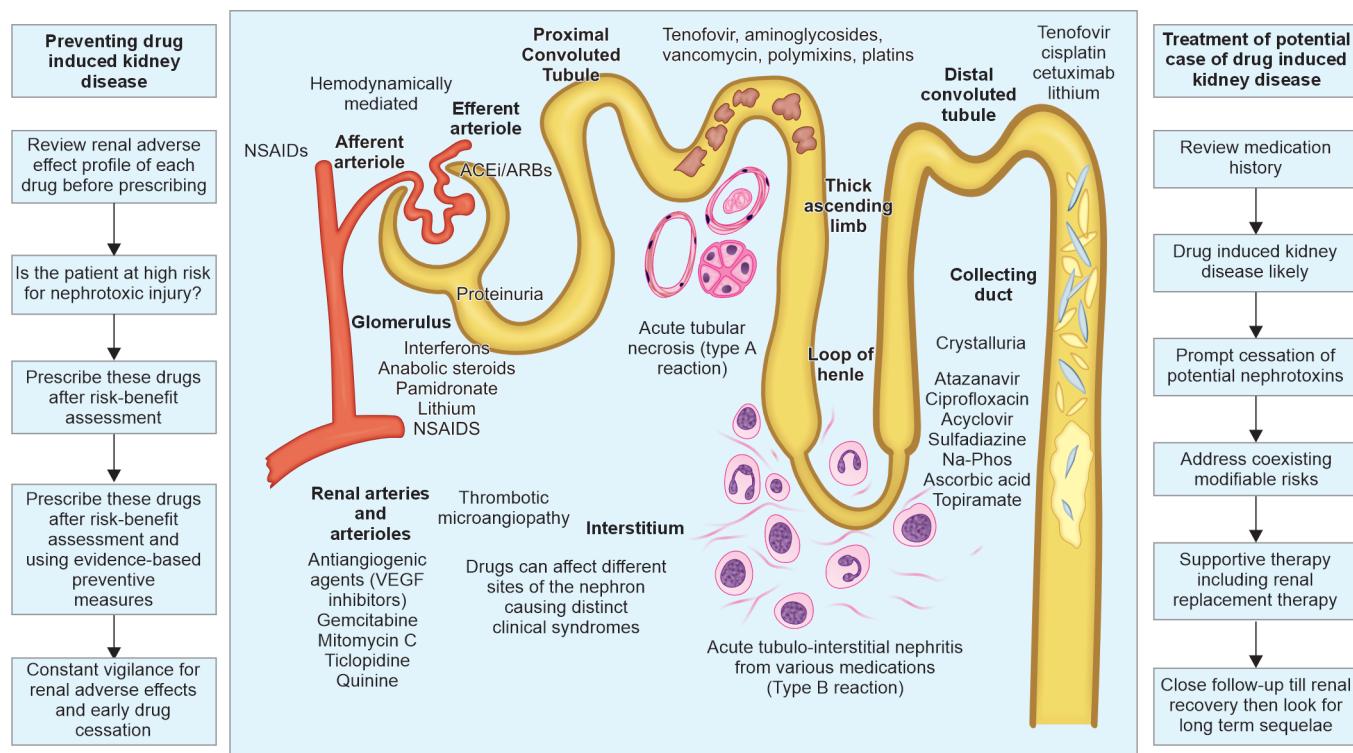


Fig. 1: General approach to DIKD

radiocontrast agent, with iso-osmolar or low-osmolar agents being safer than high-osmolar agents. The volume of agents administered, using a volume of >350 mL or >4 mL/kg and repeated administration within 72 hours, also plays a role. Additionally, arterial administration (as during coronary artery intervention) carries a higher risk compared to IV administration (as during a CT scan), likely from greater delivery of the contrast agent to the kidneys. Overall, the risk of severe AKI from contrast agents, especially that needing dialysis, is very low (0.3%).⁶

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

Nonsteroidal anti-inflammatory drugs (NSAIDs) nephrotoxicity occurs through various mechanisms.² Type A reaction, which is most common, results from the inhibition of prostaglandin (PG) synthetic enzyme cyclooxygenase (COX) (COX-1-expressed constitutively and COX-2 in inflammatory cells), which lowers renal PGE2 levels.⁴ PGE2 is a vasodilator that increases renal arterial blood flow and maintains GFR by afferent arteriolar vasodilation, especially in the setting of decreased systemic perfusion from hypovolemia, shock, or congestive heart failure.² Reduced PGE2 levels could lead to afferent arteriolar vasoconstriction and subsequent decline in GFR (prerenal

AKI), while decreased renal blood flow could cause downstream ischemic tubular injury. Additionally, PGE2 inhibition disrupts tubular sodium reabsorption and water excretion, leading to sodium and water retention.² Type B reaction from NSAIDs is rarely seen but typically manifests as AIN with significant proteinuria resulting from T-cell activation and immune-mediated podocyte damage.⁴

ANTIBIOTICS

Antibiotics are an important cause of DIKD, with multiple mechanisms being involved, as listed in Table 3. Aminoglycosides, such as gentamicin, tobramycin, and amikacin, are common culprits, causing dose-dependent reductions in renal function in up to 20% of cases.⁷ These agents primarily induce proximal tubular toxicity. IV vancomycin is also associated with direct proximal tubular toxicity, typically occurring after 4–8 days of therapy.^{2,7} Close monitoring of renal function is crucial, as toxicity can be observed at recommended trough levels (15–20 mg/L).⁷ Polymyxins (colistin and polymyxin B), which are used in multidrug-resistant gram-negative infections, exhibit one of the highest rates of dose-dependent nephrotoxicity, leading to acute tubular necrosis (ATN) and proteinuria.⁷ The antifungal amphotericin-B (AmB) acts as a potent tubule toxin, disrupting cell membranes and causing distal tubular acidosis (type 1). AmB's adverse effects

also include decreased GFR, hypokalemia, hypomagnesemia, and nephrogenic diabetes insipidus (NDI). Cumulative dose (>600 mg) is a critical risk factor for AmB nephrotoxicity.⁷ Trimethoprim (present in combination with sulfamethoxazole) has already been mentioned to cause pseudo-AKI and, in some cases, hyperkalemia by inhibiting the epithelial Na channel in principal cells.⁷ Tenofovir, an antiviral agent, is associated with proximal tubular dysfunction that may progress to CKD if not promptly recognized and managed.⁷ Indinavir primarily induces asymptomatic nephrolithiasis, while acyclovir can lead to AIN due to crystalluria.⁷ Risk factors for acyclovir nephrotoxicity include rapid IV infusion and higher doses (>1500 mg/m²).⁷ Type B reactions in the form of AIN have been observed with certain β -lactam antibiotics (particularly nafcillin and methicillin), albeit rarely with cephalosporins, carbapenems, monobactams, sulfa drugs, and fluoroquinolones (especially ciprofloxacin).⁴

CONVENTIONAL CANCER CHEMOTHERAPEUTICS

Most of these agents cause DIKD through type A reaction, with the prototype being platinum-based compounds such as cisplatin.^{4,8} Besides AKI, cisplatin can also cause hypomagnesemia, NDI, proximal tubulopathy, and rarely thrombotic microangiopathy (TMA).⁸ Amongst alkylating

Table 4: Targeted anticancer agents and immune-therapy nephrotoxicity

Medication class	Mechanism of action	Renal syndromes	Management strategies
VEGF pathway inhibitors	Anti-VEGF receptor antibodies (bevacizumab, aflibercept, anti-VEGF antibodies (ramucirumab)) VEGF-TKI inhibitors (axitinib, pazopanib, sorafenib, regorafenib, sunitinib)	TMA, FSGS/MCD TMA (sunitinib) ATN (sunitinib/sorafenib) Hypophosphatemia, hypocalcemia, hyponatremia, hypokalemia (regorafenib)	Drug discontinuation RAAS blockade? Eculizumab for TMA
EGFR pathway inhibitors	EGFR-TKI inhibitors (erlotinib, gefitinib) Anti-EGFR receptor Antibodies (cetuximab, panitumumab)	MCD/membranous nephropathy Hypomagnesemia/hypokalemia/nephrotic syndrome	Drug discontinuation
Bcr-abl TKIs	1st generation: Nilotinib, imatinib 2nd generation: dasatinib	Hypophosphatemia, reversible decrease in GFR, ATN Proteinuria	Close monitoring of renal function and dose reduction when decreased GFR Dose reduction or discontinuation; change to 1st generation Bcr-abl TKI inhibitors
IFN	Direct effects on podocyte Indirect effects by cytokine release damage microvascular endothelial cells by inducing apoptosis in a dose-dependent manner	MCD/FSGS/TMA	Drug discontinuation Steroids (MCD/FSGS)
Interleukin-2	Capillary leak syndrome leading to hypovolemia/hypoperfusion	Hemodynamically mediated AKI, ATN	Volume resuscitation
CAR-T therapy	CRS, capillary leak syndrome	Hemodynamic mediated AKI, ATN	Volume resuscitation (capillary leak) Steroids, anti-IL6 therapy: tocilizumab (CRS)
Immune checkpoint inhibitors (CTLA-4 inhibitors, PD-1 inhibitors, PD-L1 inhibitors)	Loss of tolerance, formation of new or reactivated T cells against tumor antigens that cross-react with the kidney, generation of autoantibodies against kidney tissues	ATIN (most common) Podocytopathies	Drug withdrawal Steroids

AKI, acute kidney injury; ATN, acute tubular necrosis; ATIN, acute tubulointerstitial nephritis; Bcr:abl, breakpoint chain region, +abelson; CAR-T, chimeric antigen receptor T-cell; CRS, cytokine release syndrome; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate; IFN, interferon; MCD, minimal change disease; PD-1, programmed death protein 1; +PD-L1, programmed death-ligand 1; RAAS, renin-angiotensin-aldosterone system; TKI, tyrosine kinase inhibitor; TMA, thrombotic microangiopathy; +VEGF, vascular endothelial growth factor

agents, ifosfamide is the most nephrotoxic and is associated with proximal tubular dysfunction (Fanconi's syndrome), which can occasionally be irreversible.⁸ Methotrexate, an anti-folate agent, typically develops AKI from crystalline nephropathy.⁸ TMA is typically seen with gemcitabine and mitomycin C and is a type A reaction that results from direct endothelial injury.⁸

TARGETED CANCER AGENTS

Targeted anticancer agents are a class of medications that specifically target molecules or pathways involved in the growth and survival of cancer cells. Potential nephrotoxicity from these agents is listed in Table 4.⁸ Vascular endothelial growth factor (VEGF) pathway blockade leads to inhibition of endothelial cell proliferation and widespread endothelial dysfunction, leading to hypertension (HTN), proteinuria, and TMA.

Recently, immune-checkpoint inhibitors have revolutionized cancer treatment, with their mechanism of action being to enhance the immune response to tumor antigens by binding to inhibitory receptors such as cytotoxic T-lymphocyte-associated protein 4 and programmed death protein 1 or its ligand on T-cells. Since immune activation is nonselective, this can also lead to autoimmune damage to various organs, including the kidney, where it may result in AIN and rarely glomerular diseases such as podocytopathies.

CALCINEURIN INHIBITORS (CNI)

Medications in this class include tacrolimus and cyclosporine A, which have been extensively used following transplantation and for treating autoimmune diseases. Nephrotoxicity is a major concern with these agents since they can cause afferent arteriolar vasoconstriction leading to reversible drop in

GFR, and endothelial damage leading to HTN and TMA.^{2,8} Chronic toxicity results in tubular ischemia leading to tubule-interstitial fibrosis and CKD.⁸ Key to avoiding CNI nephrotoxicity is reducing drug exposure by dosing based on target trough levels and by limiting duration of therapy to minimum.²

MAMMALIAN TARGET OF RAPAMYCIN (MTOR) INHIBITORS

Renal disease induced by mTOR inhibitors is rare as compared to CNI, and hence, it is preferred as a nonnephrotoxic drug to prevent rejection after transplantation. Very rarely, AKI, proteinuria, and TMA have been associated with its use.⁸ The combination of sirolimus and cyclosporine has shown synergistic nephrotoxicity, potentially due to increased levels of cyclosporine

Table 5: Management of DIKD

<i>Nonspecific measures</i>	<i>Specific measures</i>
Selectively use nephrotoxic medications when benefits > risk	Use low-osmolar (iopamidol) or iso-osmolar (iodixanol) radiocontrast agent for IV contrast studies
Use a minimal dose of agents: Dose adjustment based on GFR (chemotherapeutic agents, aminoglycosides, IV vancomycin, polymyxin B, colistin, IV bisphosphonates)	Specific antidote: Amifostine for preventing cisplatin nephrotoxicity Leucovorin for preventing systemic toxicity in methotrexate overdose Glucarpidase (enzyme which inactivates methotrexate) in treating methotrexate toxicity
Avoid multiple daily dose-aminoglycosides, Li	Use less nephrotoxic formulations-lipid based or liposomal amphotericin B instead of amphotericin B deoxycholate
Monitor drug trough levels (aminoglycosides, vancomycin, CNI, Li)	
Avoid exceeding cumulative dose implicated in renal toxicity (amphotericin B)	
Limit total volume of IV radiocontrast (<4 mL/kg or <2× baseline GFR)	
Prophylactic volume expansion	Urinary alkalinization
Prevention of CI-AKI: isotonic saline 1–1.5 mL/kg/hour given 1–6 hours prior to IV contrast injection and 6–12 hours after the procedure; caution in CHF, hypertensive or oliguric or edematous patient	Prevention of crystalluria and AKI in patients on methotrexate, sulfadiazine, sulfamethoxazole, triamterene
Prior to cancer chemotherapeutics	Use of amiloride to treat Li-induced NDI by inhibiting Li uptake in principal cells of cortical tubules via blockage of epithelial sodium-channel
Fluid resuscitation therapy	Increase IV infusion time (IV bisphosphonates)
Prerenal settings: postchemotherapy emesis, NSAID, diuretic, RAAS blockade associated AKI, Li toxicity	
Statins used prior to angiographic interventions (if patient not already on) to reduce risk of contrast-associated AKI	Use nonnephrotoxic agents in the same class if renal dysfunction (ibandronate instead of pamidronate or zoledronate)
Close watch for clinical and biochemical signs of renal disease, especially in those with dose-dependent nephrotoxicity and early drug discontinuation	Recommended drug trough levels For IV vancomycin: <15 mg/L (if possible) but not to exceed 20 mg/L
Avoid concomitant use of agents that cause decreased renal perfusion-diuretics, ACE inhibitors, ARBs, mineralocorticoid antagonists, SGLT-2 inhibitors	Hemodialysis Methotrexate toxicity associated with AKI
Avoid medications with systemic accumulation and toxicity caused by a drop in GFR-metformin (lactic acidosis), gabapentin (neurotoxicity), colchicine (neuromyotoxicity), pemetrexed (hematological and gastrointestinal toxicity)	Plasmapheresis Drug-induced TMA (gemcitabine, mitomycin C, mTOR inhibitors, CNI)
Hemodialysis: renal failure with uremic toxicity due to severe DIKD from any agent	Terminal complement pathway (complement 5) inhibitor-eculizumab Drug-induced TMA (gemcitabine, mitomycin C)
Reduce proteinuria and HTN associated with glomerular disease with ACE inhibitors, ARBs, mineralocorticoid receptor antagonists	

ACE, angiotensin-converting enzyme; CI-AKI, contrast-induced acute kidney injury; DIKD, drug-induced kidney disease; GFR, glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; TMA, thrombotic microangiopathy

and the fibrogenic cytokine transforming growth factor- β .⁸ Sirolimus also inhibits the elimination of cyclosporine, further enhancing its nephrotoxic effects.⁸ Overall, proteinuria is a common side effect and is seen in varying degrees in patients with focal segmental glomerulosclerosis (FSGS) when substituted for a calcineurin inhibitor. Proteinuria may be reversible upon sirolimus withdrawal. In cases when withdrawal is not possible, we recommend the use of RAAS blockade as long as tolerated.

LITHIUM (LI)

Two forms of renal disease associated with long-term Li use are NDI, and CKD.⁹ NDI occurs when antidiuretic hormone action on the principal cells in the collection ducts is inhibited, impairing urinary concentration. NDI prevalence in long-term Li users can be as high as 50–73%, with disease severity linked

to treatment duration. Reversibility becomes less likely after 2–6 years of use.⁹ CKD, often caused by chronic tubulointerstitial nephritis, features tubulointerstitial fibrosis, cortical and medullary cysts, and FSGS.⁹ Interstitial fibrosis severity correlates with treatment duration and cumulative Li dose, leading to a gradual decline in kidney function over several decades. Approximately, 17–21% of long-term Li users develop CKD, with an average latency period of 16.5–31 years from drug initiation to progression. Hypercalcemia is another rare side effect of chronic Li use that is associated with hyperparathyroidism and can lead to a reduction in renal function.⁹

PROTON-PUMP INHIBITORS (PPI)

Drug-induced kidney disease (DIKD) associated with PPIs is a rare type B reaction resulting in AIN, which may be seen anytime from days to

months after initiation of therapy.⁴ Patients often have nonspecific symptoms, making diagnosis challenging and necessitating the need for a renal biopsy. The incidence is higher in those with multiple drug allergies, autoimmune diseases, newly initiated on PPI, or those >65 years old.¹⁰ Additionally, long-term use of PPI has also been associated with 36 and 42% higher incidence of CKD and end-stage kidney disease (ESKD) than nonusers.¹⁰ Treatment involves prompt discontinuation of PPIs and use of short-duration high-dose corticosteroid therapy.¹⁰

COMPLEMENTARY/ALTERNATIVE MEDICINES

Complementary and alternative medicines from indigenous systems like Unani/Siddha or Ayurveda are increasing in popularity both in India and globally. However, concerns about renal safety with these agents are high due to

limited regulatory control.¹¹ Toxicity from these agents, which are mostly herbal products, results from undocumented adverse effects, misidentification of herbs, contamination with heavy metals due to faulty manufacturing process, or as concomitant nephrotoxins with conventional drugs with known renal ADEs.¹¹ Aristolochic acid nephropathy is a prime example, found in Chinese medicinal herbs derived from the *Aristolochia* genus (Guang Fang Ji) or *Asarum* genus (wild ginger or Xi Xin), and is proven to cause chronic interstitial nephritis as well as urothelial malignancies due to formation of toxic DNA adducts in urothelial renal tissues.¹¹ Vigilance by medical practitioners is vital while probing medication history in patients with AKI, tubular disease, HTN, proteinuria, or CKD of unclear cause.

MANAGEMENT OF DIKD

Management aspects of DIKD are highlighted in Table 5 and encompass a combination of prevention and treatment strategies tailored to the specific renal syndrome. This begins with a risk assessment involving a comprehensive review of the patient's medication history to identify potential nephrotoxic drugs or combinations thereof and promptly stop the agent to avoid irreversible renal damage. Additionally, timely nephrology consultation

is crucial when managing patients at high risk of DIKD or those with suspected or confirmed renal injury. Patient education is essential to ensure an understanding of the importance of adhering to prescribed medication regimens, promptly reporting any unusual symptoms or changes in urine output, and seeking medical attention if any concerns arise (Fig. 1).

CONCLUSION

Drug-induced kidney disease (DIKD) presents a significant clinical challenge, as its consequences can be severe, potentially leading to ESKD if not promptly managed. DIKD can occur through various mechanisms, including direct toxicity, immune-mediated injury, and drug-induced alterations in renal blood flow. Preventive measures play a crucial role, involving careful drug selection, proper dosage consideration, and addressing additional risk factors. In cases of DIKD, timely discontinuation of the responsible drug and appropriate supportive care are essential to minimize further renal damage and mitigate complications that may arise.

ACKNOWLEDGMENT

This research was supported in part by the Intramural Research Program of the NIH, the

National Institute of Diabetes and Digestive and Kidney Diseases.

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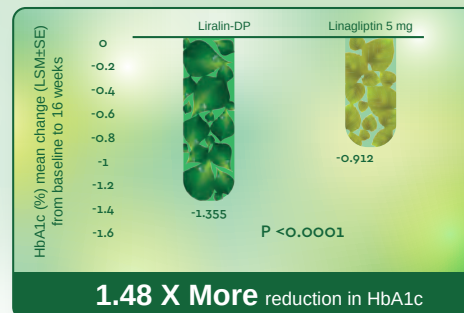
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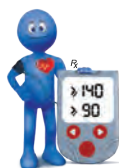
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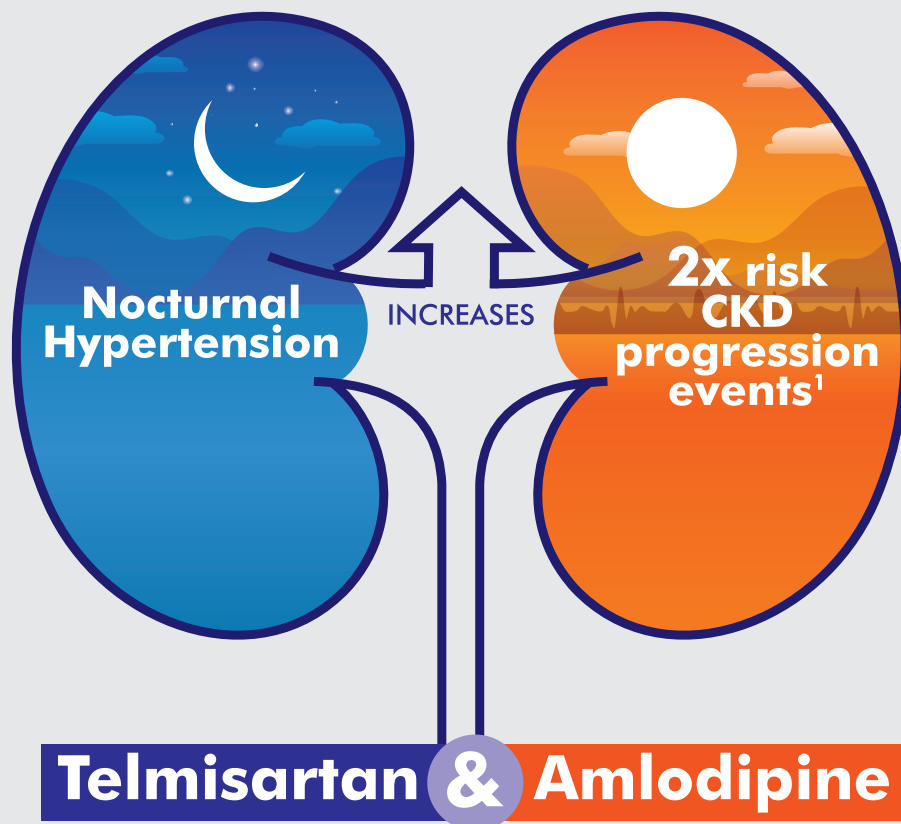
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Hyperglycemia in Cancer Patients

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Received: 07 October 2023; Accepted: 16 October 2023

ABSTRACT

Most of the cancer patients have multiple comorbid conditions, commonly diabetes mellitus, hypertension, and coronary vascular diseases. Cancer treatment involves a multidisciplinary approach targeting primary cancer-directed therapy along with optimal management of comorbid conditions as well. Hyperglycemia, which exists prior to cancer therapy initiation or if it develops during or after therapy, is associated with less desirable outcomes like treatment compromise due to increased adverse effects of therapy and higher mortality. Hence, prompt diagnoses and management of hyperglycemia become crucial during therapy. Healthcare providers working in an oncology setting, as well as primary care providers, should be aware of medications that are associated with hyperglycemia and diabetes. This paper will elucidate various cancer-directed therapies associated with hyperglycemia.

Journal of the Association of Physicians of India (2024): 10.59556/japi.71.0431

Common malignancies that are managed at the Asian Cancer Institute and Cumballa Hill Hospital include breast cancer, head and neck cancer, and esophageal, gastric, and thoracic malignancies. Hematological malignancies like Hodgkin and non-Hodgkin lymphomas and myeloma are also treated under medical oncology care. The most common chemotherapeutic agents used at our institute include anthracyclines (doxorubicin, daunorubicin, and epirubicin), fluoropyrimidines (5-fluorouracil and capecitabine), taxanes (paclitaxel and docetaxel), platinum compounds (cisplatin, carboplatin, and oxaliplatin).

Corticosteroids are also included in some of the chemotherapeutic protocols in hematological malignancies like acute lymphoblastic leukemia (ALL), multiple myeloma, and non-Hodgkin lymphoma.

Various metabolic and endocrine dysfunctions are observed after the administration of certain chemotherapy protocols, newer targeted therapy, and now, recently, immunotherapy.

One of the common endocrine dysfunctions observed in patients following cytotoxic chemotherapy is hyperglycemia. Hyperglycemia has been graded as per common terminology criteria for adverse events from grades 1 to 5.¹

- Grade 1: Abnormal glucose above baseline with no medical intervention.
- Grade 2: Change in daily management from baseline for a diabetic—oral antidiabetic agent initiated; workup for diabetes.
- Grade 3: Insulin therapy was initiated; hospitalization was indicated.

- Grade 4: Life-threatening consequences; urgent interventions indicated.
- Grade 5: Death.

CORTICOSTEROIDS AND HYPERGLYCEMIA

Dexamethasone and prednisolone are used in chemotherapeutic protocols as they have varied spectrums of activity.

Dexamethasone 12 mg on day 1 and 8 mg on days 2 and 3 has been used to prevent chemotherapeutic nausea and vomiting in high and moderate chemotherapeutic regimens.²

Prednisolone 100 mg/day for 5 days is used as a part of the chemotherapeutic protocol in many of the non-Hodgkin lymphoma treatment.^{3,4}

Prednisolone and dexamethasone also form part of ALL multi-agent induction chemotherapy and are cornerstones in bringing the disease into remission.⁵

In the management of multiple myeloma, corticosteroids have been used along with novel therapeutic agents like proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies.

L-ASPARAGINASE

L-asparaginase is an important chemotherapeutic drug used during induction chemotherapy in patients with ALL. With the incorporation of this molecule into pediatric ALL treatment protocols in the 1960s, survival rates in children have increased to nearly 90%.^{6,7} It is associated with metabolic abnormalities like hyperglycemia and hypertriglyceridemia.^{8,9}

IMMUNE CHECKPOINT INHIBITORS

Oncology has witnessed a revolution in the last two decades with the invention of immune checkpoint inhibitors. Programmed cell death protein 1/programmed cell death ligand 1 and cytotoxic T-lymphocyte-associated antigen 4 antagonists have brought new hope to patients with deadly malignancies like malignant melanoma and renal cell carcinoma, which are traditionally considered chemo-resistant. The advent of these therapeutic molecules has opened up a new set of side effect profiles that are unique to these molecules. The adverse events associated with the immunotherapy agents have been termed immune-related adverse events, which are class-specific. The most commonly used immune checkpoint inhibitors include pembrolizumab, nivolumab, ipilimumab, atezolizumab, etc. These drugs are associated with autoimmune side effects like hypothyroidism, hyperthyroidism, panhypophysitis, and diabetes mellitus, to name a few.¹⁰

TYROSINE KINASE INHIBITORS

Nilotinib

It is a second-generation *Bcr-Abl* tyrosine kinase inhibitor (TKI) that interferes with the interaction between the *Bcr-Abl* oncoprotein and adenosine triphosphate, thereby blocking the proliferation of the malignant clone in chronic myelogenous leukemia. It is frequently associated with insulin resistance, impaired glucose tolerance, and hyperglycemia.¹¹

Ceritinib

Ceritinib is a TKI therapy that targets anaplastic lymphoma kinase (ALK) gene rearrangement

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How to cite this article: Bhoraskar A, Tonse M, Agre S, et al. Hyperglycemia in Cancer Patients. *J Assoc Physicians India* 2024;72(1):83–84

and has been used in the management of metastatic ALK-positive nonsmall cell lung cancer. It is linked to hyperglycemia in patients with diabetes.¹² It is essential to monitor for this side effect, especially during the first few weeks of therapy.

Everolimus

This is a mammalian target of rapamycin inhibitor used in the treatment of malignancies like breast, renal cell carcinoma, and neuroendocrine tumors. In a meta-analysis consisting of 3,879 cancer patients, everolimus was associated with an increased incidence of all-grade and high-grade hyperglycemia.¹³ The various mechanisms responsible for everolimus-induced hyperglycemia are lipotoxicity, reduced insulin signaling, reduced glucose secretion, and reduced muscle glucose uptake.¹⁴

Alpelisib

Alpelisib is an α -selective phosphoinositide 3-kinase (PI3K) inhibitor indicated for the management of hormone-positive human epidermal growth factor receptor 2/neu negative and PIK2CA-mutated metastatic breast cancer. As the PI3K pathway plays an important role in regulating glucose

metabolism, its inhibition leads to hyperglycemia. Hyperglycemia is the most common adverse event seen with the administration of alpelisib and frequently leads to treatment discontinuation.¹⁵

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Phase IV Studies: What Clinicians Need to Know!

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Received: 18 July 2023; Revised: 05 September 2023; Accepted: 09 September 2023

ABSTRACT

Phase IV trials, also known as postmarketing safety and efficacy studies and postmarketing surveillance (PMS) studies, occur after a drug or medical device has received regulatory approval and is available in the market. These trials are designed to collect additional information regarding the product's safety, efficacy, and prolonged effects in a larger and more diverse patient population. The foremost goal of phase IV trials is to detect any rare or long-term adverse effects that may not have been identified during the prior phases of clinical development. During phase IV trials, pharmaceutical companies, academic institutions, or other research organizations conduct studies to evaluate various aspects of the product, including its real-world effectiveness, optimal use, and any potential safety concerns. The regulatory agencies play a role in overseeing these trials to ensure that they are conducted ethically and in compliance with good clinical practice (GCP) guidelines.

Journal of the Association of Physicians of India (2024); 10.59556/japi.71.0444

INTRODUCTION

In the process of drug development, clinical trials comprise four phases, with each phase having a different purpose and specific objective. Clinical trials start with lesser groups of subjects/patients with more focused objectives, gradually involving a larger population intended to collect additional information about the drug's safety and effectiveness and also the overall risk-benefit aspect for best uses.

Clinical trials are conducted in various phases to evaluate the safety and efficacy of new medical treatments or interventions. The phases of clinical trials are designed to gather increasingly more detailed information about the experimental treatment/drug, and each phase serves a specific objective.

Objectives of Different Phases of Clinical Trials

Phase I trials (safety study) are conducted with a small number of healthy volunteers or patients, with the primary objective being to evaluate the safety, dosage range, and potential side effects of the experimental treatment.¹ The focus is on determining the treatment's maximum tolerated dose and identifying any dose-limiting toxicities. Phase II trials (efficacy study) involve a larger number of patients to assess the treatment's effectiveness and further evaluate its safety. The emphasis is on determining the optimal dosage and identifying common side effects associated with the treatment. These trials provide preliminary evidence of the treatment's potential benefits. Phase III trials involve a larger population of patients

(in 100s) to confirm the treatment's efficacy, monitor safety, and compare it to existing gold standard treatments or a placebo. These trials provide more comprehensive data on the treatment's benefits, risks, and optimal usage. Phase III trials are critical for regulatory approval by health authorities. Phase IV trials, also known as postmarketing surveillance (PMS) trials, are conducted after a treatment has received regulatory approval. The objective is to collect additional information on the treatment's long-term safety, efficacy, and or effectiveness in a larger patient population. Phase IV trials help monitor rare or long-term side effects and evaluate the treatment's use in specific patient subgroups.

PHASE IV TRIALS

Also known as PMS trials or late-phase clinical trials, these refer to studies conducted once a drug or treatment has been approved and made available to the general population.¹ Regulatory authorities require drug manufacturers to conduct one or more phase IV clinical studies to get more data to generate real-world evidence.² Safety surveillance is designed to detect any rare or long-term adverse effects in a much larger patient population over a longer period. If any harmful effects are discovered during phase IV trials, the drug can be withdrawn from the market or restricted to certain uses. In this phase, further indications of drugs might be determined.³

Objective of Phase IV Studies

The primary aim of phase IV trials is to further evaluate the drug's safety, effectiveness, and

potential risks and benefits in real-world settings beyond the controlled conditions of earlier phases.¹ These trials involve monitoring the drug's performance in a larger and more diverse patient population over an extended period.

They aim to detect and assess any rare or long-term side effects, drug interactions, or unexpected adverse events that may not have been apparent during the earlier phases of clinical development. Phase IV trials also provide an opportunity to compare the new drug or treatment with existing standard therapies, different formulations or doses of the same drug, or alternative treatment strategies. They may help identify superior outcomes, improved patient adherence, or other advantages of the new intervention. Additionally, phase IV trials contribute to health economics and outcomes research (HEOR) by evaluating the cost-effectiveness, quality of life, and overall outcomes associated with the use of the drug or treatment in real-world clinical practice. They provide insights into the economic and patient-related benefits, as well as any limitations or challenges that may arise during routine use.

Phase IV trials play a crucial role in continuously monitoring and refining the understanding of a drug or treatment's safety profile and real-world effectiveness. The knowledge gained from these trials helps inform healthcare providers, regulators, and patients about the optimal use and potential risks associated with the intervention,

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How to cite this article: Trailokya A, Srivastava A, Mukaddam Q, et al. Phase IV Studies: What Clinicians Need to Know! *J Assoc Physicians India* 2024;72(1):85–87.

contributing to evidence-based decision-making in clinical practice.

INDIAN REGULATION ON PHASE IV STUDIES

As per Indian regulation led by DCGI, postmarketing trials or phase IV studies of new drugs are performed once the drug is approved by the regulatory agency and in relation to the approved indication.⁴ Such trials can go beyond the prior demonstration of the drug's safety and efficacy.

Phase III trials/studies of chronic conditions or diseases like type 2 diabetes mellitus hypertension are often linked with a shorter duration. In addition, phase III trials focus on efficacy, but knowledge of safety is also essential. Drugs may be approved after successful completion of phase III studies on the basis of intermediate or surrogate outcomes or biomarkers, such as effect on blood pressure or blood glucose or cholesterol lowering.

Phase IV trial may not have been considered vital at the time of new drug approval owing to various reasons like limitations in terms of patient exposure, duration of treatment during clinical drug development, and the need for early introduction of the new drug in the market in the interest of patients, etc. The primary aim of phase IV studies is safety.

Phase IV trials may include additional:

- Dose response or safety studies.
- Drug–drug interaction.
- Trial design supports the use of a drug under the approved indication, for example, morbidity or mortality studies and epidemiological studies, etc.

Guidance by Health and Family Welfare Ministry of India

Phase IV (postmarketing) trial: This will be conducted as per protocol, which is approved with a defined scientific objective, with defined inclusion and exclusion criteria, safety and efficacy assessment criteria, etc., with the new drug as per approved indications for use in the approved patient population.⁴

The trials should be conducted as per Good Clinical Practice (GCP) guidelines with the protection of the safety, rights, and well-being of the trial subjects as per the regulatory provisions.

In such a phase IV study, it is advisable to provide the study drug-free of cost to the subject participating in the trial, unless there is a specific reason or justification for not providing the drug-free of cost, to the satisfaction of the Central Licencing Authority and the Ethics Committee.

Postmarketing Surveillance Study or Noninterventional or Observational Study for Active Surveillance

Phase IV studies are performed with a new drug under approved conditions/indication of its use under a protocol that should be approved by the Central Licencing Authority with a scientific objective.⁴ Inclusion and exclusion of subjects are decided as per the recommended use of the drug and should be as per approved package insert (approved label) or prescribing information.

In such studies, the study drugs are part of the treatment of patients in the wisdom of the prescriber included in the protocol. The regulatory provisions and guidelines applicable for the clinical trial of a new drug are not applicable in such cases as drugs are already approved for marketing.

Common Types of Phase IV Trials

- Safety trials: These trials focus on monitoring the long-term safety and tolerability of the drug or treatment. They may identify long-term or rare side effects that were not observed during earlier phases.
- Comparative effectiveness trials: These trials compare the effectiveness of a new drug or treatment with existing standard treatments or different formulations or doses of the same drug. They help determine if the new intervention provides superior outcomes compared to alternatives.
- Pharmacovigilance trials: These trials aim to collect and analyze data on the safety of a drug in real-world settings. They help identify any potential safety concerns or rare adverse events that may not have been captured during the earlier phases of clinical trials.
- Expanded access trials: Also known as compassionate use or named patient programs, these trials provide access to investigational drugs or treatments for patients who have serious or life-threatening conditions and cannot participate in ongoing clinical trials. They help gather additional safety and effectiveness data in a broader patient population.
- Risk management trials: These trials assess the risk-benefit balance of a drug or treatment in specific patient populations or under certain conditions. They aim to optimize treatment strategies and minimize potential risks associated with the use of the intervention.
- Health economics and outcomes research (HEOR) trials: These trials evaluate the cost-effectiveness, quality of life, and

overall outcomes associated with the use of a drug or treatment in real-world clinical practice. They provide insights into the economic and patient-related benefits of the intervention.

- Subgroup analysis trials: These trials focus on specific subgroups of patients to assess the drug's effectiveness, safety, or optimal dosage within those populations. Subgroup analysis helps identify variations in treatment response and potential factors that may influence patient outcomes.

These are some examples of phase IV trials, but the specific types and designs of trials may vary depending on the nature of the drug, treatment, or medical intervention being studied.

Importance of Phase IV Trials in the Process of Drug Development (Fig. 1)

Phase IV studies, also known as PMS trials or postapproval studies, play an important role in drug development. Important reasons why phase IV studies are essential:

- Safety monitoring: Phase IV studies provide an opportunity to monitor the long-term safety profile of a drug in a larger population and over an extended period. These studies help to find rare or long-term side effects that may not have been observed during earlier phases due to the smaller sample size or shorter duration of exposure.
- Real-world effectiveness: While clinical trials conducted during earlier phases provide valuable data on a drug's efficacy, they are often conducted in controlled settings with carefully selected participants. Phase IV studies evaluate the drug's effectiveness and performance in real-world clinical practice, where factors such as patient adherence, comorbidities,



Fig. 1: Significance of phase IV trials in drug development process

and concomitant medications can impact treatment outcomes.

- **Dosage optimization:** Phase IV studies can help refine the optimal dosage or dosing regimen of a drug. The data collected during earlier phases may not capture the full range of dosages or variations in administration schedules that may be encountered in real-world clinical practice. Phase IV studies provide an opportunity to assess the drug's efficacy and safety across different dosages and refine dosing recommendations if necessary.
- **Patient subgroup evaluation:** Phase IV studies allow for the evaluation of the drug's effectiveness and safety in specific patient subgroups that may not have been adequately represented in earlier phases. These subgroups can include different age groups, ethnicities, patients with specific comorbidities, or those taking other medications concurrently. Understanding the drug's performance in diverse populations helps ensure its appropriate and effective use.
- **Comparative effectiveness:** Phase IV studies can compare the drug's effectiveness and safety to other treatments available in clinical practice, including standard-of-care therapies or alternative interventions. These comparative effectiveness studies provide valuable information for healthcare providers and decision-makers to make informed treatment choices based on real-world evidence.
- **Label expansions:** Phase IV studies can generate additional evidence that may support label expansions, allowing the drug to be approved for new indications, patient populations, or dosing regimens. These expansions can broaden the drug's use and provide healthcare providers with more treatment options.
- **Risk management and pharmacovigilance:** Phase IV studies contribute to ongoing pharmacovigilance efforts by monitoring

Vioxx (rofecoxib): Vioxx was a nonsteroidal anti-inflammatory drug (NSAID) used for pain relief. It was approved in 1999 but was voluntarily withdrawn from the market by Merck in 2004 due to increased cardiovascular risks, including heart attacks and strokes, observed in a phase 4 trial called APPROVe (Adenomatous Polyp Prevention on Vioxx).⁵ (N Engl J Med 2005; 352:1092–1102.)

Troglitazone: Troglitazone was an oral antidiabetic medication used to treat type 2 diabetes. It was withdrawn from the market in 2000 due to reports of severe liver toxicity, including cases of liver failure, which were identified during phase 4 surveillance and post-marketing reports.⁷ (Diabetes. 2005 Apr; 54(4): 1150–1156.)

Avandia (rosiglitazone): Avandia was an oral antidiabetic medication used to treat type 2 diabetes. It came under scrutiny due to safety concerns related to an increased risk of cardiovascular events. The drug's use was restricted in some countries after a meta-analysis of phase 4 studies raised concerns, and the US FDA imposed restrictions on its use in 2010.⁶ (Diabetol Int. 2022 Jan; 13(1): 49–65.)

Propulsid (cisapride): Propulsid was a medication used to treat gastrointestinal disorders such as gastroesophageal reflux disease (GERD). It was withdrawn from the market in 2000 due to safety concerns regarding serious cardiac arrhythmias, particularly when used in combination with certain medications or in patients with pre-existing cardiac conditions.⁸ (Neurogastroenterol Motil. 2018 Jun; 30(6): e13302.)

Fig. 2: Market-exited drugs due to safety concerns identified during or after phase IV trials

and assessing adverse events, drug interactions, and potential drug-related risks. This information helps update safety information, refine prescribing guidelines, and ensure patient safety during widespread use.

Drugs that were Withdrawn from the Market due to Safety Concerns Identified during or after Phase IV Trials (Fig. 2)

These examples highlight the importance of phase IV trials and PMS in detecting safety concerns that may not have been apparent during earlier phases of clinical development. Identifying and addressing these safety issues is crucial for ensuring patient safety and maintaining the trust and integrity of the pharmaceutical industry.

CONCLUSION

Overall, phase IV studies play a crucial role in PMS, providing important insights into the real-world safety and effectiveness of interventions. By continuously monitoring and

evaluating their performance, researchers, healthcare providers, and regulatory agencies can make informed decisions to optimize patient care and ensure the ongoing safety and effectiveness of approved interventions.

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The Promise of Cilnidipine in Hypertension with Comorbidities: National Consensus Statement

National Consensus Group Comprises Cardiologists, Nephrologists, and Diabetologists from India in a National Meet at New Delhi held on 22nd May 2022



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Received: 07 June 2023; Accepted: 20 August 2023

ABSTRACT

The rapidly increasing burden of hypertension is responsible for premature deaths from cardiovascular disease (CVD), renal disease, and stroke, with a tremendous public health and financial burden. Hypertension detection, treatment, and control vary worldwide; it is still low, particularly in low- and middle-income countries (LMICs). High blood pressure (BP) and CVD risk have a strong, linear, and independent association. They contribute to alarming numbers of all-cause and CVD deaths. A major culprit for increased hypertension is sympathetic activity, and further complications of hypertension are heart failure, ischemic heart disease (IHD), stroke, and renal failure. Now, antihypertensive interventions have emerged as a global public health priority to reduce BP-related morbidity and mortality. Calcium channel blockers (CCB) are highly effective vasodilators, and the most common drugs used for managing hypertension and CVD. Cilnidipine, with both L- and N-type calcium channel blocking activity, is a promising 4th generation CCB. It causes vasodilation *via* L-type calcium channel blockade and inhibits the sympathetic nervous system (SNS) *via* N-type calcium channel blockade. Cilnidipine, which acts as a dual L/N-type CCB, is linked to a reduced occurrence of pedal edema compared to amlodipine, which solely blocks L-type calcium channels. The antihypertensive properties of cilnidipine are very substantial, with low BP variability and long-acting properties. It is beneficial for hypertensive patients to deal with morning hypertension and for patients with abnormal nocturnal BP due to exaggerated sympathetic nerve activation. Besides its BP-lowering effect, it also exhibits organ protection *via* sympathetic nerve inhibition and renin-angiotensin-aldosterone system inhibition; it controls heart rate and proteinuria. Reno-protective, neuroprotective, and cardioprotective effects of cilnidipine have been well-documented and demonstrated.

Journal of the Association of Physicians of India (2024); 10.59556/japi.71.0400

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How to cite this article: Chopra HK, Wander GS, Ponde CK, *et al.* The Promise of Cilnidipine in Hypertension with Comorbidities: National Consensus Statement. *J Assoc Physicians India* 2024;72(1):88–95

APPROACH TO THE DEVELOPMENT OF CONSENSUS STATEMENT

A group of experts in cardiology, nephrology, and diabetes across India participated in a National Meet, wherein they discussed evidence-based latest clinical data on hypertension in association with its complications, namely CVD, chronic kidney disease (CKD), and stroke. They also discussed antihypertensives and CCBs, focusing on cilnidipine, a safe and effective L/N-type CCB, and its potential in hypertension with comorbidities. Postdiscussion consensus statements on the role of cilnidipine for cardiorenal and neuroprotection in clinical practice were formulated. All participating experts approved the finalized consensus statement.

INTRODUCTION

Globally, around 1.28 billion adults in the age group of 30–79 suffer from hypertension. Most of them (two-thirds) belong to low- and middle-income countries (LMICs). Risk factors, such as obesity, high sodium intake, low potassium intake, alcohol consumption, lack of physical activity, and unhealthy diet, have reached epidemic proportions in LMICs.¹

Hypertension, a leading contributor to heart disease and stroke, imposes a significant public health and economic burden on a global scale. According to statistics, about 30% of adults in India have hypertension,

with urban areas showing a prevalence of 34% and rural areas at 28%. Considering a prevalence of around 7% among young adults aged 20–39 years, it is estimated that there are approximately 27 million young adults in India living with hypertension.² Traditional risk factors for cardiovascular disease (CVD), chronic kidney disease (CKD), and stroke are high blood pressure (BP), diabetes and hypertension, the silent epidemic in India, have been co-prevalent in patients as high as 62%. The association of diabetic CKD with hypertension is recorded as high as 78.7% in India.³

HIGH BP, CVD, CKD, STROKE, AND MORTALITY

There is a strong association between earlier age onset and elevated risk for CVD, premature death, and all-cause mortality in patients with hypertension.⁴ Coronary artery disease (CAD) and hypertension also have an epidemiological correlation, which accounts for 25–30% of acute myocardial infarctions. Hypertension elevates the risk of both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Hypertensive patients with HF face worsening clinical outcomes and increased mortality.⁵

An accurate diagnosis is made possible by ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM), particularly for white-coat and

masked hypertension. 24-hour ABPM provides information on physiological dipping [a reduction in systolic blood pressure (SBP) by 10–20% during nighttime] and circadian variations in BP, if any. Higher CVD risk is linked to the lack of (“nondipping”) or reverse (“rising”) SBP-dipping.⁴

In 2015, approximately 10.7 million all-cause deaths (equivalent to 19.2%) were estimated to be associated with SBP levels equal to or higher than 110–115 mm Hg. Additionally, about 7.8 million all-cause deaths (14.0%) were due to SBP levels ≥ 140 mm Hg.⁶ Individual cause of death due to SBP ≥ 140 mm Hg was 3.6 million [40.1% of ischemic heart disease (IHD) deaths], 1.1 million (38.1% of ischemic stroke deaths), and 1.4 million (42.5% of hemorrhagic stroke deaths).⁶

Several large-scale studies have shown that elevated BP is a significant independent risk factor for chronic renal disease and end-stage renal disease (ESRD). In the MRFIT trial ($n = 32,544$ men aged 35–57 years and did not have ESRD at baseline), during an average of 16 years of follow-up, a significant independent linear correlation between systolic and diastolic blood pressure and the prevalence of ESRD was found.⁷

Various randomized controlled trials (RCTs) have demonstrated that antihypertensive medications, including calcium channel blockers (CCBs), reduce the occurrence of CVD and all-cause mortality. A large meta-analysis of 123 clinical trials ($n = 613,815$ patients) is clear

evidence for risk reductions of CVD and all-cause mortality proportional to the magnitude of BP reductions. Every 10 mm Hg decrease in SBP considerably lowered the incidence of 20% of serious CVD, 17% of IHD, 27% of stroke, 28% of heart failure, and 13% of all-cause mortality.⁷ In a similar way, the SPRINT trial in 9,361 patients with SBP of 130 mm Hg and CVD risk found that intensive BP lowering treatment with an SBP target of 120 mm Hg is advantageous in comparison to a standard target of 140 mm Hg in decreasing cardiovascular morbidity and mortality as well as all-cause mortality in high-risk hypertensive patients.^{6,8}

Stroke is an established risk of developing hypertension, and BP regulation can greatly reduce stroke incidence.⁵ In a meta-analysis of four randomized clinical trials ($n = 4,895$ patients), it was found that intensive BP control can reduce the risk of recurrent stroke compared with standard BP control [relative risk 0.78; 95% confidence interval (CI) 0.64–0.96; $p = 0.02$].⁹

HYPERTENSION CONTROL

In various RCTs, it is reported that antihypertensive medication and lifestyle changes can lower BP and the risk of CVD.

Even though there are effective interventions available, awareness, treatment, and BP control are still unacceptable, especially low in LMICs.⁶

Worldwide, just 21% of persons with hypertension have it under control, 46% of adults with hypertension are undiagnosed, and only 42% are receiving treatment.¹

As per the latest estimates, there is a population of 207 million individuals in India who have been diagnosed with hypertension.¹⁰ In India, a comprehensive study conducted among 1.3 million adults aged 18 years and above revealed a notable prevalence of 25.3% hypertension.¹¹ Despite the high prevalence of hypertension in India, a significant gap exists in terms of awareness (32% for men, 42% for women), treatment (25% for men, 35% for women), and control (11% for men, 18% for women) rates. This alarming situation will likely contribute to a rise in vascular and renal complications among the Indian population.¹¹

With the goal of achieving the tighter BP control recommended by guidelines in hypertensive patients with comorbidities, interventions to enhance hypertension management include lifestyle changes, body weight control, effective treatment of

the other risk factors (such as blood glucose, lipids), regularity in antihypertensive drugs, and adherence to treatment (Table 1).¹¹

The 2018 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines¹² recommended combining two antihypertensive drugs in a single pill to enhance adherence and increase BP control rates. They recommended starting treatment with a single pill combination (SPC), including two drugs in the majority of patients, to increase the speed, effectiveness, and predictability of BP control. Renin-angiotensin system (RAS) blockers plus CCBs or diuretics are the most preferred two-drug combos. When there is a specific indication for a β -blocker, such as angina, postmyocardial infarction, heart failure, or heart rate regulation, an alternative combination is a β -blocker with a diuretic or any other drug from the major classes. The recommendations also suggest utilizing a three-drug SPC that combines a diuretic, a CCB, and a RAS blocker if BP is not controlled with a two-drug SPC. Additionally, spironolactone can be added to treat resistant hypertension unless contraindicated.

In diabetic hypertensive patients, combining CCBs, particularly novel molecules

Table 1: 2020 International Society of Hypertension Global hypertension Practice Guidelines⁵

Hypertension with comorbidity	Goal BP	Recommended drug	
Hypertension and CAD	Target <130/80 mm Hg (<140/80 in old patients)	RAS blockers, β -blockers regardless of BP levels, including or excluding CCBs, are first-line drugs in hypertensive patients	
Hypertension and previous stroke	Target <130/80 mm Hg (<140/80 in elderly patients)	RAS blockers, diuretics, and CCBs as first-line drugs	
Hypertension and CKD	Target <130/80 mm Hg (<140/80 in elderly patients)	RAS inhibitors are considered first-line medications due to their ability to not only control BP but also reduce albuminuria. CCBs and diuretics can be added	
Hypertension and HF	Target between 130/80 mm Hg and 120/70 mm Hg	In patients with established HFREF, using RAS blockers, β -blockers, and mineralocorticoid receptor antagonists has effectively improved clinical outcomes. The evidence for diuretics is primarily limited to symptomatic improvement. CCBs are indicated only when BP control is inadequate	For the management of HFREF, the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril-valsartan is recommended as an alternative to angiotensin-converting enzyme inhibitors (ACEIs) or ARBs, even in hypertensive individuals. While the optimal treatment strategy for HFpEF is not yet fully understood, a similar treatment approach can also be considered for HFpEF patients

For hypertension with CAD/CKD/stroke, BP should be reduced if $\geq 140/90$ mm Hg and treated with the goal of achieving a target <130/80 mm Hg (<140/80 in elderly patients); hypertension and HF, BP should be reduced if $\geq 140/90$ mm Hg and treated with the goal of achieving a target <130/80 mm Hg, but >120/70 mm Hg

Table 2: Comparison of cilnidipine and amlodipine in outcomes for urinary protein creatinine ratio

	Cilnidipine	Amlodipine	p-value
Urinary protein/creatinine ratio (mg/gm)	1308.6 $\pm$ 121.2	1881.1 $\pm$ 188.8	$p < 0.05$
Percentage change from baseline	-14.4 $\pm$ 5.6%	+13.9 $\pm$ 7.7%	–

like cilnidipine, with angiotensin receptor blockers (ARBs) (telmisartan) is recommended by the Research Society for the Study of Diabetes in India (RSSDI) for improved cardiovascular and renal protection while avoiding the risks of cardiovascular events and hyperglycemia associated with β -blockers or diuretics.¹³

CALCIUM CHANNEL BLOCKERS (CCBs) ARE ONE OF THE MAJOR CORNERSTONES IN HYPERTENSION THERAPY

Calcium channel blockers (CCBs) inhibit calcium currents through L-type calcium channels and are potent vasodilators. Some CCBs have the capacity to block additional calcium channels. Dihydropyridines CCBs (e.g., nifedipine, amlodipine, azelnidipine, cilnidipine, efonidipine) are among the most widely employed drugs managing hypertension and CVD.¹⁴

Calcium channel blockers (CCBs) are safe for senior patients who regularly have large-vessel stiffness and are beneficial in managing hypertension in any age group.^{15,16} CCBs are very effective at reducing BP and decreasing the risk of stroke and CVD. When additional BP lowering is necessary to meet strict targets, CCBs may be added, even in heart failure or CKD.¹⁷

Dihydropyridines, which were first introduced during the 1960s, have undergone numerous modifications aimed at enhancing their effectiveness and ensuring their safety. Cilnidipine, a newer dihydropyridine, can block both L- and N-type calcium channels. Cilnidipine selectively inhibits the SNS because N-type calcium is transported in the brain and along the nerve. Clinical research and animal experiments have shown that cilnidipine has reno-protective, neuroprotective, and cardioprotective properties.¹⁵

CILNIDIPINE IN THE MANAGEMENT OF HYPERTENSION

For many years, CCBs, which have two subclasses, dihydropyridines and nondihydropyridines, have been a mainstay of hypertension treatment. Dihydropyridines are the most often utilized CCBs for the management of CVD. Different generations of dihydropyridines (e.g., nifedipine, nicaidipine, felodipine, amlodipine, azelnidipine, cilnidipine, efonidipine) that were developed based on variations in their chemical structures offer heterogeneity in these agents' actions.¹⁵

Cilnidipine, being 4th generation CCB with L/N blocking properties, has prolonged antihypertensive properties and is one of the main antihypertensive drugs now in use. A CCB of the L/N type, cilnidipine reduces BP through potent vasodilation and suppression of the SNS at the peripheral sympathetic nerve endings. It lowers systolic as well as diastolic blood pressure, but it has no effect on pulse rate (PR) or plasma catecholamine levels.¹⁷

A study evaluating the hypertensive effects of cilnidipine found that cilnidipine significantly reduced the 24-hour blood pressure by 6.5 ± 1.7 mm Hg systolic ($p < 0.01$) and 5.0 ± 1.1 mm Hg diastolic ($p < 0.01$).¹⁸

The Ambulatory Blood Pressure Control and Home Blood Pressure (Morning and Evening) Lowering By N-Channel Blocker Cilnidipine (ACHIEVE-ONE), a significant clinical study on patients ($n = 2319$) with essential hypertension, looked at how cilnidipine affected BP and PR in real-world situations. The study spanned 12 weeks and aimed to evaluate the outcomes of cilnidipine treatment in this patient population. Clinic SBP was significantly lowered after a 12-week treatment of cilnidipine, reduced by 19.6 mm Hg from the baseline value of 155.0 mm Hg. Similarly, morning SBP showed a notable decrease of 17.0 mm Hg from 152.9 mm Hg. Cilnidipine has been efficacious significantly in reducing BP and PR in patients with hypertension, particularly in the morning and in cases of higher BP and PR levels. These findings highlight the effectiveness of cilnidipine in managing hypertension in both clinical and home settings.¹⁹

Sympathetic nerve activity is one of the main factors implicated in the development

and complications of hypertension, which is a multifactorial and multifaceted disease. Plasma norepinephrine/epinephrine enhances procoagulant platelet activation, increases the risk of coronary thrombosis and is an important prognostic marker of mortality in congestive heart failure (CHF).²⁰

Cilnidipine decreases norepinephrine release from sympathetic nerve endings, causing vasodilation, a reduction in heart rate, and an improvement in renal blood flow (Fig. 1).²¹

According to reports, it is beneficial in hypertensive individuals with morning hypertension, which is caused by sympathetic nerve overactivity. Cilnidipine was also found to significantly lower BP in hypertensive individuals with aberrant nocturnal BP, particularly during sleep when enhanced sympathetic nerve activation takes place. It is helpful in the long-term management of cardiovascular issues since it also reduces vascular endothelial dysfunction.¹⁷

Novel mechanisms of reno-protection by cilnidipine: The N-type calcium channel is inhibited by cilnidipine, which blocks renal sympathetic nerve activity and causes vasodilation of the efferent arterioles. This mechanism can potentially reduce glomerular hypertension, prevent the development of microalbuminuria, and slow the progression of renal disease.¹⁷

Cilnidipine induces dilation of the efferent arteriole, reducing damage to the glomeruli and suppressing podocyte injury. By reducing oxidative stress, it exerts a reno-protective effect. Cilnidipine exerts higher antioxidant activity than amlodipine²² and better regulation of proteinuria when compared with L-type CCB.^{17,22}

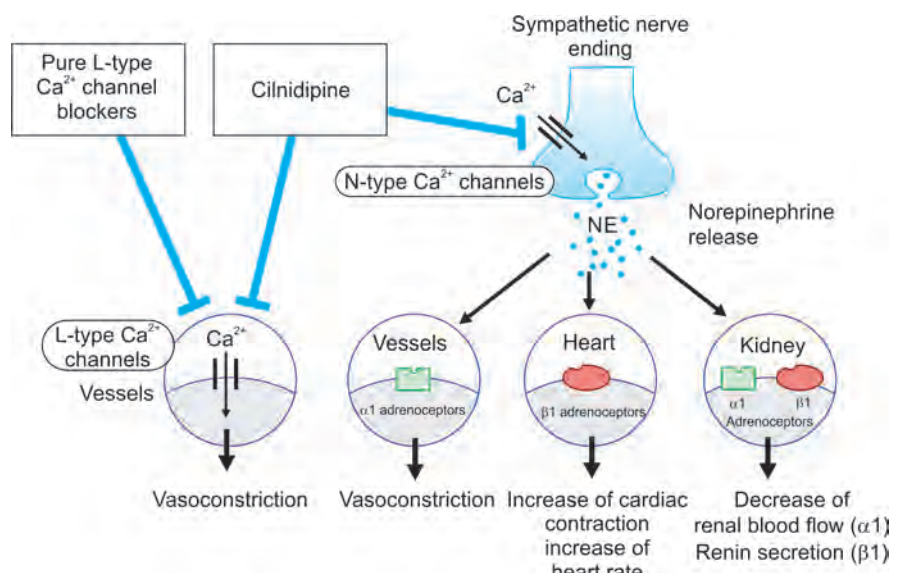


Fig. 1: L/N dual action of cilnidipine¹⁵

Pharmacokinetics of Cilnidipine

Cilnidipine has considerable long-lasting antihypertensive effects and has good oral absorption. Drug concentrations after oral administration reach their maximum at 1.8–2.2 hours and have a half-life of 7.5 hours. Cilnidipine exhibits an extended duration of antihypertensive action while having a shorter half-life. Because of its high protein binding (98%) and high lipophilicity, cilnidipine's effect is prolonged.¹⁷

The benefit of cilnidipine is that it lessens reflex tachycardia and reduces pedal edema.²² Up to 15% of patients develop pedal edema with amlodipine, possibly leading to discontinuation. When compared with amlodipine, cilnidipine causes a lesser incidence of pedal edema. Further studies have also documented the resolution of amlodipine-induced pedal edema with cilnidipine.^{23–25} This effect could be due to suppressing sympathetic activity and reducing plasma renin and vasopressin (VAS) levels.²⁶ Cilnidipine has also been shown to enhance insulin sensitivity in studies.²²

Cilnidipine Potential for Treatment of Hypertension with Comorbidities

Inhibiting sympathetic nerve activation by blocking the N-type channel by cilnidipine may have reno-protective or cardioprotective effects that can help manage comorbidities and hypertension. Stroke, heart failure, and renal failure are complications of hypertension that have been linked to abnormal sympathetic activity. Abnormal circadian rhythm is also a hypertension-linked comorbidity. Sympathetic nerve inhibition *via* N-type channel blockade by cilnidipine may also help treat hypertension comorbidities. Depending on the patient's circadian variation, cilnidipine can lower nighttime BP more than daytime BP in the riser's group and the dippers. The daytime BP decrease is greater than seen in the nighttime; this positive effect may be intended to partially correct the circadian rhythm. Reducing abnormal sympathetic activity by cilnidipine can potentially reduce cardiovascular events. Potent coronary vasodilation and moderate reflex-induced sympathetic stimulation correlate to avoidance of increased heart rate and cardiac contractility by cilnidipine in HF animal model.²⁷

In individuals with hypertensive heart disease (HHD), cilnidipine reduces cardiac sympathetic overactivity by blocking N-type calcium channels and enhances LV diastolic function.²⁸

Telmisartan, an ARB, and cilnidipine are useful antihypertensive drugs with

unique properties for preventing vascular complications. A study was conducted to compare the long-term effects of BP control using cilnidipine or telmisartan on markers for vascular complications in hypertensive patients, in which intima-media thickness (IMT) of the carotid arteries, urinary albumin excretion (UAE), and pulse wave velocity (PWV) were measured to assess the extent of vascular damage before and after treatment. A significant improvement was observed in both UAE (a reduction in intraglomerular pressure by telmisartan or by efferent arteriolar dilation by cilnidipine) and PWV (improvement in lipid metabolism by telmisartan or the reduction in plasma aldosterone by cilnidipine in telmisartan and cilnidipine group, but significant reduction in IMT only in the cilnidipine group).²⁹

Lesser pedal edema has been reported with cilnidipine compared to other CCBs, especially amlodipine.^{24–26} It can be of practical significance to add antihypertensive medications to the regimens of hypertensive patients with heart failure who also have disease-related pedal edema.

Proteinuria is a recognized cardiovascular risk factor and a predictor of the subsequent progression of renal disease. Proteinuria was associated with a threefold rise in mortality in the Framingham cohort and was also linked with other risk factors for CVD.³⁰ Proteinuria significantly predicted total mortality and all cardiovascular endpoints in a subanalysis of the Systolic Hypertension in Europe (Syst-Eur) study.³¹

According to experimental and clinical findings, reduced proteinuria in CKD protects against renal and cardiovascular risk. Antiproteinuric antihypertensive medications are therefore thought to be more effective for people with renal disease.³¹ In hypertensive patients, cilnidipine dilates both efferent and afferent arterioles, which has the potential to protect the kidneys by reducing the excretion of liver-type fatty acid-binding protein (L-FABP), 8-hydroxy-20-deoxyguanosine, and urine albumin to a greater extent than amlodipine, this effect could also be through its additional antioxidative properties.¹⁷

In hypertensive patients with metabolic syndrome, cilnidipine is found to increase glucose tolerance and insulin sensitivity without changing body weight or adiposity.²⁸

Cilnidipine has better antiproteinuric activity than amlodipine as it can block N-type calcium channels and the resultant sympathetic nerve inhibition. Due to this, in hypertensive patients with renal disease and significant proteinuria and who are already under a treatment regime with an

RAS inhibitor, the addition of cilnidipine can be more effective than amlodipine. The combined treatment approach comprising cilnidipine and an ARB plays a vital role in not only achieving stringent BP control but also preventing the advancement of kidney disease.¹⁹

To patients who have already undergone hemodialysis, intradialytic hypertension associated with sympathetic overactivity is one of the weak prognostic markers. Pre- and post-dialytic SBP are reduced by cilnidipine, and it may also attenuate intradialytic SBP increase.³²

In a large population cohort, it was found that an elevation in resting PR from <70 bpm to over 85 bpm over 10 years was linked with a 1.9-fold increased risk of death from IHD. This highlights the significance of an elevated PR as a risk factor for cardiovascular events. PR lowering effect of cilnidipine is reported in several studies.¹⁹

Hypertension is one of the major contributing factors to the occurrence and recurrence of stroke, making it a crucial risk factor associated with this condition. Research investigating the administration of antihypertensive medications to lower BP and prevent recurrent strokes has consistently demonstrated a decreased risk of stroke recurrence. CCBs are advised as the drug of preference for post-stroke patients.³³ Treatment with cilnidipine lowers home BP in the morning and evening (when the incidence of stroke is higher). It has shown a positive antihypertensive impact on post-stroke hypertensive patients' home BP, thus reducing cerebrovascular episodes.^{34,35}

Cilnidipine Benefits, Documented by Mega-trials: ACHIEVE-ONE, CARTER, Stroke J, CA-ATTEND, and CA-ATTEND Sub-set Data

ACHIEVE-ONE Trial

Home morning hypertension raises the risk of cardiovascular problems and chronic renal disease. Additionally, a high PR raises the risk of cardiovascular illness and mortality. Therefore, controlling high PR and morning hypertension is crucial for avoiding cardiovascular events. Several studies have demonstrated effective BP reduction, including morning BP and PR, with cilnidipine treatment.³⁴

Cilnidipine has also been reported to significantly reduce BP, particularly when sleeping, in hypertensive individuals with aberrant nocturnal BP and excessive sympathetic nerve activation.¹⁷

The ACHIEVE-ONE trial included patients ($n = 2319$) with essential hypertension and analyzed the effects of the L-N-type Ca

channel blocker cilnidipine on BP and PR assessed at the clinic, at home, and by ABPM for 12 weeks. Cilnidipine significantly decreased BP and PR in hypertensive patients in the clinic and at home, especially in those with high BP and high PR in the morning. This was due to independently lowering BP and PR through neuronal N-type Ca channel blocking (Fig. 2).

Prior to treatment, patients were grouped based on their nocturnal dipping status basis altered circadian rhythms—extreme dippers, dippers, nondippers, or risers. All four groups had decreased 24-hour BP with cilnidipine treatment. The nocturnal dipping status of extreme dippers and risers, who typically have abnormal diurnal patterns, was improved by cilnidipine treatment. Cilnidipine is found

to be more effective than amlodipine for patients with higher BP and PR, especially in the morning. The main conclusions from this study were that cilnidipine effectively decreases BP by directly affecting sympathetic nerve activation and vascular stiffness, as well as indirectly affecting circadian rhythms.²⁸

Although cilnidipine also lowers 24-hour BP by blocking L-type calcium channels in hypertensive patients, it is N-type calcium channel blockage that restores aberrant nocturnal dipping status toward a normal dipping pattern in risers.³⁴

CARTER STUDY

The antiproteinuric effects of cilnidipine vs amlodipine were examined in a cilnidipine vs

amlodipine randomized trial for evaluation in renal disease (CARTER). It includes hypertension patients with renal disease ($n = 339$) who were already under RAS inhibitor treatment.

Regarding the primary endpoint, the cilnidipine group exhibited a significant reduction in the urinary protein/creatinine ratio compared to the amlodipine group. This finding demonstrates that cilnidipine has a more pronounced antiproteinuric effect than amlodipine (Fig. 3).

Compared to the amlodipine group, the urine protein/creatinine ratio was significantly lower in the cilnidipine group (Table 2).

N-type calcium channel blocking by cilnidipine reduces renal sympathetic nerve activity, and the efferent arteriolar vasodilation that results from it protects the glomeruli by

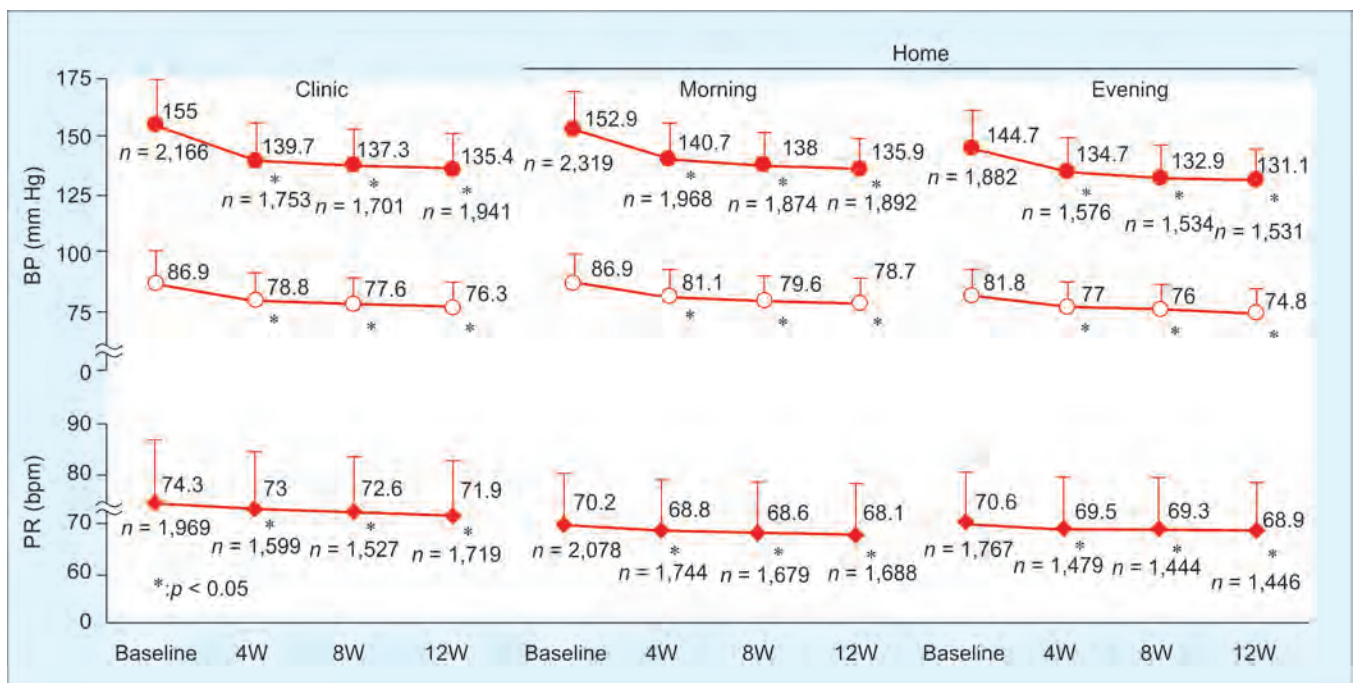
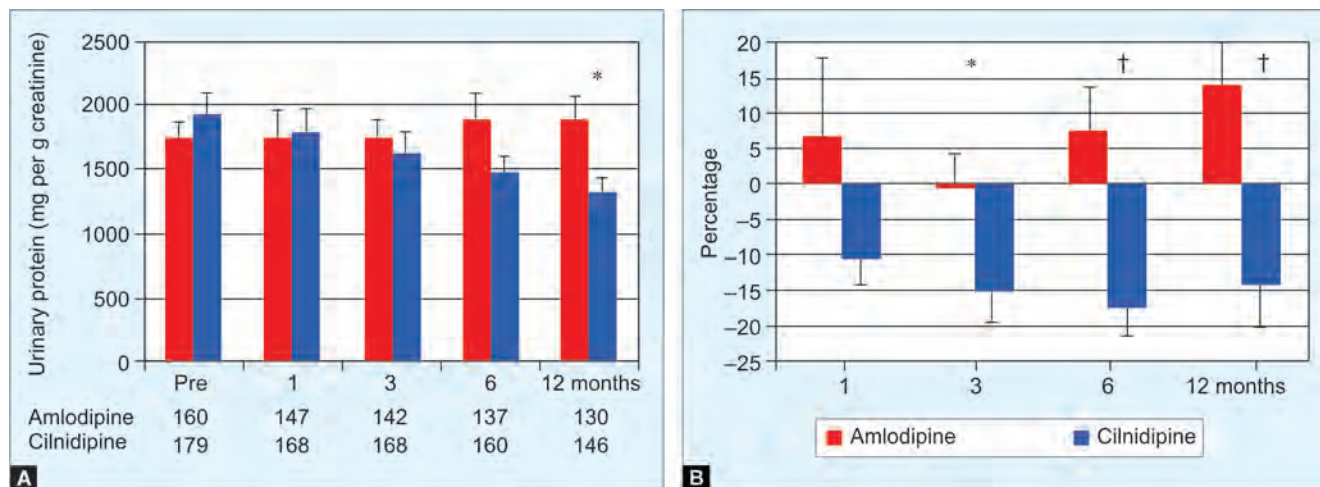


Fig. 2: Variation in BP, pulse rate (PR) at the clinic and home³⁵



Figs 3A and B: Variation in urinary protein/creatinine ratio over the course of treatment³³

reducing glomerular hypertension. CARTER's study suggests that adding cilnidipine to an RAS inhibitor is more efficacious than amlodipine in inhibiting the progression of proteinuria in hypertensive patients with kidney disease beyond its BP-lowering effects.¹⁹

CILNIDIPINE EXHIBITS LOWER BP VARIABILITY IN CHRONIC CEREBROVASCULAR DISEASE

There is an association between BP fluctuations and an increased risk of damage to target organs, and effective antihypertensive medication treatment can minimize BP variability and lower the risk of stroke in patients with cerebrovascular events. A study was conducted in which 24-hour BP fluctuation was evaluated in patients with a history of cerebrovascular disease ($n = 309$) and who were under treatment with CCBs, angiotensin-converting enzyme inhibitors, β -blockers, ARBs, or CCBs.

Daytime BP variability was significantly higher ($p < 0.05$) in patients with cerebrovascular disease treated with blockers (14.3 ± 3.1) compared to those treated with ARBs (11.5 ± 3.1) or CCBs (12.6 ± 3.4). The study implies that ARBs and CCBs, particularly cilnidipine, may be more beneficial for BP management in individuals with cerebrovascular disease than β -blockers due to lower BP fluctuation.³⁵ Nishioka et al.³⁵ investigated the 24-hour BP variability in 309 patients with a history of cerebrovascular disease and who were treated with antihypertensive drugs from four different classes—angiotensin-converting enzyme inhibitors, ARBs, blockers, or CCBs. BP variability was found to be higher in the group of patients under treatment with β blockers (14.3 ± 3.1) compared to those who were under treatment with an ARB (11.5 ± 3.1) or CCBs (12.6 ± 3.4) ($p < 0.05$). Furthermore, blockade of N-type calcium channels upon treatment with ARBs and cilnidipine demonstrated a more frequent association with lower BP variability ($p = 0.0202$ and 0.0467 , respectively). These data imply that ARBs and CCBs, particularly cilnidipine among CCBs, may be better options for controlling BP in people with cerebrovascular disease.

THE CAROTID ATHEROSCLEROSIS-ANTIHYPERTENSIVE TREATMENT TRIAL, EFFECT OF N-TYPE CCB FOR CEREBROVASCULAR DISEASE (CA-ATTEND) STUDY

Guidelines from 2013 ESH/ESC strongly recommended CCBs as class-I antihypertensive

medications for post-stroke hypertensive patients. Japanese Guidelines³⁶ for the Management of Stroke 2015 and the Japanese Society of Hypertension Guidelines³⁷ for the Management of Hypertension 2014 (JSH2014) also advised CCBs as a grade A option for hypertension treatment.

The CA-ATTEND trial is a large-scale prospective post-marketing surveillance research of cilnidipine medication efficacy and safety in post-stroke hypertension patients ($n = 2667$). In Japanese post-stroke hypertensive patients, cilnidipine medication proved effective against uncontrolled BP and was well-tolerated. During cilnidipine medication, the percentage of patients with well-controlled clinic BP increased from 21.5 to 65.3%.³⁵

Common carotid IMT and its progression may act as a marker for atherosclerosis and further risk of cerebral events such as incident stroke and recurrent stroke, as well as cardiovascular events. Similarly, common carotid inter-adventitial diameter (IAD) is reported as a stronger predictor of ischemic stroke. Subset of CA-ATTEND study patients ($n = 603$) were under observation for 12 months to analyze the efficacy of cilnidipine on the regression of atherosclerosis in post-stroke hypertensive patients. Cilnidipine promoted the common carotid IMT regression (-0.09 mm, 95% CI -0.13 to -0.05), especially in the thick group ($n = 156$). Cilnidipine also reduced the IAD in both normal (-0.14 mm, 95% CI -0.22 to -0.05) and thick groups (-0.12 mm, 95% CI -0.21 to -0.03).³⁸

14 POINTS CONSENSUS ON POTENTIAL OF CILNIDIPINE IN HYPERTENSION WITH COMORBIDITIES

- Consensus 1: In hypertension management, along with control of the numbers, end-organ protection is also crucial; most studies and guidelines support this as well.
- Consensus 2: Increased BP is a strong and independent risk factor for CAD, CKD, and heart failure development. Despite the high prevalence, our country's awareness, treatment, and control rates remain low, leading to increased vascular and renal complications in the Indian population.
- Consensus 3: The benefits of cilnidipine due to its N-channel blocking potential have been well documented in ACHIEVE-ONE, CARTER, Stroke J, CA-ATTEND, and CA-ATTEND Subset.

- Consensus 4: Cilnidipine is a 4th generation CCB, which can block both N and L-type calcium channels, thus having improved benefits than the older CCBs.
- Consensus 5: Cilnidipine has been shown to offer smooth and sustained control 24-hour BP control [HBPM, clinic blood pressure monitoring (CBPM), ABPM].
- Consensus 6: In studies, cilnidipine has been shown to reduce nocturnal BP, improve the dipping status, and have beneficial effects on morning and nocturnal hypertension; these benefits are due to the sympatholytic activities of the molecule due to N-channel blockade.
- Consensus 7: Cilnidipine does not cause reflex tachycardia [improves baroreflex sensitivity (BRS), $\downarrow$ SNS].
- Consensus 8: Cilnidipine decreases proteinuria by decreasing the intraglomerular pressure, dilates the afferent and efferent arterioles equally, has antioxidative properties, inhibits renal RAS, and suppresses podocyte injuries.
- Consensus 9: Cilnidipine causes minimal pedal edema, $<2\%$ vs amlodipine, which causes pedal edema up to 11%.
- Consensus 10: It is a lipophilic molecule, has a high volume of distribution, and hence has been shown in studies to have 24-hour action.
- Consensus 11: Metabolically friendly, long-acting, although half-life is 2–8 hours, usual dose 5–10 mg daily, maximum dosage is 20 mg per day.
- Consensus 12: Cilnidipine improves cerebral blood flow, is shown to be beneficial in hypertension management in poststroke patients, and reduces carotid intima-media thickness (cIMT) and IAD.
- Consensus 13: The young Indian population exhibits high sympathetic activity due to stressed lifestyles. Sympatholytic antihypertensive drugs, such as cilnidipine, have better outcomes and should be preferred in hypertension management.
- Consensus 14: Cilnidipine, along with telmisartan, is a good choice of combination therapy in patients with essential hypertension and diabetic hypertension. Most international guidelines also recommend combination therapies to be initiated in hypertensive patients.
- Consensus 15: Hypertension management in our country requires the creation of more awareness and education among the people, not only about the disease but also for its monitoring and control.

CONCLUSION

The consensus discussion concluded that cilnidipine, the novel CCB, is preferred in

hypertension management as it can block L- and N-type Ca^{2+} channels. Cilnidipine is a cardio, reno- and neuroprotective CCB as is seen through well-documented studies. It is well tolerated and has consistent, effective, and smooth control of 24-hour BP as evaluated by HBPM, ABPM, and CBPM. It does not cause reflex tachycardia, reduces proteinuria by decreasing intraglomerular pressure in both afferent and efferent arterioles of glomeruli, with a low incidence of pedal edema and has anti-aldosterone, anti-atherosclerotic, anti-renin, and anti-inflammatory effects. It decreases insulin resistance and is superior to amlodipine in hypertensive patients in multiple ways. For combination therapy, cilnidipine with telmisartan is superior and offers tight control of hypertension in patients with comorbidities.

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An Unusual Case of Treatment-naïve HIV Patient Presenting with Acute Pancreatitis in Sepsis with Infective Endocarditis and Bilateral Pulmonary Thromboembolism



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Received: 14 June 2023; Accepted: 04 July 2023

ABSTRACT

Acute pancreatitis is seen in patients with human immunodeficiency virus (HIV) as a result of antiretroviral drug therapy and hypertriglyceridemia. Thrombotic complications are known in patients of HIV as a result of endothelial dysfunction, and right-sided infective endocarditis (IE) is seen in HIV patients mostly due to intravenous (IV) drug abuse. However, the occurrence of acute pancreatitis with sepsis, IE, and bilateral thromboembolism in the same patient is rare. Here, we report this case of a treatment-naïve nondrug abuser HIV patient with acute pancreatitis in sepsis, IE, and bilateral pulmonary thromboembolism who recovered completely with treatment.

Journal of the Association of Physicians of India (2024); 10.59556/japi.71.0447

INTRODUCTION

Acute pancreatitis is a serious medical condition that is characterized clinically by abdominal pain, nausea, vomiting, and biochemically by elevations of lipase and/or amylase. It has a higher incidence in human immunodeficiency virus (HIV) patients as compared to the general population. Apart from the usual causes (alcohol, gallstones, and hyperlipidemia), drug toxicity secondary to nucleoside reverse transcriptase inhibitors (NRTIs) and opportunistic infections represented the most frequent causes in HIV patients. Several cases of venous thrombosis with an increased incidence of venous thromboembolic disease have been described in the setting of underlying HIV infection. Hypercoagulability and endothelial cell dysfunction are likely the major factors contributing to increased venous thromboembolism. People living with HIV/AIDS (PLHA) tends to exhibit deficiencies in anticoagulant proteins, such as protein S, protein C, heparin cofactor II, and antithrombin. Right-sided infective endocarditis (IE) is also seen in PLHA and is mostly associated with intravenous (IV) drug abuse. Other causes are central venous catheters, implantable electronic cardiac devices, systemic infections, and congenital heart disease (CHD). We hereby report this case of treatment-naïve nondrug abuser HIV patient presented with acute pancreatitis with sepsis complicated by right-sided IE leading to acute tricuspid regurgitation (TR) and bilateral pulmonary thromboembolism.

CASE DESCRIPTION

A 33-year-old lady with no known comorbidities presented to us with chief complaints of abdominal pain for the last 7 days, abdominal distention and high-grade fever for the last 4 days, multiple episodes of vomiting since last 2 days, and breathlessness for 1 day. The patient was recently diagnosed to be HIV positive and was not yet started on treatment. The patient had a history of spontaneous abortion 2 months back at the gestational age of 8 weeks. The patient had no history of high-risk behavior and alcohol intake and was in a monogamous relationship with her husband.

On general examination, the patient was alert, conscious, and oriented to time, place, and person. The patient's BP was 100/60 mm Hg with tachycardia and tachypnea, oxygen saturation of 90% under room air, and the temperature was 100.5°F. Pallor was present; there were no signs of icterus, cyanosis, clubbing, lymphadenopathy, or pedal edema. Cardiovascular system examination examination revealed raised jugular venous pressure (JVP) and pansystolic murmur in the tricuspid area with loud P2. Per abdomen, there was diffuse tenderness with shifting dullness, tender hepatomegaly 3 cm below the right subcostal margin, and bowel sounds were sluggish. A respiratory examination revealed a central trachea with absent breath sounds in the bilateral infraaxillary area.

Electrocardiogram at admission showed sinus tachycardia and chest X-ray showed bilateral pleural effusion (Fig. 1A). Investigations that were done at the time of admission are given in Table 1.

Ultrasonography was done, which showed hepatomegaly, moderate ascites with bulky head and body of pancreas with no retained products of conception. Two-dimensional (2D) echocardiography was done, which showed dilated right atrium and right ventricle, severe TR, ejection fraction = 55–50%, right ventricular systolic pressure of >42, tricuspid annular plane systolic excursion = 2.7 cm, and vegetation on tricuspid valve, no regional wall motion abnormality (RWMA). Venous Doppler of lower limbs was normal. There was no evidence of malignancy elsewhere.

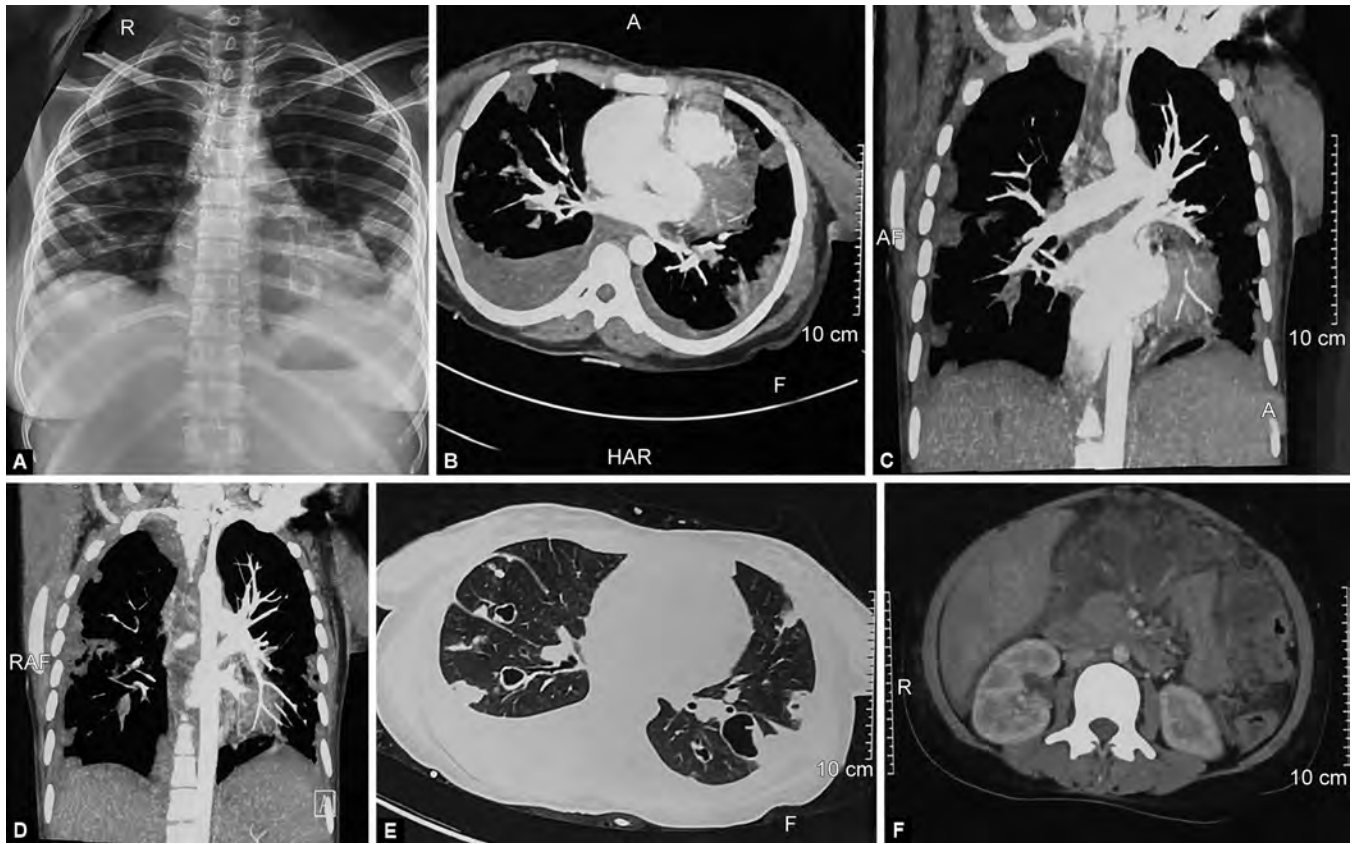
Contrast-enhanced computed tomography (CECT) chest + CT pulmonary angiogram was done, which showed pulmonary thromboembolism in the right apical segmental artery, medial and lateral segmental artery, superior, anterior basal, lateral basal, and posterior basal segmental arteries, left anterior segmental artery, superior lingular segmental artery, bilateral multiple pulmonary infarcts, and multiple cavitary nodules in bilateral lung fields (likely septic emboli) (Figs 1B to E). CECT abdomen showed ascites, thickened peritoneum, and mesenteric fat stranding, likely sequelae to acute pancreatitis with peripancreatic collection of size 7 × 6 × 3 cm (Fig. 1F).

Protein C, protein S, and immunoglobulin 4 levels could not be done as the patient could not afford them.

The patient was initially managed conservatively with IV fluids, IV antibiotics, and bowel rest. The patient improved

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How to cite this article: Bhatia R, Kampani G, Sharma B, et al. An Unusual Case of Treatment-naïve HIV Patient Presenting with Acute Pancreatitis in Sepsis with Infective Endocarditis and Bilateral Pulmonary Thromboembolism. *J Assoc Physicians India* 2024;72(1):96–98.



Figs 1A to F: (A) Chest X-ray showing blunting of bilateral costophrenic angles suggestive of bilateral pleural effusion; (B) Axial section of CT pulmonary angiogram showing hypodensities in branches of bilateral pulmonary arteries and bilateral infarcts in lung parenchyma; (C and D) Coronal sections of CT pulmonary angiogram showing nonenhancing filling defects in segments of bilateral pulmonary arteries and bilateral patches of consolidations s/o pulmonary infarcts; (E) Axial section of CT chest showing multiple cavitary lesions in bilateral lung fields (septic emboli); (F): Axial section of CT abdomen showing ascites, thickened peritoneum and mesenteric fat stranding and peripancreatic collection

partially with antibiotics; her fever decreased, and total leukocyte count (TLC) improved, but continued to be dyspneic. After the 2D echo showed vegetation on the tricuspid valve, antibiotics were added for Infectious endocarditis, and anticoagulation was started in view of pulmonary thromboembolism. The patient responded to the treatment, and her tachycardia and tachypnea settled. She started maintaining oxygen saturation under room air. A repeat echo was done, which showed chordae tendineae rupture of the tricuspid valve. The patient improved with antibiotics and antiretroviral therapy and was discharged. A final diagnosis of PLHA with acute pancreatitis in sepsis with acute TR and bilateral pulmonary thromboembolism secondary to tricuspid valve IE was made.

Discussion

Pancreatitis is a well-described complication of HIV infection and its combination with ART. It is seen mostly with NRTIs such as stavudine and didanosine and sometimes rarely with protease inhibitors causing hypertriglyceridemia. The incidence of acute pancreatitis is higher in HIV patients (6.1/1000

PYs) as compared to the general population (17–30 cases per 100,000 population per year).¹ Studies have shown the incidence to be higher in females gender, and the risk of development of acute pancreatitis increases with lower cluster of differentiation 4 (CD4) counts due to a higher degree of immune suppression, opportunistic infections like cytomegalovirus, tuberculosis, toxoplasma, etc., and usage of medications for prevention and treatment of opportunistic infections like pentamidine, sulfamethoxazole-trimethoprim. It has also been shown that CD4 cells could be important in preventing acinar cell necrosis, which leads to clinical acute pancreatitis.² There are few reports describing HIV infection as primarily causing pancreatitis, and the mechanism underlying is the inflammation caused by viral replication.³ In our patient, in light of the evidence for HIV infection and the exclusion of other causes of acute pancreatitis, it appears that primary HIV infection led to acute pancreatitis with peripancreatic collections.

Human immunodeficiency virus (HIV) infection is associated with a two to 10-fold increased risk of venous thrombosis in

comparison with the general population of the same age. Hypercoagulability and endothelial cell dysfunction are likely the major factors contributing to increased venous thromboembolism in HIV patients.⁴ Other risk factors that demonstrated a strong association with thromboembolism are low CD4⁺ cell count, deficiency of protein S, protein C, heparin cofactor II, and antithrombin.⁵ In a multistate adult and adolescent spectrum of HIV disease surveillance project sponsored by the Center for Disease Control, the incidence of thrombosis was lower for asymptomatic HIV infection (1.3/1,000 person-years) than for persons with clinical AIDS (6.2/1,000 person-years). Rasmussen et al. found that the 5-year risk of venous thromboembolism was 8.0% in IV drug user HIV-infected patients, 1.5% in noninjecting drug use HIV-infected patients, and 0.3 % in the population comparison cohort.⁶ Our patient had a CD4 cell count of 773/mm³, no history of IV drug abuse, and no evidence of deep venous thrombosis; still, she developed bilateral pulmonary thromboembolism, which led to multiple pulmonary infarcts in bilateral lung fields.

Table 1: Investigation tests done at the time of admission and their results

Hemoglobin	8.3 gm/dL	Serum Na ⁺ /K ⁺ Serum Ca ²⁺	143/4.4 mmol/L 8.8 mg/dL
TLC	29,000 per mm ³	Serum amylase	921 U/L
DLC	N 86%, L 10%, E 2%, M 2%	Serum lipase	363 U/L
Platelets	1 lakh per mm ³	D-dimer	5290 ng/mL
Serum urea	271 mg/dL	CD4 cell count	773 cells/mm ³
Serum creatinine	2.5 mg/dL	Antinuclear antibody	Negative
Serum bilirubin	1.1 mg/dL	Antiphospholipid antibodies	Negative
Serum glutamic oxaloacetic transaminase/serum glutamic pyruvic transaminase/alkaline phosphatase	412/123/250 U/L	TORCH profile	Negative
Serum protein	7.2 gm/dL	Cholesterol	140 mg/dL
Serum albumin	2.2 gm/dL	Triglyceride	150 mg/dL
Quantitative C-reactive protein	17 mg/dL	High-density lipoprotein/low- density lipoprotein/very low- density lipoprotein	40/70/50 mg/dL
Serum homocysteine	Normal	Hepatitis B surface antigen, anti- hepatitis C virus	Nonreactive
Blood cultures	Sterile	Sputum for acid-fast bacilli, cartridge-based nucleic acid amplification test	Negative
Ascitic fluid	3,500 cells/mm ³ (90% polymorphs), protein = 3.9 gm/dL, albumin = 1.4 gm/dL		

DLC, differential leukocyte count

The prevalence of IE in HIV-infected patients is mostly attributed to concomitant IV drug abuse, which varies from 6.3 to 34% independently of HAART regimens. Right-sided valves are predominantly affected, and the most frequent agents are *Staphylococcus aureus* (>75% cases), *Streptococcus pneumoniae*, and *Haemophilus influenzae*. Patients with HIV generally have presentations and survival from IE similar to those without HIV (85 vs 93%).⁷ However, right-sided IE in nondrug abusers can occur in conditions including CHD, intracardiac devices, central venous catheters, immunocompromised patients, and community-acquired infections. The most common complications of right-sided IE are valvular insufficiency, abscess formation, and septic pulmonary embolism. Pulmonary involvement occurred in 80% of these cases

and varied from minor atelectasis to large infiltrates, pleural exudates, and cavitation, generally involving the lower lobes.⁸ There was no history of IV drug abuse, cardiac devices, or CHD in our patient; she was in sepsis that caused the tricuspid valve IE, which led to septic emboli and the formation of cavitary lesions in bilateral lungs; also, the IE caused the rupture of chordae tendineae resulting into acute TR. The patient was managed conservatively with IV antibiotics and anticoagulation, and she recovered completely. Organisms could not be isolated as the patient had already received antibiotics before blood cultures were drawn.

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Digital Gangrene as a Paraneoplastic Manifestation of Peripheral T-cell Lymphoma Not Otherwise Specified Type

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Received: 03 May 2023; Accepted: 02 June 2023

ABSTRACT

Background: Peripheral T cell lymphoma (PTCL), not otherwise specified (NOS) is a heterogeneous group of predominantly nodal T cell lymphomas that generally presents with lymphadenopathy with or without extra nodal involvement. Acral vascular syndrome clinically presents as digital ischemia with Raynaud's phenomenon and acral cyanosis. Although, this condition is commonly associated with connective tissue disorder, smoking and vasculitis, its association with lymphoid malignancy is very rare. Here, we present a case report of a patient with digital gangrene of all toes and fingers as a presenting symptom of PTCL-NOS.

Case description: A 62 year old male presented with digital ischemia associated with pain, low grade fever, loss of appetite and significant weight loss of 6 kilograms over a period of 3 months. On examination, he was found to have bilateral inguinal and axillary lymph nodes with gangrenous changes over toes and fingers but peripheral pulses were palpable. On evaluation he had anemia, elevated ESR and CRP. CT angiogram revealed thinned out digital arteries with multifocal areas of narrowing. Patient was screened for other causes of digital gangrene and was tested negative for ANCA, ANA, cryoglobulins and viral markers. Lymph node biopsy with IHC was suggestive of peripheral T-cell lymphoma-NOS and was started on CHOP regimen. Lymph nodes size decreased and gangrenous changes resolved.

Conclusion: Though digital ischemia is a rare paraneoplastic presentation of lymphoma, it should be considered if there is a rapid progression of gangrene. Early initiation of chemotherapy may result in the reduction of further progression of digital gangrene and thus prevent permanent disability. In our patient, progression of gangrene was prevented even though it was an aggressive variant of T cell lymphoma.

Journal of the Association of Physicians of India (2024): 10.59556/japi.71.0370

INTRODUCTION

Acral vascular syndrome (AVS) clinically presents with manifestations of digital ischemia—Raynaud's phenomenon, acrocyanosis, and digital gangrene.¹ The presentation of digital ischemia has a broad differential diagnosis. This condition is commonly associated with smoking, autoimmune connective tissue diseases, vasculitis, antiphospholipid syndrome, atherosclerosis, hemostatic conditions, chemotherapeutic and vasoconstrictive drugs, and, very rarely, cancer with a prevalence of paraneoplastic AVS (PAVS) of 2.2–8%.^{1,2}

Paraneoplastic syndromes are symptoms that occur at sites distant from a tumor or its metastases. Paraneoplastic syndrome with vascular involvement was first described by Trousseau in 1865.³ The coexistence of digital ischemia and carcinoma was first reported by O'Connor in 1884.⁴ PAVSs are reported in solid tumors and very rarely in hematological malignancies. The possible mechanisms of digital ischemia associated with cancer are vasospasm, vasoconstrictor overproduction, vasculitis, immune complex, or drug toxicity.² Diagnosis mainly depends on the clinical symptoms, including pain, permanent digital

blanching or cyanosis, and desquamation or ulceration of the fingers. The association of paraneoplastic cutaneous vasculitis and non-Hodgkin's lymphoma (NHL) was first reported in 1995,⁵ whereas the association of digital gangrene with Lennert lymphoma, a variant of peripheral T-cell lymphoma—not otherwise specified (PTCL-NOS), was reported in 2021.⁶ The case report of digital gangrene in a patient with PTCL-NOS was published in 2022.⁷

CASE DESCRIPTION

A 62-year-old male, a chronic smoker, and a farmer by occupation presented to our Medicine Department with complaints of severe pain over both hands and feet over a period of 2 months, following which he developed blackish discoloration over all toes, left index, and right ring finger for the last 10 days (Fig. 1). He had no claudication symptoms and no history of Raynaud's phenomenon. Initially, he had pain in both feet and 1 week later, he also developed severe pain in both his hands, for which he consulted a nearby medical practitioner and was prescribed antiplatelet, pentoxifylline and was advised to quit smoking. In spite of smoking cessation and the use of these medications, his symptoms worsened. He had a loss of appetite and a significant loss of weight of 6 kg over a 3-month period. He also had low-grade fever during the 2-month period, but there was no history of night sweats. He had a history of fatigue but no history of skin rashes, joint pain, cough, abdominal pain, or weakness of limbs. The patient was a smoker (30 pack years), but he had stopped 2 months back. He had no previous comorbidities. He



Figs 1A and B: Gangrenous changes over all toes, left index, right index, and ring fingers

¹Final Year MD General Medicine Postgraduate;

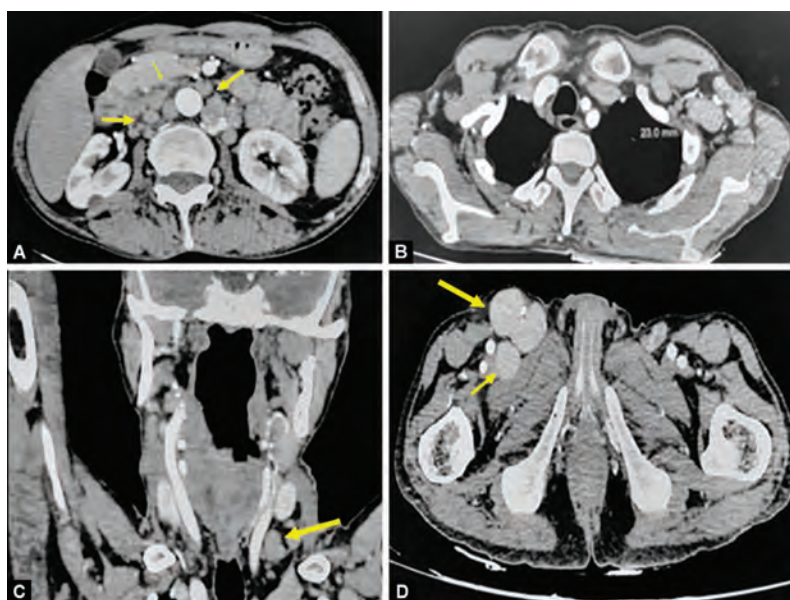
²Professor of Medicine; ^{3,4}Assistant Professor of Medicine, Department of General Medicine; ⁵Professor and HOD, Department of Medical Oncology, Coimbatore Government Medical College & Hospital; ⁶Consultant Hematopathologist, GKNM Hospital, Coimbatore, Tamil Nadu, India; *Corresponding Author

How to cite this article: GS M, T G, G B, et al. Digital Gangrene as a Paraneoplastic Manifestation of Peripheral T-cell Lymphoma Not Otherwise Specified Type. J Assoc Physicians India 2024;72(1):99–102

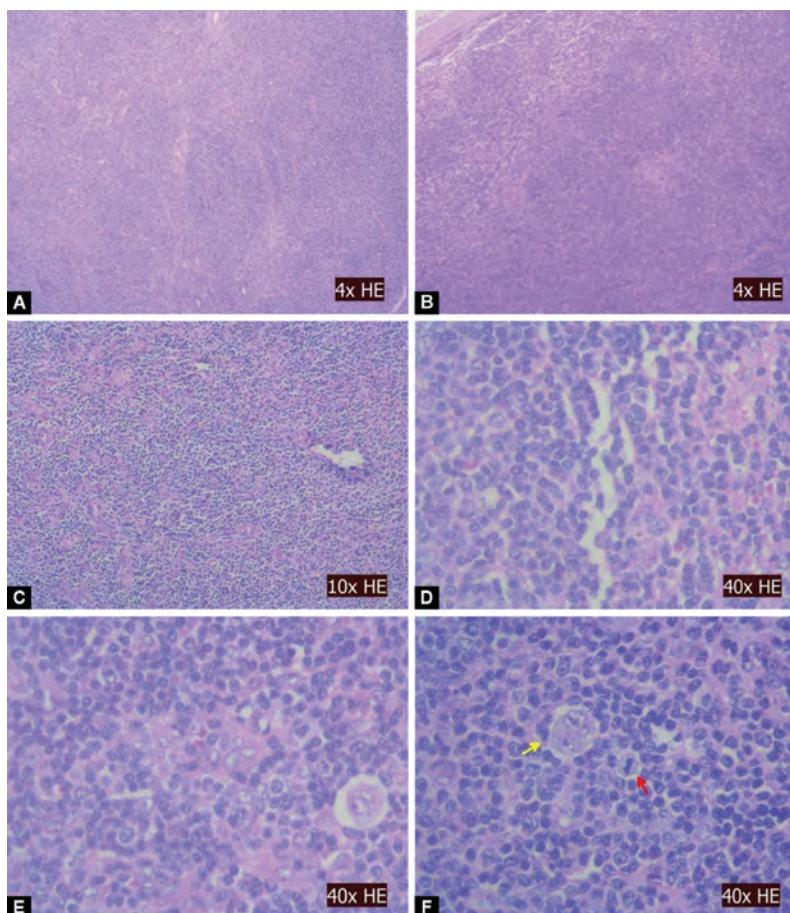
denied drug intake except for the drugs that were prescribed for his present complaints. On examination, the patient was febrile (100°F), pale with bilateral inguinal (three discrete nodes with the largest measuring 2 × 2 cm) and axillary lymph node measuring 2 × 1 cm. The lymph nodes were firm, nontender, and mobile. He had a desquamation of skin over his palms and feet with multiple small ulcers. He had gangrenous changes over all his toes up to the metatarsophalangeal joint, right ring and index fingers, and left index finger extending up to the distal interphalangeal joint. Pulse rate was 92/minute, regular rhythm, normal volume, no specific character, no radio radial or radio femoral delay, and felt equally in all palpable peripheral vessels. Blood pressure was 110/70 mm Hg, and respiration rate was 16/minute with normal room air saturation. System examination was normal, with no organomegaly. A complete hemogram showed microcytic hypochromic anemia with hemoglobin of 9.9 mg/dL, elevated total count (14,300 cells/mm³) with a neutrophilic predominance, and platelet count of 4,40,000 cells/mm³. His random blood sugar value was 104 mg/dL; coagulation profile, liver, renal parameters, and lipid profile were within normal limits. Erythrocyte sedimentation rate (132 mm/hour), lactate dehydrogenase (480 u/L), and uric acid (7 mg/dL) were elevated with a C-reactive protein value of 5.8 mg/L. The patient tested negative for human immunodeficiency virus, syphilis, and hepatitis B and C viruses. The rheumatoid factor was negative. Computed tomography (CT) angiogram showed thinned-out digital arteries and multifocal areas of narrowing were noted in digital arteries in both hands and feet (Fig. 2). Bilateral paraaortic, aortocaval, celiac, bilateral level two, and three cervical lymph nodes were present on imaging, but there was no hepatosplenomegaly (Fig. 3). Two-dimensional echocardiogram showed normal valve and normal left ventricular systolic function with an ejection fraction of 60%. Antineutrophilic

cytoplasmic antibody, antinuclear antibody, antiphospholipid antibodies, and cryoglobulins were negative. A lymph node biopsy was taken from the left axilla, which showed diffusely effaced architecture, interfollicular

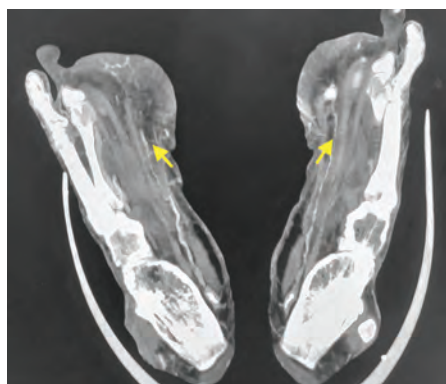
infiltration of medium-sized atypical cells, and scattered multinucleated large cells with brisk mitotic activity; these features were suggestive of high-grade NHL (Fig. 4). We then proceeded with immunohistochemistry (IHC)



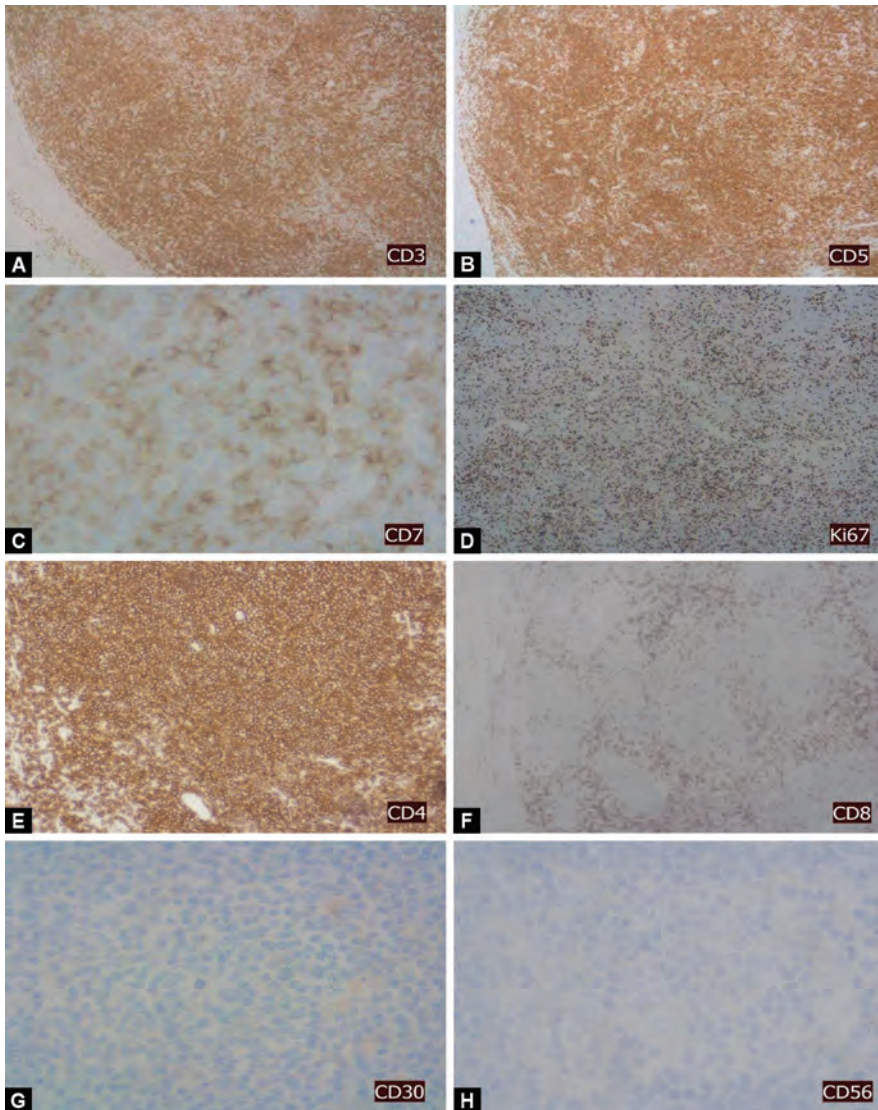
Figs 3A to D: Bilateral paraaortic, aortocaval, celiac, axillary, and bilateral level two, and three cervical and bilateral inguinal lymph nodes showing homogenous contrast enhancement



Figs 4A to F: Lymph node biopsy was taken from the left axilla, which showed diffusely effaced architecture, interfollicular infiltration of medium-sized atypical cells, scattered multinucleated large cells with brisk mitotic activity suggestive of high-grade NHL



Figs 2A and B: Thinned-out digital arteries on CT angiogram with multifocal areas of narrowing



Figs 5A to H: Immunohistochemistry (IHC) showing LCA—positive, CD3—positive, CD7—weak positive, CD5—strong positive, CD4—positive (CD4 >> CD8), Ki67—focally high up to 80% with CD 30, 15, 56, 10, and BL6 negative suggestive of PTCL–NOS type



Figs 6A and B: Regression of gangrenous changes after chemotherapy

which revealed leucocyte common antigen (LCA)—positive, cluster of differentiation (CD) 3—positive, CD7—weak positive, CD5—strong positive, CD4—positive (CD4 >> CD8), Ki67—focally high upto 80% suggestive of

PTCL–NOS type (Fig. 5). Patient had prognostic index score of 4—high risk. The patient had no bone marrow involvement. He was diagnosed as a case of high-grade NHL—PTCL–NOS type with AVS as a paraneoplastic manifestation.

He was started on a CHOP regimen—*injection* cyclophosphamide 1050 mg in 500 mL, 5% dextrose over 2 hours (750 mg/m²), *injection* adriamycin 70 mg in 100 mL normal saline over 15 minutes (50 mg/m²), *injection* vincristine 2 mg intravenous bolus (1.4 mg/m²), T. prednisolone 100 mg for 5 days, and was also started on antiplatelets and morphine for pain relief. After the first cycle of chemotherapy, the progression of gangrene halted, and after two cycles of chemotherapy, gangrenous changes resolved, and lymph node size decreased (Fig. 6). As of now, the patient has completed four cycles of chemotherapy, and he is under regular follow-up.

DISCUSSION

The patient with AVS may present with pain, permanent digital blanching or cyanosis, and desquamation or ulceration of the fingers. Digital gangrene in patients with age greater than 50 years at the time of presentation and poor response to vasodilating agents may indicate an underlying malignancy.^{8,9} In contrast to primary rheumatologic disorders with digital ischemia, which occur more frequently in young women, these conditions occur with equal frequency in both men and women.⁸ Our patient is a chronic smoker. Hence, Beuger's disease [thromboangitis obliterans (TAO)] was considered. However, it usually occurs in young male tobacco smokers and manifests as nonatherosclerotic segmental inflammatory thrombosis of the distal upper and lower limb arteries. Also, he did not have the angiographic findings suggestive of TAO and had rapid progression of symptoms even after cessation of smoking. He had no other predisposing factors for the occurrence of peripheral arterial disease except smoking. He had no history of claudication pain, and his angiography did not reveal atherosclerotic plaques. Hence, peripheral arterial disease was ruled out. There was no clinical history suggestive of connective tissue disorders, antiphospholipid syndrome, or vasculitis, and he also tested negative for the same. After ruling out all other possibilities of digital gangrene and with the lymph node biopsy report, we finally diagnosed this patient as a case of high-grade NHL PTCL–NOS specified type with the AVS as a paraneoplastic manifestation and anemia of chronic disease. Treatment of gangrene associated with the PAVS was initiation of chemotherapy for the underlying malignancy. The proposed mechanisms for PAVS are ischemia due to the deposition of tumor antigen immune complex in the small vessels of the digits, the release of vasoconstrictor substances due to

tumor infiltration into the cervical plexus, direct invasion of tumor cells in vascular endothelium, and hypersensitivity reaction.^{4,9} PTCLs comprise a heterogeneous group of generally aggressive neoplasms of T-cell origin that manifest as lymphadenopathy or extranodal involvement. Although PTCL includes multiple subtypes that are distinguished by clinical, pathologic, or genetic features, together, they account for <15% of all NHL in adults. In PTCL–NOS, no consistent immunophenotypic, genetic, or clinical features have been defined. At present, PTCL–NOS is a diagnosis of exclusion for mature T-cell NHLs that do not meet criteria for other defined subtypes of PTCL.¹⁰ Patients diagnosed with PTCL–NOS have a worse prognosis. Skin and gastrointestinal tract are the most common extranodal sites involved.¹⁰ Some cases are associated with diffuse maculopapular rash, ulcer, and urticarial plaque.¹¹ Treatment regimen for PTCL–NOS

was the CHOP regimen. In patients <60 years, a cyclophosphamide, adriamycin, vincristine, etoposide, and prednisone regimen can be opted.⁶ Aggressive PTCLs usually have a poor prognosis, with a 5-year survival of 30% even with chemotherapy. Although our patient had high-grade lymphoma with high mitotic activity, he responded to chemotherapy, and the progression of gangrene and pain halted after starting chemotherapy. Though digital ischemia is a rare paraneoplastic presentation of lymphoma, it should be considered if there is a rapid progression of gangrene.

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Challenges in Diagnosis of Esophageal Tuberculosis

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Received: 22 January 2023; Revised: 03 August 2023; Accepted: 03 August 2023



ABSTRACT

Esophageal tuberculosis (TB) is a rare manifestation of extrapulmonary TB, accounting for <0.2% of all TB cases. Esophageal TB most commonly presents with dysphagia, odynophagia, retrosternal pain, and systemic symptoms like decreased appetite, loss of weight, and low-grade fever as associated or other presentations. We report a similar case recently encountered as an elderly male patient presented with chronic dysphagia to solids, loss of appetite, and significant loss of weight. Radiological and endoscopy pictures looked like esophageal cancer with histopathological examination (twice) negative for the same. Diagnosis of esophageal TB was confirmed by GeneXpert Ultra of biopsy sample and histopathological examination was suggestive of granulomatous esophagitis. The patient improved on 6 months antitubercular therapy. The unique aspect of this case was how the lesion mimicked an esophageal carcinoma on imaging which posed a diagnostic challenge.

Journal of the Association of Physicians of India (2024): 10.59556/japi.71.0402

INTRODUCTION

Primary esophageal tuberculosis (TB) is extremely rare and is seen in both immunocompetent and immunocompromised individuals.¹ Esophageal cancer is a close differential. Esophageal TB may mimic esophageal cancer both clinically, endoscopically, and radiologically. Although similar presentations, both are managed differently. Dysphagia is the most common symptom reported for esophageal TB, but retrosternal pain, abdominal discomfort, odynophagia, hematemesis, and weight loss can also be present.² Such symptom spectrum overlaps carcinoma esophagus. It is necessary to keep esophageal TB as an important differential diagnosis, particularly in cases of biopsy-negative malignant dysphagia. Here, we present a similar case of a 67-year-old male with esophageal TB mimicking esophageal carcinoma.

CASE

A 67-year-old male patient presented to our outpatient clinic with a 1-month history of difficulty in swallowing solids (modified Takita grade IV) with gradual loss of appetite (>50%) and significant loss of weight (approximately 5% in 1 month). Dysphagia was insidious in onset, gradually progressive, associated with each meal, and not associated with episodes of regurgitation. There was no history of change in voice, hoarseness, nasal regurgitation on lying down, or changes in teeth. There was a past history of cerebrovascular accident in the form of left-sided hemiparesis 2 years back that has recovered partially.

Otherwise patient's past medical and surgical history was unremarkable with no history of any accidental corrosive intake or other comorbidities.

The patient had a history of chronic alcohol dependence for 20 years, with an approximate intake of 60 gm/day of hard liquor at 40% (weight in volume). He had his last intake 2 years back. He was also a chronic tobacco chewer.

There was no history of long-standing diseases including cancer in his family. On general examination including vital signs were within normal limits. Oral cavity examination was within normal limits with uvula positioned centrally. Per abdomen examination was soft without any palpable mass. Chest examination was within normal limits. A central nervous examination revealed that the patient was conscious and oriented to time and place, and the person with left-sided hemiparesis (power 3/5 in the left upper and lower limb, extensor plantar, and increased tone) with normal cranial nerve examination. Based on the above examination findings, our provisional diagnosis was mechanical dysphagia mostly a case of malignant esophageal stricture. Considering the age of the patient with rapidly progressive dysphagia over 1-month with considerable loss of weight without any respiratory complaints, past history of Koch's or history of Koch's contact with the above examination findings, we had a high clinical suspicion of mechanical dysphagia mostly a case of malignant esophageal stricture.

The patient was evaluated initially at another hospital for the above complaints with upper gastrointestinal (GI) endoscopy, computed tomography (CT) scan, orodynamic

study (ODS), neck, thorax, and abdomen with positron emission tomography (PET) CT scan.

The upper GI scope done outside was suggestive of strictures smooth narrowing at 27 cm. A biopsy was taken which was inconclusive. CT ODS—neck plus thorax plus abdomen was suggestive of asymmetrical circumferentially enhancing mural thickening of esophagus extending from D4 to D8 vertebral body (length—9.8 cm, thickness—8 mm) with maintained fat planes with aorta and trachea with contact with aorta <90° suspicious of neoplastic etiology. CT also showed nonnecrotic mediastinal lymph node of size 10 × 13 mm in the left paratracheal location with nodular lesions in the anterior segment of the left upper lobe (lung) possibly inflammatory or metastatic etiology. Ultrasound and CT-guided biopsy of the lymph node were not feasible as they were of small size.

The PET-CT done outside active hypermetabolic heterogeneously enhancing asymmetric circumferential transmural infiltrative mucosal thickening arising from the middle third of the thoracic esophagus with multiple metastatic mediastinal, left axillary and left supraclavicular lymphadenopathy with small volume soft tissue density nodular lesion noted involving left lung upper lobe.

All routine investigations were done.

Upper GI scope was done—suggestive of stricturous narrowing at 27 cm with smooth overlying mucosa. Stricture dilatation using Savary Gilliard dilators 7, 9, and 11 mm. Post dilatation—stricture seen from 27 to 32 cm. Examination is done till the second part of the duodenum—normal. A stricture site biopsy was taken. Histopathological examination was suggestive of acanthotic and stratified squamous epithelium admixed with granulation tissue with dense lymphoid aggregates with no evidence of malignancy.

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How to cite this article: Gandhi H, Chandnani S, Rath P, et al. Challenges in Diagnosis of Esophageal Tuberculosis. J Assoc Physicians India 2024;72(1):104–105

Due to a negative tissue biopsy, we did a repeat oesophagogastroduodenoscopy (OGD)scopy and dilatation. Repeat stricture site biopsy was suggestive of ulcerated esophageal mucosa covered with extensive granulation tissue and mixed inflammation with no evidence of viral, fungal infection, granuloma, or malignancy. This forced us to take a biopsy a third time. Post dilatation, we found a longitudinal ulcer along the posterior wall from 26 to 30 cm, occupying 50% of the circumference. This time, tissue biopsy was taken in formalin and normal saline. Histopathological examination was suggestive of granulomatous esophagitis and we sent GeneXpert Ultra which detected *mycobacterium* TB (rifampicin sensitive). The patient was sent to directly observed therapy, short-course, and was started on weight-based category 1 antitubercular treatment (ATT). On follow-up after 6 months of completion of ATT, there is symptomatic improvement such that the patient is able to take a solid diet (modified Takita grade I) with weight gain. We did a follow-up endoscopy after 6 months of completion of ATT which showed healed lesions.

Discussion

Esophageal TB is an extremely rare extrapulmonary manifestation of TB (2.8% of total GI TB cases).³ Primary esophageal TB is defined as the primary involvement of the esophagus without any systemic manifestations of TB. It is definitely rare as squamous epithelium and esophageal peristalsis have a strong protective effect against TB.⁴ Secondary esophageal TB occurs due to direct extension from pulmonary, mediastinal, and spinal TB with concomitant pulmonary TB seen in <50% of the patients.⁵ In this patient, there was no previous history of TB along with the absence of any signs of active or past pulmonary TB on imaging, suggesting primary esophageal TB.

Dysphagia, odynophagia, and retrosternal pain or discomfort are common presentations in addition to constitutional symptoms (low-grade fever, weight loss, decreased

appetite, etc). Dysphagia is the most common presentation including 90% of esophageal TB.⁶ Patients may present rarely with life-threatening complications like broncho-esophageal fistula, hematemesis, or aspiration pneumonia. The middle one-third of the esophagus near the carina is the most commonly affected site due to its close proximity to mediastinal lymph nodes, more commonly seen with secondary TB.⁷

Diagnosis of esophageal TB is made by esophagoscopy and biopsy of the lesion. Histopathology report and Mycobacterium Growth Indicator tube/Gene Xpert (MGIT/GXP) of biopsy specimen are investigations of choice.⁸ Histology shows epithelioid granulomas with Langhans cells, central necrosis, and acid-fast bacilli. The sensitivity of identifying typical caseating granulomas on histopathology of biopsy samples ranges from 25.0 to 60.8% which is low.⁹ This is because of either low density of tuberculous granulomas in affected tissue or insufficient representation of the submucosal layer which is the main site of tuberculous granulomas, on endoscopic biopsies.

[¹⁸F]Fluorodeoxyglucose (¹⁸F-FDG) PET has been used to detect TB granulomas and assess disease activity and the extent of the disease.¹⁰ Active TB (both pulmonary and extrapulmonary lesions) avidly takes up ¹⁸F-FDG and can be very useful to assess the extent of active TB. Since ¹⁸F-FDG is a nonspecific tracer, it cannot reliably distinguish tuberculomas from malignant lesions and frequently gives rise to a false-positive diagnosis in patients evaluated for malignancy. Though a high standardized uptake value (SUV), greater than 2.5, is attributed to malignant lesions, high values of peak SUV, up to 21.0 (range 2.2–21.0), have been encountered in tuberculous lesions.¹¹ In our case, imaging including PET-CT was suspicious of esophageal carcinoma. Initial histopathology examination of biopsy specimens was also negative for malignancy. So, the unique aspect was the lesion mimicked an esophageal carcinoma on imaging which posed a diagnostic challenge.

Standard ATT comprising of four drugs, that is, isoniazid, rifampicin, pyrazinamide, and ethambutol for 6 months is the treatment of choice for GI TB (rifampicin sensitive patients).¹² Surgery is reserved for complicated cases only like fistula, abscess, stricture, or perforation.

Conclusion

Esophageal TB mimics carcinoma esophagus. It is a curable cause of dysphagia which is usually missed. So there should be a high index of suspicion especially in TB endemic regions particularly with biopsy negative for malignancy. Therefore, a diagnostic strategy that takes into account TB is essential. So, unnecessary esophagectomy for patients with an esophageal lesion can be avoided that is histologically unproven to be malignant.

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Mediastinal Lipomatosis

Ananda Datta^{1*}, Raghavendrun Sivasankar²

Received: 15 April 2023; Accepted: 05 May 2023



Mediastinal lipomatosis is a benign condition characterized by excessive deposition of unencapsulated mature adipose tissue in the mediastinum.¹ The exact prevalence is not known. The available literature mainly consists of some case series and a bunch of case reports.

A 45-year-old woman was referred from the surgical department for assessment of the abnormality in the chest radiograph,

which was found during the preoperative evaluation for cholelithiasis. She denied any history of respiratory symptoms. Her past medical history was unremarkable. She had no comorbid illness. She neither used to smoke nor used to take any drugs regularly. Her body mass index was 26.1 kg/m.² On chest auscultation, the intensity of breath sound was diminished on the left infraaxillary and infrascapular regions. Routine blood

investigations revealed no abnormality. The thyroid profile, lipid profile, blood glucose levels, and serum cortisol levels were within normal limits. The chest radiograph showed a widening of the mediastinum with an increased cardiothoracic ratio. A homogenous opacity was also present in the left lower zone with obliteration of the left costophrenic angle (Fig. 1). Ultrasonography of the chest showed a hyperechoic lesion above the left diaphragm. Transthoracic echocardiography revealed no abnormality. Computed tomography (CT) scan of the thorax revealed a large homogenous fat density lesion involving the anterior mediastinum and left paracardiac region extending up to the left supradiaphragmatic area. The lesion is devoid of any definite capsule and has a density between -90 and -100 Hounsfield units (HU) (Fig. 2). The radiological picture is diagnostic of mediastinal lipomatosis.

The condition has been reported in association with Cushing's syndrome, chronic steroid therapy, hypothyroidism, diabetes, and obesity.² Most cases are asymptomatic and



Fig. 1: Chest radiograph showing widening of the mediastinum with an increased cardiothoracic ratio and a homogenous opacity involving the left lower zone with obliteration of the left costophrenic angle

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How to cite this article: Datta A, Sivasankar R. Mediastinal Lipomatosis. J Assoc Physicians India 2023;2024;72(1):106-107.

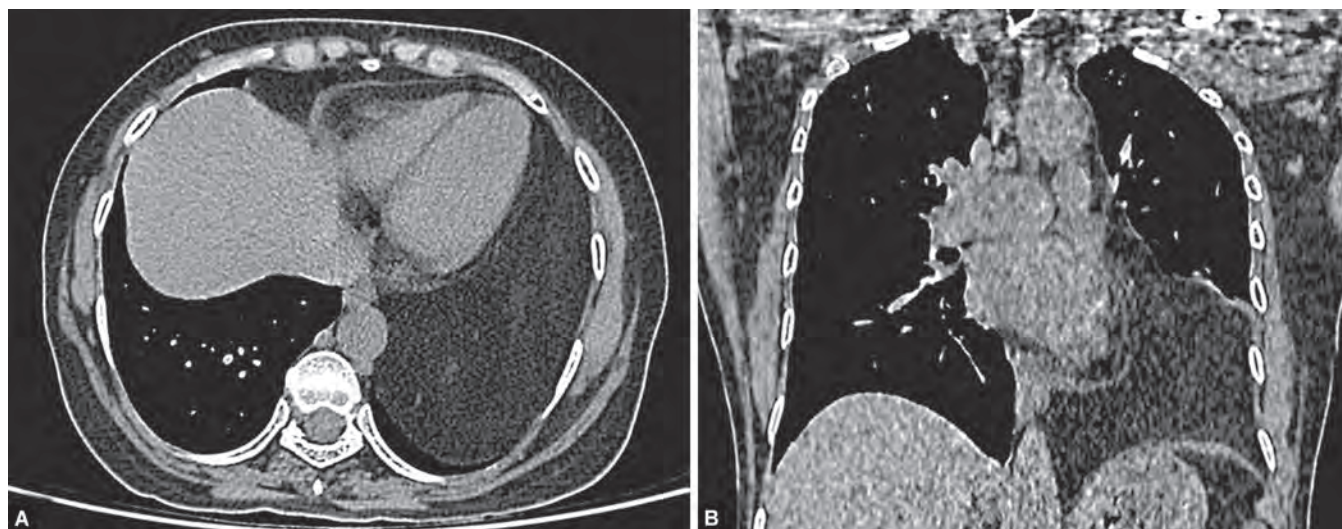


Fig. 2: Computed tomography (CT) scan of thorax (A, axial and B, coronal) showing a large homogenous unencapsulated fat density (-90 to -100 HU) lesion involving the mediastinum and left paracardiac region extending up to the left supradiaphragmatic area

get detected incidentally. Rarely, compression of various intrathoracic structures may lead to cough, dyspnea, chest pain, dysphonia, and arrhythmias. Unusual presentations like superior vena cava compression, right ventricular outflow tract obstruction, and infiltration to interatrial septum have been reported.³⁻⁶ The CT scan finding of mediastinal lipomatosis (ML) includes a homogenous unencapsulated fat-attenuating (–60 to –120 HU) lesion confined to the mediastinum, that sharply outlines the major vessels and airways.⁷ The typical radiological feature confirms the diagnosis and invasive diagnostic tests for histopathological confirmation are not required.² ML does not require specific

treatment. The therapeutic strategy is mainly directed towards the control of the predisposing conditions. Overweight and obese patients are encouraged to maintain an ideal body weight. In rare instances, surgical debulking of fat may be required when clinically significant compression to the surrounding structures is present.¹

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Young Girl with Right Arm Cramps while Writing

Manoj Kumar Sundarka*

Received: 06 July 2023; Revised: 23 September 2023; Accepted: 26 September 2023



A 15-year-old girl arrived with her father. She reported experiencing discomfort and cramps in her right arm while writing for the past 3 months. Her father had observed a palpable lump medially in her right mid-arm. She mentioned variations in the size of the lump on occasion. She denied experiencing any notable pain in the lump. During the physical examination at the clinic, a smooth lump approximately 2 × 1.5 cm in size was found, which could move from side to side but could not move in the vertical plane. No signs of neurovascular compromise or trophic changes were detected. The arm's girth was normal, and the lump remained unnoticeable upon inspection. Percussion over the lump area did not elicit any tingling sensations in the arm, forearm, or hand. She denied a history of fever, injury, clotting disorders, or any other symptoms. There was no history of headache, abnormal movements, or any observable lump elsewhere. She underwent high-resolution ultrasonography, which revealed a well-defined, thin-walled cystic structure measuring 11.3 × 11 mm in the intermuscular plane of the right arm medially. An echogenic focus was observed within, surrounded by perilesional edema (Fig. 1). The radiological impression indicated cysticercosis. Routine blood tests fell within the normal range, and the electrocardiogram (ECG) showed normal sinus rhythm. Concerned about tuberculous infection, which is common in this region, the family sought a second opinion. The chest X-ray and computed tomography (CT) scan of the head were reported as normal. Anti-cysticercosis

antibody [enzyme-linked immunosorbent assay (ELISA)] immunoglobulin M (IgM) tested positive.

The potential diagnosis of cysticercus cyst was explained, and a conservative management approach was adopted with the family's consent. She responded positively to a course of steroids and albendazole, with complete resolution of the cyst and her symptoms within 2 weeks. She was advised against squeezing the lump to prevent rupture and complications.

Human cysticercosis can affect any body tissue. There have been a few reported cases of isolated intramuscular cysticercosis in the pediatric population. Radiographs may reveal multiple calcifications in the muscles or subcutaneous tissues if the cysts become calcified.¹ Albendazole and praziquantel are commonly used anti-cysticercal drugs. Albendazole is given as 5 mg/kg tid for 15–30 days.² Steroids are typically administered at the onset of anthelmintic treatment, especially when a large single lesion is causing symptoms due to its mass effect.² Ultrasonography should be considered an initial investigation to rule out intramuscular cysticercosis, and in uncertain cases, invasive techniques such as fine needle aspiration cytology (FNAC) or fine needle aspiration biopsy (FNAB) may be performed for diagnosis.³ Differential diagnoses for soft tissue cysticercosis include lipoma, neurofibroma, sebaceous cyst, fibroma, myositis, muscle contusion-hematoma, cold abscess, pyogenic abscess, or hydatid cyst. Preventing cysticercosis involves minimizing

opportunities for ingesting fecally-derived eggs through good personal hygiene, effective fecal disposal, and the treatment and prevention of human intestinal infections. Due to immigration from endemic countries where *Taenia solium* is prevalent, cases have been reported in developed countries as well. Jain et al. reported a case of isolated cysticercosis of the biceps' muscles in a young man, which was successfully managed with surgical excision.⁴

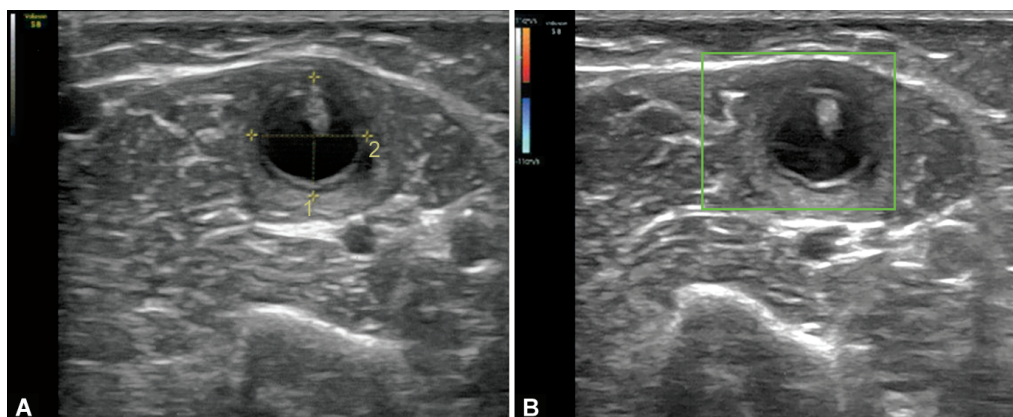
Although solitary intramuscular cysticercosis is rare, it should be considered in patients presenting with an intramuscular or subcutaneous lump, especially in endemic areas. Ultrasonography and magnetic resonance imaging are valuable noninvasive diagnostic tools for confirming the diagnosis.⁵ The nodule or swelling may be visible or palpable on the body. In our case, the cramping was possibly caused by intermittent leaks due to manual squeezing, leading to nerve or muscle irritation in the vicinity.

ACKNOWLEDGMENT

I acknowledge manuscript text correction help from Yamini S, a postgraduate student at the University of Edinburgh, Scotland.

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How to cite this article: Sundarka MK. Young Girl with Right Arm Cramps while Writing. J Assoc Physicians India 2024;72(1):108–109.



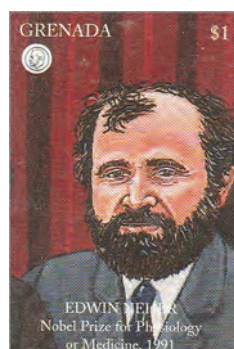
Figs 1A and B: Well-defined, thin-walled cyst with an echogenic focus within, surrounded by perilesional edema

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Neher and Sakmann: Single Ion Channels

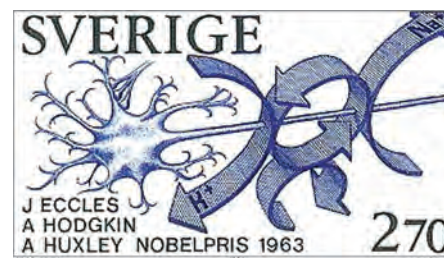
J V Pai-Dhungat



Erwin Neher, Nobel Prize 1991 Stamp, Granada, 1995



Bert Sakmann, Nobel Prize 1991 Uganda, 1995



Hodgkin, Eccles, and Huxley, Nobel Prize for axonal ion exchange, 1963. Sweden, 1964

Most biological functions have their basis in a rapid change in cell membrane permeability. Hodgkin and Huxley showed regulation of the flow of molecules and ions between the nerve cell and its environment (Nobel Prize 1963), by recording macroscopic currents. Two Germans Neher and Sakmann showed that specific ion channels actually exist, and specific membrane proteins act as gates or agents for active transport regulating in physiological and pathological processes.

Erwin Neher (born 1944) near Munich, Germany, and earned a degree in physics in 1963 from the Technical University in Munich and then attended the University of Wisconsin at Madison. Here, he obtained his master's science degree in 1967. From 1968 to 1972, Neher did his graduate and postdoctoral work at the Max Planck Institute for Psychiatry, Munich. He first developed the idea of the patch clamp technique using small suction pipettes, to measure the local current flow during his doctoral thesis and earned a PhD from the University of Munich (1970). Neher then moved to the Max Planck Institute for Biophysical Chemistry, now in Gottingen in 1972.

Bert Sakmann (born 1942) near Stuttgart Germany, graduated in medicine from the University of Gottingen in 1974, and became interested in research. He worked as a scientific assistant at Munich's Max Planck

Institute for Psychiatry in Neurophysiology of Munich University. Sakmann completed his medical dissertation, "Electrophysiology of Neural Light Adaption in Cat Retina," at the Medical Faculty of Gottingen University. Sakmann was also interested in ion channel at the neuromuscular junction and moved to the University College, London for his postdoctoral studies in the Department of Biophysics (1969–1970) under Bernard Katz.

Sakmann returned as research assistant in the department of neurophysiology at the Max Planck Institute for Psychiatry Gottingen; it was here, that Sakmann met Neher. Neher was working with single ion channel recording in artificial membranes; Sakmann had experience in neuromuscular junction. The pair agreed to collaborate, aiming at the measurement of single ion channel currents. This collaboration continued despite Neher's moving to the University of Washington in Seattle and, later, to Yale University. Collaboration involved developing and refining the patch clamp technique for measuring currents in the tiny picoampere range. Neher and Sakmann reported using simple tiny pipette suction electrode pressed up against a frog muscle cell to record opening and closing of a single ion channel in 1976, for the first time. The patch clamp technique not only confirmed the existence

of ion channels, but quickly gave researchers the tool they needed to uncover much of the detail of how such channels functioned. Many other diseases depend entirely, or partially, on defect in regulation of ion channels, and a number of drugs act directly on ion channels. Many pathological mechanisms have been clarified during the eighties through ion channel studies, for instance cystic fibrosis (chloride ion channels), epilepsy (sodium and potassium ion channels), several cardiovascular diseases (calcium ion channels), and neuromuscular disorders like Eaton–Lambert disease (calcium ion channels). These discoveries have enabled the development of new and more specific drug therapies.

Erwin Neher and Bert Sakmann were awarded the 1991 Nobel Prize in Physiology or Medicine jointly for "their discoveries concerning the function of single ion channels in cells."

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How to cite this article: Pai-Dhungat JV. Neher and Sakmann: Single Ion Channels. J Assoc Physicians India 2024;72(1):110–110

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FDC: Fixed dose combination HbA1c: Glycosylated hemoglobin UTI: Urinary tract infection GTI: Genitourinary tract infection T2D: Type 2 diabetes

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Digital Technology in Clinical Medicine: Correspondence

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Dear Editor,

We found the article on “The Digital Technology in Clinical Medicine: From Calculators to ChatGPT” interesting.¹ According to Kulkarni et al., humanity has witnesses four important social system changes, starting with the primitive hunters-gatherers and progressing to horticultural, agricultural, industrial, and the current fifth, which is based on digital information technology and has altered the way we present, recognize, and utilize different factors of production. In clinical medicine, digital technology has advanced significantly since the days of computations. According to Kulkarni et al., we have to benefit from these advancements as we all improve the lives of our patients while being cautious not to overturn the doctor–patient relationship. If technology, clinical expertise, and humanistic values are properly balanced, Kulkarni et al. concluded that the future is quite glorious.¹ Regulatory organizations are pushing for improvements through clinical trials as a result of recognition of the expanding influence of digital technology in healthcare delivery. The “World Health Organizations Guidelines for Digital Interventions” and the “Food and Drug Administration’s Digital Health Center of Excellence” are only two of the projects that are currently being highlighted in the study as efforts to analyze and implement digital health services.

The introduction and uptake of digital health services may face difficulties despite the fact these projects are encouraging. For instance, there can be worries about privacy and security of data and the need for sufficient training assistance for healthcare professionals and patients to use digital health technologies. Inequities in access to digital health services may also exist, particularly in low-income or rural locations.

An important worry is that there is a chance that ChatGPT is used to generate incorrect or deceptive published data in scholarly or academic journals, which might be the cause of lured information that will be harmful if it is further applied patient care. The situation is possible in case ChatGPT is prompted to give output answers with a

dishonest, inaccurate aim. If it is applied for producing output which are unreliable or gone out of date. Without appropriate human control, artificial intelligence must be applied in generating, modification, or approval critical material.² As artificial intelligence algorithms advance, it might be predictable that they might influence people’s unexpected practices in uncontrollable directions, intruding on their right to autonomy and seclusion. Another problem is artificial intelligence security, namely the possibility that artificial intelligence systems are being used intentionally or unintentionally in a harmful way to humans. To prevent dangers and protect human well-being, continuous study, development, and regulation will be required. The challenges of developing artificial intelligence technology into medical practice are currently insurmountable due to issues with professional development, data privacy, and liability.

Authors’ Contribution

- Amnuay Kleebayoon 50% ideas, writing, analyzing, approval.
- Viroj Wiwanitkit 50% ideas, supervision, approval.

Conflict of Interest

Corresponding author ask for waiving for all charge from the journal.

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Pancytopenia Due to Folate Deficiency

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Sir,

Folate deficiency is a common side effect of anti-seizure medications (ASM). Most of the ASMs including newer ones are associated with reduced blood levels of folate and vitamin B₁₂. Most common clinical manifestation is anemia. Folate deficiency anemia occurs in about four per 100,000 people. Folate deficiency pancytopenia is rare. We report a case of pancytopenia caused by folate deficiency induced by ASM. When

persons with epilepsy present with anemia or pancytopenia, folate deficiency has to be ruled out.

This 28-year-old male with drug-resistant focal epilepsy since childhood presented with decreased food intake and vomiting for 3 days. There was no history of fever. There was no history of alcohol abuse. He is a nonvegetarian. There is a past history of tuberculous lymphadenitis 2 years back and syndrome of inappropriate antidiuresis while on oxcarbazepine. He was on carbamazepine (CBZ) 1000 mg/day, phenobarbitone 120 mg/day, clobazam 30 mg/day, and lacosamide 200 mg/day. On examination, he is well-built and well-nourished. His vitals were normal. He had pallor. There was no icterus. There was no hepatosplenomegaly or lymphadenopathy. Neurological examination showed gaze-evoked nystagmus and gait ataxia. Investigations showed pancytopenia. Peripheral smear showed macrocytic anemia, leukopenia, and thrombocytopenia. There were no hypersegmented neutrophils or macroovalocytes (Table 1). Plasma homocysteine was not done at admission. Patient was not willing for bone marrow study.

His serum CBZ level was elevated. As he had pancytopenia and features of ASM toxicity, his CBZ was changed to brivaracetam. As he developed recurrent seizures, he was initiated on phenytoin and perampanel with which his seizures subsided. He was treated with blood transfusion and injection of folic acid. He was continued on l-methylfolate. One month after the admission, his hemoglobin level was 12.6 gm%, total white blood cell (WBC) count was 6080/mm³, and platelet count was 3.63 L/mm³. One year later, his hemoglobin is 16.2 gm%, mean corpuscular volume (MCV) 96 fL, serum folic acid 12.39 ng/mL, and serum homocysteine 6.12 μmol/L (normal 5–15), and he is on folate supplements in addition to his ASMs.

Pancytopenia is a fairly common hematological condition, and its causes include aplastic anemia, megaloblastic anemia, acute leukemia, hypersplenism, multiple myeloma, and myelodysplastic syndrome. One major cause is megaloblastic anemia due to B₁₂ or folate deficiency. Folate deficiency is less common than vitamin B₁₂ deficiency. In a study of 140 patients with pancytopenia in North India, megaloblastic anemia due to vitamin B₁₂ deficiency was the most common cause of pancytopenia. In western countries, most of the pancytopenia is due to aplastic anemia or malignancy.¹ Macrocytic anemia was the initial clue to the diagnosis in our patient. In an Indian study evaluating the causes of macrocytosis, it was found that 73.6% cases were due

Table 1: Blood investigations

Parameters	Patient	Normal range
Hemoglobin	6 gm%	13.2–16.6 gm%
Total WBC count	2,430/mm ³	4,000–11,000/mm ³
Neutrophils	60%	40–70%
Lymphocytes	40%	20–40%
Platelet count	98,000/mm ³	150,000–450,000/mm ³
Red blood cell count	2.46 million/mm ³	4.7–6.1 million/mm ³
MCV	125.6 fL	80–100 fL
Erythrocyte sedimentation rate	72 mm/hour	<14 mm/hour
C-reactive protein	8.8 mg/L	<6 mg/L
Random blood sugar	98 mg%	80–140 mg%
Na	139 mEq/L	136–145 mEq/L
K	4 mEq/L	3.5–5.5 mEq/L
Urea	7 mg%	17–44 mg%
Ca	7.4 mg%	8.5–10.5 mg%
Phosphorus	2.39 mg%	2.8–4.5 mg/dL
Total bilirubin	0.7 mg%	0.1–10 mg/dL
Serum glutamic oxaloacetic transaminase	42 U/L	8–45 U/L
Serum glutamic pyruvic transaminase	24 U/L	7–56 U/L
Alkaline phosphatase	93 U/L	44–147 U/L
Vitamin B ₁₂	>2000 pg/mL	160–950 pg/mL
Ferritin	152.5 ng/mL	24–336 ng/mL
Folate	<0.6 ng/mL	4.6–18.7 ng/mL

to alcoholism, vitamin B₁₂ deficiency, or drugs.² Study by Khanduri et al. showed pure folate deficiency in only 6% of their patients compared to cobalamin deficiency (65%) in their 175 patients with megaloblastic anemia. Physical examination showed pallor, glossitis, icterus, and hyperpigmentation in 85, 29, 25, and 18%, respectively. Hematological findings were MCV 77–123 fL, red cell distribution width (RDW) 16–44%, pancytopenia in 62% of patients, reticulocyte count >2% in 42% of patients, and megaloblastic blood films in all patients.³ In a study of hospitalized patients in Canada who had testing for vitamin B₁₂ and folate levels, vitamin B₁₂ deficiency was observed in 3.1% of patients. About 13.5% had vitamin B₁₂ levels in the low normal range.

Folate deficiency (assessed using red blood cell folate) was seen in 0.16%.⁴ Folate and vitamin B₁₂ metabolism are linked in such a way that deficiency of either vitamin leads to megaloblastic anemia. The neurologic manifestations of vitamin B₁₂ deficiency overlap with that of folate deficiency and include peripheral neuropathy, subacute combined degeneration of the spinal cord, dementia, and depression.

Serum folate levels <2 ng/mL are considered deficient, while levels >4 ng/mL are considered normal. Levels between 2 and 4 ng/mL needs confirmation by measurement of serum homocysteine and methylmalonic acid (MMA) levels. Folate deficiency can be confirmed with an elevated homocysteine

levels and normal B₁₂ and MMA levels. Serum homocysteine is elevated in 91% of patients with folate deficiency.⁵ Folic acid is present in green leafy vegetables, liver, yeast, and fruits. Cooking depletes folic acid content by as much as 90%.⁶

Megaloblastic anemia is characterized by oval macrocytes and hypersegmented neutrophils.

Hypersegmented neutrophils can be absent in megaloblastic anemia if there is severe neutropenia or marked left shift. Macroovalocytes are more sensitive but less specific in predicting megaloblastic bone marrow changes.

Serum and red blood cell folate are reduced in up to 90% patients receiving CBZ, phenytoin, or barbiturates.⁶ Use of ASMs, in particular CBZ and valproic acid, is associated with a ninefold increased risk of aplastic anemia.⁷ Since folate is required as a cofactor in drug hydroxylation, it is postulated that folate depletion results from increased demand for the cofactor. Even though aplastic anemia due to ASM was considered initially, it was ultimately proved to be pancytopenia due to folate deficiency induced by enzyme-inducing ASMs, CBZ and phenobarbitone.

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