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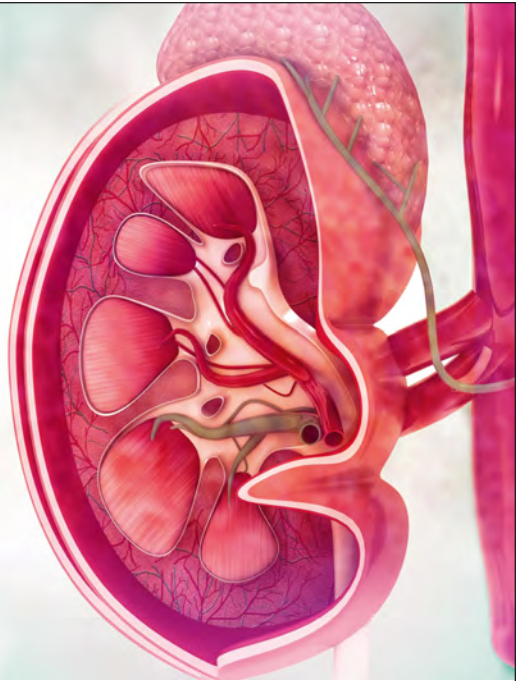
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Second and third trimesters of pregnancy. Biliary obstructive disorders. Severe hepatic impairment. The concomitant use of Telmisartan with aliskiren containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m²). **Warnings And Precautions - Fetal Toxicity** Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Telmisartan as soon as possible. **Hypotension** In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with Telmisartan. Either correct this condition prior to administration of Telmisartan, or start treatment under close medical supervision with a reduced dose. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized. **Hyperkalemia** may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Periodic determinations of serum electrolytes to detect possible electrolyte imbalances should be considered particularly in patients at risk. **Impaired Hepatic Function** As the majority of Telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Telmisartan should be initiated at low doses and titrated slowly in these patients. **Impaired Renal Function** as a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function should be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results have been reported with Telmisartan. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of Telmisartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated. **Dual Blockade of the Renin-Angiotensin-Aldosterone System:** Dual blockade of the RAS with angiotensin-receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. In most patients no benefit has been associated with using two RAS inhibitors concomitantly. In general, combined use of drugs from different classes of RAS inhibitors should be avoided. Blood pressure, renal function and electrolytes in patients on Telmisartan and other agents that affect the RAS should be closely monitored. Aliskiren must not be co-administered with Telmisartan in patients with diabetes. Concomitant use of aliskiren with Telmisartan in patients with renal impairment (GFR < 60 mL/min/1.73 m²) must be avoided. **Nonclinical Toxicology:** Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no evidence of carcinogenicity when Telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m² basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of Telmisartan. These same doses have been shown to provide average systemic exposures to Telmisartan > 100 times and > 25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day). Genotoxicity assays did not reveal any Telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* and *E. coli* (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test. No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m² basis, the MRHD of Telmisartan. This dose in the rat resulted in an average systemic exposure (Telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day). **Use In Specific Populations: Nursing Mothers:** It is not known whether Telmisartan is excreted in human milk, but Telmisartan was shown to be present in the milk of lactating rats. **Pediatric Use:** Safety and effectiveness of Telmisartan in pediatrics has not been established. Thus, the drug is not recommended in pediatrics. **Geriatric Use:** No dose adjustment is needed in elderly patients



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The dose may be up-titrated 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<60ml/min/1.73m²). • Biliary obstructive disorders • Severe hepatic impairment • Pregnant Women **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. 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Concomitant use of aliskiren with Telmisartan in patients with renal impairment (GFR <30 mL/min/1.73 m²) must be avoided. **Nonclinical Toxicology Carcinogenesis, Mutagenesis, Impairment of Fertility** There was no evidence of carcinogenicity when Telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m² basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of Telmisartan. These same doses have been shown to provide average systemic exposures to Telmisartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day). Genotoxicity assays did not reveal any Telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with salmonella and E. coli (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test. No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m² basis, the MRHD of Telmisartan. This dose in the rat resulted in an average systemic exposure (Telmisartan AUC as determined on day 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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Abbreviations: ARB, angiotensin II receptor blocker, ACE, angiotensin-converting enzyme, BP, blood pressure, MACE, major adverse cardiovascular events

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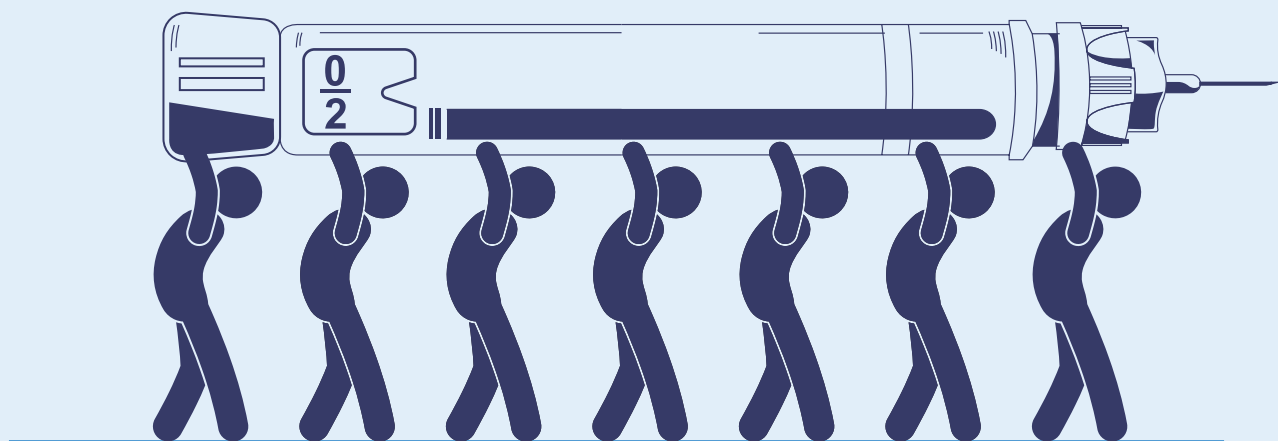
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Takayasu Arteritis: Early Diagnosis and Informed Medical Management is Key

Rohini Samant^{1*}, Bishakha Swain²

Takayasu disease (TAK) is a chronic granulomatous vasculitis affecting the aorta and its primary branches. Vascular inflammation can lead to multifocal concentric narrowing of the vessels usually involving the ostia, and can cause aneurysmal dilatation of the aorta. The disease has a predilection for Asian women (F:M—9:1) but is seen across all races and ethnicities.

Takayasu disease has been classified based on the criteria proposed by Ishikawa (1988),¹ American College of Rheumatology (ACR) (1990),² and the modified criteria by Sharma et al.³ in 1995. The commonly used ACR 1990 criteria require three of six clinical criteria to be met for classification as Takayasu arteritis (TA). These included (1) age <40 years, (2) claudication of an extremity, (3) reduced brachial artery pulse, (4) blood pressure difference >10 mm between two extremities, (5) bruit over the subclavian artery or aorta, and (6) angiographic evidence of narrowing or occlusion of the aorta and its primary branches. The recent ACR/European League Against Rheumatism (EULAR) 2022⁴ criteria have proposed age of disease onset <60 years (as compared to age <40 in previous criteria) and added more detailed imaging criteria to the clinical criteria. It must be added that since these are all classification criteria for established disease, they have limited utility in early diagnosis.

Early diagnosis of TAK is challenging. The clinical presentation is varied and can be broadly divided into early (prepulseless) and late (pulseless) phases. Recognizing the disease in the prepulseless phase holds the promise of possible prevention of progression to the pulseless phase. The systemic or “prepulseless” period is characterized by nonspecific constitutional symptoms like fever, myalgia, joint pains, and night sweats. We and others have highlighted the importance of erythema nodosum as a harbinger of TAK in this phase.^{5,6} In a large study (1,372 patients) on newly registered Takayasu patients, systemic complaints (40%) like fever, malaise, and joint pains, head and neck symptoms (22%) like dizziness, anterior neck pain, headache, and upper limb symptoms (17%) were the most commonly reported.⁷

In a recent study (275 patients) on patterns of clinical presentation in TAK by Quinn

et al.,⁸ constitutional symptoms were seen in 8%, carotidynia in 13–15%, other vascular symptoms in 43–47%, major ischemic event in 28–30%, and 2–6% were asymptomatic. Majority of the patients presented when the disease had progressed to the pulseless phase. A high index of suspicion in patients with pyrexia of unknown origin (PUO) or unexplained high inflammatory markers having nonspecific symptoms like upper back/anterior neck/chest pain, syncope/giddiness, visual loss singly or in combination, followed by judicious imaging is likely to be rewarding. B-mode ultrasonography is helpful in identifying edema of the carotid arteries in early disease. Contrast computed tomography (CT) angiography can demonstrate mural thickening of the aorta and its branches. Magnetic resonance imaging (MRI) of patients with TA shows wall mural contrast enhancement on T1-weighted images and edema on T2-weighted images. The fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT should be reserved for patients with PUO. It can pick up increased uptake in the aorta and its branches. Reversal of pulse loss following early diagnosis and treatment has been demonstrated in few studies.^{9,10} An awareness of the spectrum of disease manifestations and judicious use of imaging is crucial for the same.

Even after diagnosis, problems with monitoring of disease activity continue to plague physicians. Prevention of new pulse loss or acute ischemic event in the cerebrovascular/intestinal/ocular or coronary circulation are the goals of treatment but the tools to achieve these goals are inadequate. Some progress was made with a more detailed clinical scoring system; the Disease Extent Index in Takayasu Arteritis (DEI. Tak),¹¹ and the Indian Takayasu activity score (ITAS2010)¹² and ITAS-A, derived from DEI. Tak which have been validated. However, they will be more meaningful when used in conjunction with imaging characteristics and these are yet to be validated. Symptoms of limb claudication, syncope, transient ischemic attack (TIA), chest pain, and carotidynia may suggest ongoing disease activity which is amenable to medical treatment or may indicate a critical level of ischemia warranting

endovascular or surgical treatment. The presence of raised inflammatory markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in this context are suggestive of active disease. However, ESR and CRP have been shown to be normal in the presence of demonstrable active vasculitis in vascular biopsies of patients undergoing revascularization procedures.¹³ Conversely, the significance of elevated ESR and CRP in the absence of clinical activity is not clear.¹⁴ Other biomarkers like pentraxin 3 and inflammatory cytokines like serum interferon- γ , interleukin-6, interleukin-23, interleukin-17, interleukin-10, and transforming growth factor- β levels have been studied but the evidence is inconsistent.^{15,16} Magnetic resonance angiography (MRA) has the advantage of avoiding ionizing radiation, but cannot be done repeatedly due to financial constraints. Same is the case with FDG PET/CT scan where there is additional risk of radiation. Another confounding factor is that angiographic abnormalities can progress due to vascular remodeling even in the absence of active TAK making their interpretation challenging.^{17,18} The field of disease assessment in Takayasu needs to evolve further, for the present, an understanding of currently available tools is paramount to guide treatment decisions.

TA is steroid responsive but is notorious for being a frequently relapsing disease. The 2021 ACR/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis conditionally recommend the use of a steroid sparer with glucocorticoids, rather than steroids alone in patients with active TAK.¹⁸ No single steroid sparing drug has an edge over the others, and there are no randomized controlled trials (RCTs) comparing them which is a significant

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knowledge gap faced by treating physicians/rheumatologists. Methotrexate, azathioprine, mycophenolate mofetil, leflunomide, and tacrolimus have all shown efficacy and have been sometimes used in combination. Tumor necrosis factor (TNF) α blockers and tocilizumab are usually reserved for resistant disease.¹⁹ They have also been used in the context of critical ischemia, for example, unstable angina, recurrent transient ischemic attacks (TIAs), etc., to bridge the gap pending surgical or endovascular intervention.

The importance of medical treatment for TAK in the Indian context has been emphasized only in recent years. In an editorial on Indian perspectives in TAK published in 2007, the editors commented that as most Indian patients present in the chronic phase, steroid therapy has not been used very commonly though it is being used more frequently than in the past.²⁰ In a recent meta-analysis of outcomes from 50 uncontrolled studies including 832 TAK patients treated with disease modifying drugs, clinical response was noted in 78%, acute phase reactants normalized in 90%, and angiographic stabilization was achieved in 85% of patients. Overall, the results were similar for conventional and biologic disease modifying antirheumatic drugs (DMARDs) and no superiority was noted among the two biologicals, that is, tocilizumab and TNF α blockers.²¹

Recent studies have emphasized the fact that adequate medical treatment is paramount in preventing disease progression in TAK. In a large single cohort study from India, duration of symptoms before initiation of immunosuppressant drugs was positively associated with disease extent and damage as reflected by the DEI, Tak and Takayasu Arteritis Damage Score (TADS).²² Similar associations have been reported from cohorts in United States and Italy.^{23,24} To address the problems of assessment and inadequate treatment, an expert panel from Japan recently undertook a Delphi exercise to establish a frame work for a treat to target algorithm for TAK. There was a 95.5% concordance among the expert researchers that remission in disease activity should be achieved at 1 year with a prednisone dose <10 mg/day.²⁵

The challenges with surgical/endovascular intervention in TA have been highlighted in several recent papers. Open bypass graft surgery, endovascular stenting and balloon angioplasty are the commonly used modalities of intervention. The availability of local expertise, and the nature of the vessel needing intervention is often critical

in the choice of procedure. The short- and long-term complications of both bypass surgery and endovascular intervention in TA such as restenosis, graft occlusion, and anastomotic site aneurysm far exceed those seen in atherosclerotic occlusive disease. The presence of longer and more fibrotic vessels and possible persistence of vessel wall inflammation despite clinical and laboratory remission reduce the success of intervention in TA.²⁶ The use of immune suppressants and corticosteroids carries additional risks for major surgical procedures. The importance of medical treatment versus surgical/endovascular intervention in the management of TA has been underlined in the 2021 recommendations for treatment of TAK. These recommendations suggest that barring impending/progressive tissue or organ infarction, medical treatment should always be the first line of treatment. Even in the subgroup undergoing intervention, in the presence of active disease, the use of high-dose glucocorticoids in the periprocedure period has been conditionally recommended.¹⁸

To summarize, early diagnosis of TAK through greater awareness of its varied clinical presentation and judicious imaging is the need of the hour. Since patients with TAK can present to various specialists like physicians, nephrologists, gastroenterologists, cardiologists, and rheumatologists, this awareness needs to extend across all subspecialties of medicine. Better composite outcome tools and biomarkers are needed for assessment of disease activity. Medical management guided by disease activity is the mainstay of treatment in TAK and is rewarding in a majority of patients in experienced hands. Interventions should be reserved for refractory disease or critical organ ischemia. A team approach including interventional radiologists and vascular surgeons can ensure the highest level of care for these complicated patients.

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Thyroid Disorders among Type 2 Diabetes Mellitus: A Cross-sectional Study from a District Hospital in West Bengal

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ABSTRACT

Introduction: The coexistence of diabetes mellitus (DM) (both type 1 and type 2) and thyroid dysfunction, two common endocrine problems, is scientifically predictable. The prevalence of thyroid disorders among type 2 diabetics (more prevalent in India) was studied among patients visiting the outpatient department (OPD) of a district hospital in West Bengal to assess its relation with different characteristics of type 2 DM.

Materials and methods: A total of 120 patients suffering from type 2 DM (already diagnosed and on treatment) were randomly selected from the OPD (irrespective of their glycemic status). The thyroid status of all those patients was assessed. All diabetic patients were studied with a predesigned schedule and lab investigations for the prevalence of thyroid dysfunction and its association with pertinent variables from January to December 2019.

Results: This study found a 28.3% prevalence of thyroid dysfunction among diabetics. It was significantly associated with poor glycemic control [rising hemoglobin A1c (HbA1c) level] (actual p -value for HbA1c vs abnormal thyroid status = 2.4×10^{-21}) but not with other variables, including the duration of diabetes.

Conclusion: Screening for thyroid dysfunction among diabetic persons should be routine, and strict glycemic control is essential.

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INTRODUCTION

Hyperglycemia, the metabolic disorder associated with diabetes mellitus (DM), resulting from defects in the secretion or mode of action of insulin (or both), is associated with long-term complications related to different organs, namely eyes, kidneys, nerves, heart, and blood vessels. The pathologies behind these abnormalities range from insulin deficiency, resulting from autoimmune destruction of β -cells of the pancreas, to insulin resistance, thus promoting deranged metabolism of carbohydrates, fat, and protein.¹

Again, thyroxine (T4) and triiodothyronine (T3), the hormones secreted by the thyroid gland, help in the optimum metabolism of tissues by promoting oxygen consumption and regulating carbohydrate and fat metabolism; thus, they influence body mass and mentation.²

There is evidence that there is a relationship between the effects of thyroid hormone and insulin secretion.³ Though reduced glucose-induced insulin secretion by beta cells is seen in hypothyroidism, the response of beta cells to glucose or catecholamines is increased in hyperthyroidism. An enhanced clearance of insulin is also seen in thyrotoxicosis.⁴⁻⁶ Moreover, several studies show an increased prevalence of thyroid dysfunction in patients suffering from type 2 DM, which is again

related to the degree of hyperglycemia. Uncontrolled hyperglycemia may affect the metabolism of thyroid hormones, thus altering their plasma levels.^{7,8}

Though hyperthyroidism may increase blood glucose levels by various mechanisms such as increased absorption of glucose, glycogenolysis, and increased hepatic production of glucose,⁹ increased insulin resistance,¹⁰ and by shortening the half-life of circulating insulin;¹¹ reverse is true for hypothyroidism.¹² Again, the abnormalities associated with hypothyroidism (namely dyslipidemia, insulin resistance, obesity, and endothelial dysfunction) increase the risk of cardiovascular diseases.¹³

PATHOLOGICAL MECHANISMS COMMON TO THYROID DISORDERS AND DIABETES

Both thyroid hormones and insulin act on some common target organs, namely liver, skeletal muscle, and adipose tissue. The role of thyroid hormones in maintaining glucose homeostasis has been exemplified by their effects on intestinal absorption, hepatic production, and peripheral utilization of glucose, as well as their role in maintaining a balance between circulating insulin and counterregulatory hormones. For this to happen, thyroid hormones upregulate the expression of genes, such as glucose

transporter type 4 and phosphoglycerate kinase. They also regulate another gene, the C transcription factor hypoxia-inducible factor 1 α , having roles in glycolysis and glucose transport. Thus, thyroid disorders and glucose homeostasis are closely related.^{14,15}

As per the International Diabetes Federation (IDF) in 2020, the diabetic population in India stands at 77 million people.¹⁶ China holds the greatest number of diabetic people in the world, followed by India. The number of Indians living with diabetes increased to more than double from 1990 to 2016. Around 700,000 Indians have died due to diabetes-related complications in 2020. About 17% of the world's diabetic population is from India,¹⁷ whereas as of 2018 India holds 17.5% of the total global population.¹⁸

Type 2 diabetes is more common in the Indian population, accounting for 90–95% of Indian diabetics, and about one-third of them have a body mass index (BMI) above 25.¹⁹ This may be related to changes in lifestyle and environment as an aftereffect of industrialization, rural–urban migration, and urbanization.^{20,21} Again, after analyzing a number of studies on thyroid disorders, it has already been extrapolated that the number of people in India living with thyroid-related problems approximates 42 million.²²

Since the publication of the first studies in 1979²³ regarding the association between DM and thyroid dysfunction, multiple studies

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have been performed in different parts of the world, demonstrating that there is a variation in the prevalence of thyroid disorders in the general population (ranging from 6.6 to 13.4%) and even greater in the diabetic population (10–24%).^{24–26} The above discrepancies can be explained by the variation of iodine intake in different regions of the world and by different modes of diagnostic criteria with variable sensitivities regarding the value of thyroid stimulating hormone (TSH), along with diverse population settings.⁶

North 24 Parganas, being the most populous district²⁷ of West Bengal and since 2014²⁸ the most populated district in India, there is always a need for conducting population-based studies regarding the association between two common endocrine problems, DM and thyroid disorders in this district. For this to happen, the present study has been conducted in the district hospital at Barasat (district headquarters) to assess the relationship between thyroid disorders and type 2 DM.

MATERIALS AND METHODS

The institution-based cross-sectional study was carried out in the outpatient department (OPD) of the district hospital of North 24 Parganas from January to December 2019, with the objective of identifying the prevalence of thyroid dysfunction among type 2 DM patients, including its association with age, sex, and selected diabetic parameters.

The study population included type 2 DM patients aged 40 years and above, irrespective of their control and treatment status (oral hypoglycemic agents/insulin), attending the OPD during the study period (a total of 2,634 during the study period). Though the average age of onset of type 2 diabetes is 45–64 years,²⁹ considering the declining trend in the age of diagnosis,³⁰ the age of entry of the study population (where they have been already diagnosed³¹ and on treatment) has been taken as 40 years. The nomenclature type 2 was used for those patients who were obese (lean elderly individuals might also be included), did not require insulin therapy initially, and the illness might be associated with conditions like hypertension, cardiovascular diseases, dyslipidemia, a sedentary lifestyle, polycystic ovarian syndrome, or there might be a family history of diabetes.^{32,33} Signs of insulin resistance, namely abdominal obesity and acanthosis nigricans, were given due importance. Exclusions included patients with type 1 DM, gestational DM, pancreatitis including fibrocalculous pancreatitis, steroid-induced DM, and all those genetically defined,

monogenic forms of DM or maturity-onset diabetes of the young. Already diagnosed patients with a thyroid disorder and on treatment were also excluded.

The sample size in this study was calculated by taking the prevalence of thyroid dysfunction among diabetic patients as 29% (0.29)³⁴ with a 20% relative precision (absolute 0.058) and 80% confidence level ($Z = 1.28$), which came to be 100. Considering a 20% nonresponse allowance in the hospital setting and simple random sampling for selecting the study subjects, the final sample size was estimated as 120.

After obtaining prior permissions from the respective authorities (North 24 Parganas District Hospital) and approval from the Institutional Ethics Committee (IEC) of R G Kar Medical College and Hospital, Kolkata, type 2 diabetic patients attending the OPD of Barasat District Hospital, and meeting our inclusion and exclusion criteria, were randomly selected (simple random sampling) using computer-generated random numbers. The sampling frame (dynamic) consisted of all type 2 diabetic patients who had attended the OPD from 1st January to 31st December 2019 ($N = 2,634$). Appropriate ethical considerations were maintained throughout the study, including obtaining informed consent from participants, assuring patients' treatment rights in the event of nonparticipation, ensuring no personal identification (no name), and maintaining confidentiality of personal information, etc.

Patients were then subjected to biochemical evaluation for thyroid function tests biochemically, that is, they were screened for thyroid profile (T3, T4, and TSH) by enzyme-linked immunosorbent assay (ELISA) method, and also screened for the glycemic status, that is, hemoglobin A1c (HbA1c), by high-performance liquid chromatography (HPLC) method. Data were collected with a predesigned and pretested schedule and entered into Microsoft Excel (2016) to create the database. Statistical analysis was done by Statistical Package for the Social Sciences software version 16, Windows compatible. Descriptive analysis of data was presented as frequencies and percentages. The association between DM-related variables and thyroid dysfunction was tested using the Chi-squared and *t*-tests, considering a *p*-value < 0.05 as statistically significant.

RESULTS

Characteristics of 120 diabetic patients are depicted in Table 1. It shows that almost all (118, 98.3%) of the diabetic patients are >40 years of age (mean age of onset 47 years

and duration 11 years) with a slight female predominance (72, 60%). Nutritionally, 25% were overweight and obese, although most (85, 70.8%) are normal. A total of 73 out of 120 patients (60.8%) had a family history of DM, with 48 patients (40%) having HbA1c values equal to 7% or more (the target goal for HbA1c was <7%).³⁵ This can be further mentioned in this regard that in large clinical trials [UKPDS (United Kingdom Prospective Diabetes Study) ACCORD (Action to control cardiovascular risk in diabetes), ADVANCE (Action in Diabetes and Vascular Diseases: Preterax and Diamicron MR Controlled Evaluation) and VADT (Veterans Affairs Diabetes Trial)], where glycemic control of type 2 diabetic patients has been compared with cardiovascular risk factors, it has been demonstrated that more intense glycemic control may have deleterious effects³⁶ (however, improved glycemic control reduces microvascular complications of diabetes). Although most of the patients (86, 71.7%) were euthyroid, 34 (28.3%) had abnormal thyroid status, and the majority (23, 19.1%) had subclinical hypothyroidism (SCH). One-fifth of the patients had a family history of thyroid disorders, with 10 (8.3%) having goiter. One-fifth (24) of the patients had a history of hospitalizations, with the majority (12, 50%) having one episode.

Associations of thyroid disorders (abnormal thyroid status) have been depicted in Table 2. It shows that poorly controlled diabetes (HbA1c $\geq 7\%$) is significantly associated with abnormal thyroid status ($p = 2.4 \times 10^{-21}$) with a strong dose-response relationship, while age, sex, and duration of DM did not have any association.

DISCUSSION

The present study was done to find out the association (coexistence) of type 2 DM and thyroid disorders and ultimately to explore the need for annual screening of thyroid profiles in type 2 DM patients attending North 24 Parganas District Hospital.

In this study, 98.3% of diabetic patients were above 40 years of age, with a mean age of onset of 47 years. Similar findings (51.3 ± 16.4 years) were observed by Aljabri³⁷ in the study conducted by them at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabian the year 2018. The present study observed a female predominance among diabetics (60 vs 40%), which was similar to the study conducted by Kumar et al.³⁸ (52.13 vs 47.87%) in the Department of Medicine, S P Medical College and the associated group of P B M Hospitals, Bikaner. It observed a family history of DM among 60.8% of the patients and a

family history of thyroid disorder among approximately 20%.

The current status of thyroid disorder was abnormal in 34 (28.33%) of 120 patients. Thus, the prevalence of thyroid dysfunction among type 2 DM patients was 28.33% in this study. Similar results (35.8%) were seen by Kumar et al.³⁸

Out of 34 (28.33% of all) patients who had abnormal thyroid status, 23 (19.1% of

all) had SCH, and 9 (7.5% of all) had clinical hypothyroidism. Females were predominant among SCH patients (84.6%). Similar results were observed by Singh et al. in their study involving the Punjabi population published in 2011,³⁹ where 30% of patients had abnormal thyroid hormone levels and the levels of T3, and T4 were significantly lower while the level of TSH were significantly higher in type 2 diabetics compared to nondiabetics and

by Pasupathi et al.,⁴⁰ in Coimbatore, Tamil Nadu (KG Hospital and Postgraduate Medical Institute, Coimbatore, Tamil Nadu, India, from January 2007 to March 2008), where 55% were euthyroid and 28% had low plasma thyroid hormone levels but 17% had high levels. Likewise, in their study, Ravishankar et al. from Bengaluru, observed that thyroid disorders were present among 29% of diabetics; hypothyroidism (1%), hyperthyroid (13%), and subclinical hypothyroidism (15%). The elderly population had more prevalence than those below 60. SCH was more common among females. Diabetics with hyperthyroidism had poor glycemic control.

We did not observe any association between the duration of DM and thyroid dysfunction ($p > 0.05$). Most of the patients who had thyroid dysfunction had DM for 11–15 years, followed by 6–10 years. A contemporary study showing such an association is not readily available for comparison.

No thyroid dysfunction was seen in DM patients who had HbA1c values $<7\%$, whereas this was 8 (36.4%) and 26 (100%) in DM patients having HbA1c values 7–10% and $>10\%$, respectively. This difference is statistically highly significant ($p = 2.4 \times 10^{-21}$; Table 2). Conversely, the mean and standard deviation of HbA1c values (%) among euthyroid ($n = 86$) and abnormal thyroid function groups ($n = 34$) were 6.5 ± 0.57 and 10.92 ± 1.04 , respectively which is also statistically highly significant ($t_{df118} = 29.84$, $p = 8.2 \times 10^{-57}$ assuming equal variances; $t_{df41,0} = 23.73$, $p = 2.0 \times 10^{-25}$ not assuming equal variances). Similar results were also observed by Kumar et al.³⁸ where the mean HbA1c (%) was 8.81 ± 1.96 , and 9.68 ± 1.35 for type 2 diabetes patients without and with abnormal thyroid function group, respectively.

Limitations of the Study

The study was carried out at a district hospital in West Bengal, so the results might not be reproducible among patients in other geographical areas or at different healthcare institutions.

CONCLUSION

The study shows that poorly controlled diabetes (as shown by HbA1c $>7\%$, especially $>10\%$) is significantly associated with abnormal thyroid status, while the duration of diabetes has no such implication. In the present study, there is a slight predominance of female sex, and SCH is the most common thyroid disorder.

TAKE-HOME MESSAGE

Poor control of type 2 DM is significantly associated with thyroid dysfunction, thereby

Table 1: Characteristics of diabetic patients ($N = 120$)

Characteristics		Number (%)
Age (completed years)	Up to 40	2 (1.7)
	41–60	52 (43.3)
	>60	66 (55.0)
Sex	Male	48 (40.0)
	Female	72 (60.0)
Nutritional status (BMI)	Underweight (<18.5)	5 (4.2)
	Normal (18.5–25)	85 (70.8)
	Overweight (25.1–30)	16 (13.3)
	Obese (>30)	14 (11.7)
DM	Family history present	73 (60.8)
	Age of onset (years)	Mean = 47.02 SD = 5.15
	Duration (years)	Mean = 11.05 SD = 5.4
	HbA1c status	$<7\%$ 72 (60.0) 7–10% 22 (18.3) $>10\%$ 26 (21.7)
Thyroid status	Family history present	24 (20.0)
	Goiter present	10 (8.3)
	Current thyroid status normal	86 (71.7)
	Abnormal	34 (27.3)
	SCH	23 (19.1)
	Clinical hypothyroidism	9 (7.5)
Number of hospitalizations	Subclinical hyperthyroidism	2 (1.7)
	Nil	96 (80.0)
	Once	12 (10.0)
	Twice	4 (3.3)
	3–4 times	8 (6.7)

Table 2: Associations of thyroid disorders among diabetic patients with pertinent variables ($N = 120$)

Variables		Number	Abnormal thyroid status No. (%)	Significance	
				Chi-square	p-value
Age (years)	Up to 60	54	14 (25.9)	0.28	0.596
	>60	66	20 (30.3)		
Sex	Male	48	13 (27.1)	0.062	0.804
	Female	72	21 (29.2)		
HbA1C status (%)	<7	72	0 (0.0)	94.9	2.4×10^{-21}
	7–10	22	8 (36.4)		
	>10	26	26 (100)		
Duration of diabetes (years)	Up to 5	12	2 (16.7)	0.932	0.628
	5–10	42	12 (28.6)		
	>10	66	20 (30.3)		

highlighting the importance of glycemic control and regular assessment of thyroid status among type 2 DM patients.

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Study of Diagnostic Yield of Nucleic Acid Amplification Test among Tuberculous Cervical Lymphadenitis in Immunocompetent Patients

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ABSTRACT

Background: The most common form of extrapulmonary tuberculosis (TB) is tuberculous lymphadenitis, which constitutes about 30–40% of all extrapulmonary TB cases. A new diagnostic method like the nucleic acid amplification test (NAAT) is a very sensitive and rapid test for diagnosing tuberculous cervical lymphadenopathy. It also detects rifampicin sensitivity among positive patients.

Objectives: (1) To evaluate the diagnostic yield of TrueNAT for detecting *Mycobacterium tuberculosis* bacteria in the fine-needle aspirated samples of cervical lymph nodes compared with Ziehl–Neelsen (ZN) staining; (2) to evaluate the diagnostic yield of TrueNAT for diagnosis of tuberculosis through comparison with the cytology report of fine-needle aspiration (FNA) sample of cervical lymph node and with necrotic cervical lymph node on ultrasonography (USG) neck.

Materials and methods: A total of 50 patients enrolled in this prospective study from January to December 2022. Demographic profile and clinical history were noted. Fine-needle aspirate samples were sent for TrueNAT assay, cytological examination, and ZN staining. USG neck was done for necrotic findings in the cervical lymph nodes.

Results: The TrueNAT positivity rate was 70%. TrueNAT sensitivity and specificity were assessed according to the cytology report, acid-fast bacilli (AFB) positivity on ZN stain, and the finding of necrosis in the cervical lymph node on the USG neck. The sensitivity and specificity of the TrueNAT assay were 80.49 and 77.78%, respectively, in accordance with necrosis on FNA cytology; 17.14 and 93.33%, respectively, in accordance with AFB positivity on ZN stain; and 74.29 and 33.33%, respectively, in accordance with lymph node necrosis on USG neck.

Conclusion: The TrueNAT assay should be used as an adjunctive test in addition to the conventional cytological examination of the FNA sample of lymph nodes for the rapid diagnosis of tuberculosis. It also detects rifampicin resistance simultaneously.

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INTRODUCTION

Tuberculosis (TB) is a chronic, infectious, and communicable disease that causes considerable morbidity and mortality if not diagnosed early and treated correctly.¹ In 2021, about 10.6 million people fell ill with TB, and 1.6 million TB patients died due to TB.² The prevalence of extrapulmonary TB is about 15–20% of all TB cases.³ In India and other developing countries, tuberculous lymphadenitis is the most common form of extrapulmonary TB, which accounts for about 30–40% of cases. NTM is the most common cause of lymphadenopathy in the developed world. In a country like India, where TB is high, there is a high chance of initial drug resistance in pulmonary and extrapulmonary TB. So, early identification of drug resistance will help in the early initiation of appropriate treatment. Treatment of lymph node TB is frequently started based on histopathological demonstration of granuloma in excision biopsy or fine-needle aspirate specimens without definitive microbiological evidence of TB.

Lymph node TB has been traditionally diagnosed by histopathological examination and other corroborative evidence, such as a positive mantoux test and elevated erythrocyte sedimentation rate. A definitive diagnosis of tuberculous lymphadenitis requires a demonstration of the *Mycobacterium tuberculosis* organism in the fine-needle aspiration (FNA)/biopsy specimen or the growth of the organism in a culture of the sample. Diagnosis of lymph node TB is challenging due to its paucibacillary nature. Smear examination of FNA for acid-fast bacilli (AFB) has very low sensitivity ranging from 27 to 50%. Diagnosis of lymph node TB by cytological examination is based on finding AFB and granulomatous inflammation, frequently with caseous (cheese-like) necrosis (necrotizing granulomas). Various factors like the quality and quantity of the sample, interobserver variability, and characteristic microarchitectural patterns on cytology are shared with other diseases, making the diagnosis of tuberculous lymphadenitis more difficult by cytological examination. Culture

has reduced sensitivity in paucibacillary TB, and also it takes several weeks for results and requires a highly equipped laboratory. Due to the abovementioned factors, the recent focus has been shifted to molecular diagnosis or nucleic acid amplification (NAA) methods, which detect the mycobacterial DNA in the samples and also detect rifampicin resistance.

There are two types of NAAT available in the market—one is CBNAAT/Gene Xpert, and the other one is TrueNAT. Both tests are objective tests with little or no variations in the result. CBNAAT/Gene Xpert detects *M. tuberculosis* bacteria and simultaneously detects rifampicin resistance within 2 hours from biological samples, but it requires continuous electricity and an advanced laboratory setup. In contrast, TrueNAT can run without electricity and doesn't require an advanced laboratory setup. Regarding culture, the pooled sensitivity and specificity of the NAAT method for diagnosing TB in patients with cervical lymphadenopathy were 83.1 and 93.6%, respectively. NAAT can help to confirm a diagnosis in patients suspected of lymph node tuberculosis (LNTB) when considered alongside the results of Fine needle aspiration cytology (FNAC), noting that a negative NAAT test does not rule out LNTB.³

In the current study, we evaluated the diagnostic yield of TrueNAT for the early diagnosis of tuberculous cervical lymphadenitis.

MATERIALS AND METHODS

Study Design

After obtaining Institutional Ethics Committee clearance (No. IECBHR/32-2020, Dated 25.01.2022), a prospective study

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was conducted to evaluate the diagnostic yield of NAAT among tuberculous cervical lymphadenitis patients who consulted the Department of Pulmonary Medicine at Medical College Baroda, Vadodara, Gujarat, India between January and December 2022.

Objectives

- To evaluate the diagnostic yield of TrueNAT for detecting *M. tuberculosis* bacteria in the fine needle aspirated samples suggestive of tuberculous cervical lymphadenitis compared with Ziehl–Neelsen (ZN) staining.
- To evaluate the diagnostic yield of TrueNAT for the diagnosis of TB in comparison with the cytology report of FNA samples of cases of tuberculous cervical lymphadenitis.
- To evaluate the diagnostic yield of TrueNAT for the diagnosis of TB in necrotic cervical lymph nodes on ultrasonography (USG) neck.

Inclusion Criteria

- Age >12 years.
- Immunocompetent patients with palpable or radiologically detected cervical lymphadenopathy.
- Lymph node FNA cytology is suggestive of granulomatous inflammation with or without necrosis, or lymph node FNA showing AFB on ZN staining.

Exclusion Criteria

- Age <12 years.
- Patients who did not give consent for this study.
- Patients who were taking anti-TB treatment.
- Patients with a history of human immunodeficiency virus and on immunosuppressants.

Methodology

Demographic data and clinical data, including clinical symptoms and signs related to cervical lymphadenopathy, were noted for all enrolled patients at the time of consultation. The previous history of sputum-positive pulmonary TB and contact history with sputum-positive pulmonary TB patients were recorded. USG neck was performed to assess features of necrotic lymph nodes. USG-guided lymph node aspiration was conducted using the FNA method in all patients, and aspirated samples were sent for (1) the cytological examination, (2) ZN staining for AFB, and (3) TrueNAT assay to detect AFB and rifampicin-resistance. Patients with cervical lymphadenitis whose FNA cytology report suggested granulomatous inflammation with or without necrosis or demonstrated AFB on ZN staining were enrolled in our study. TrueNAT, among the

NAAT tests, was considered for the study of the diagnostic yield of NAAT. TrueNAT is one type of NAAT that can be conducted without electricity and without advanced laboratory setup. It can detect *M. tuberculosis* Bacilli from the biological sample within 2 hours.

Statistical Analysis

Data were preprocessed using Microsoft Excel to calculate mean, median, and standard deviation. The *t*-test was used for parametric variables to compare groups of subjects. Quantitative data are expressed as mean $\pm$ standard deviation or median (interquartile range), while qualitative

variables are expressed as numbers and percentages. The Chi-squared test was used to check the association between two categorical data. *p*-values < 0.01 were considered significant. The data were captured and analyzed using the software package Statistical Package for the Social Sciences (SPSS) version 20 (SPSS Inc., Chicago, Illinois, United States of America).

RESULTS

The demographic, clinical, radiological, and microbiological characteristics of the enrolled patients in the study are described in Table 1.

Table 1: Demographic, clinical, and radiological variable

Characteristics	Sample size (n = 50)
Demographic characteristics	
Age (years)	33.28 $\pm$ 13.26
Sex (M:F)	2:3
BMI	18.31 $\pm$ 3.92 kg/m ² In TrueNAT positive: 17.78 $\pm$ 3.85 kg/m ² In TrueNAT negative: 19.66 $\pm$ 4.03 kg/m ²
Symptoms and signs	
Swelling over the neck	50 (100%)
Pain over neck swelling	25 (50%)
Anorexia	33 (66%)
Weight loss	33 (66%)
Low-grade fever	24 (48%)
Night sweats	23 (46%)
Cough	12 (24%)
TrueNAT result	
Positive	35 (70%)
Negative	15 (30%)
Site of cervical lymphadenopathy on USG neck	
Left side only	28 (56%)
Right side only	16 (32%)
Bilateral	6 (12%)
Comorbidities	
Diabetes mellitus	7 (14%)
Hypertension	5 (10%)
Hypothyroidism	4 (8%)
ischemic heart disease	1 (2%)
History of pulmonary TB (PTB)	
Previous history of sputum-positive PTB	3 (6%)
Contact history of sputum-positive PTB	9 (18%)
AFB positivity	
ZN stain positive	7 (14%)
TrueNAT positive	35 (70%)
Occupation	
Semi-skilled worker*	22 (44%)
Housewife	16 (32%)
Student	7 (14%)
Skilled worker**	5 (10%)

*Semi-skilled workers, truck drivers, retail salespersons, bartenders, flight attendants, taxi drivers, waiters, and security guards; **Skilled workers, law enforcement officers, financial technicians, nurses, representatives, and electricians

DISCUSSION

In our study, 50 patients with cervical lymphadenopathy and FNA cytology reports suggestive of TB were enrolled. The TrueNAT result of the cervical lymph node aspirate was compared with the cytology result, ZN staining for AFB, and necrotic findings in the cervical lymph node on the USG neck.

Among the 50 patients enrolled, 20 (40%) patients were male, of which 16 (32%) were TrueNAT positive, and 30 (60%) patients were female, of which 19 (38%) were TrueNAT positive on cervical lymph node fine needle aspirate (FNA). The M:F ratio of 2:3. The mean age of the patients was 33.28 ± 13.26 years. Most patients, 28 (56%), were 21–40 years. The median age of the patients was 28 years, with an interquartile range of 21–39 years. Purohit et al.,⁴ Kamal et al.,⁵ Mukhida et al.,⁶ Tanwir,⁷ and Goyal⁸ observed female predominance with a comparable peak age onset in their studies. Female preponderance may be due to the country's social dynamics. Most females stay or work inside their houses in a closed environment. So, less air ventilation tends to increase the overall risk of developing infectious diseases. There was no significant statistical correlation of age and gender with the TrueNAT result of the patients with cervical lymphadenopathy (Chi-square = 1.823; $p = 0.1770$). The mean body mass index (BMI) of the patients with a TrueNAT positive result was 17.78 ± 3.85 kg/m², and the mean BMI of the patients with a TrueNAT negative result was 19.66 ± 4.03 kg/m². Overall, the mean BMI of the patients was 18.31 ± 3.92 kg/m². There was no statistical association between the BMI of the patients and the TrueNAT result (unpaired t -test = 1.53; $p = 0.13$).

In our study, 22 (44%) patients were semi-skilled workers, followed by 16 housewives (32%), 7 students (14%), and 4 skilled workers (8%). Among all the patients, 18 semi-skilled workers (36%) were positive for TrueNAT results, followed by 10 housewives (20%) and 6 students (12%). Kamal et al.⁵ had 37 housewives (56.8%), followed by 16 students (24.6%), 11 semi-skilled workers (16.9%), and 6 skilled workers (9.2%) in their study. No significant statistical correlation existed between occupation and TrueNAT results of the patients with cervical lymphadenopathy.

In our study, palpable cervical swelling (100%) was the most common presenting feature, followed by anorexia in 33 (66%) patients, weight loss in 33 (66%) patients, pain over the neck swelling in 25 (50%) patients, fever in 24 (48%) patients, night sweats in 23 (46%) patients, and cough in 11 (22%) patients. The frequency of localized and systemic

symptoms described by Purohit et al.,⁴ Kamal et al.,⁵ and Tanwir⁷ are comparable with our study.

In our study, nine (18%) patients had a contact history of sputum-positive pulmonary TB patients, of which five were positive on TrueNAT. There is no statistically significant association between the contact history of pulmonary TB and the TrueNAT result of the patients with cervical lymphadenitis (Chi-square = 0.0107, $p = 0.9177$, and not significant at $p < 0.01$). Purohit et al.,⁴ Kamal et al.,⁵ and Nur⁹ observed a history of contact with sputum-positive pulmonary TB patients in 10.13, 26.2, and 18.3% of patients, respectively.

In our study, 41 (82%) patients showed necrotic granuloma on the cytology report. The sensitivity and specificity of the TrueNAT method for diagnosing TB in patients with cervical lymphadenitis were 80.49% and 77.78%, respectively, compared with the necrosis finding on the cytology report of cervical lymph node FNA (Table 2). The positivity rate for TrueNAT was 70%. Studies done by Purohit et al.,¹ Tanwir,⁷ Nur,⁹ Haridas et al.,¹⁰ Jha,¹¹ Sharma et al.,¹² and Nishal et al.¹³ reported necrotic granuloma in 42.86, 62.28, 58.4, 60.89, 63.8, 80, and 91.7%, respectively. Our study showed a statistically significant association between the cytology report showing necrosis and TrueNAT results in diagnosing TB in patients with cervical lymphadenitis. (Chi-square = 9.317, $p = 0.0022$ and significant at $p < 0.01$). Goyal⁸ showed a sensitivity of 77.27% and specificity of 57.1% compared to the cytology of cervical lymph node aspirated samples, and the

positivity rate for cartridge-based nucleic acid amplification test (CBNAAT) was 72.5%. Another study by Denkinger et al.¹⁴ showed a sensitivity of 83.1% and specificity of 93.6% compared to the cytology of lymph node aspirated samples for Xpert *M. tuberculosis*/rifampicin resistance assay (MTB/RIF). Mukhida et al.⁶ showed a sensitivity of 85.71% and specificity of 48.54% compared to cytology for cervical lymph node aspirated samples, and the positivity rate for Xpert MTB/RIF was 61.37%. Habous et al.¹⁵ observed a sensitivity of 76.92% and specificity of 100% compared to the cytology of lymph node aspirated samples for GeneXpert. Bankar et al.¹⁶ observed a sensitivity of 100% and specificity of 64.06%, compared to the cytology of lymph node aspirated samples. The positivity rate was 41.43% for Xpert MTB/RIF.

There was no statistically significant association when granulomatous inflammation, irrespective of necrosis in the cytology report, was compared with the TrueNAT result (Chi-square = 0.2702, $p = 0.6032$, and not significant at $p < 0.01$) (Table 3). This signifies that whenever there is necrosis in the FNAC report, the sensitivity and specificity of the TrueNAT method to detect *M. tuberculosis* increase.

In our study, 7 (14%) patients showed AFB positivity on ZN staining of FNA samples of cervical lymph nodes, of which 6 (85.71%) patients were TrueNAT positive. Among 29 patients (58%) with AFB negative on ZN staining, 17 (58.62%) were TrueNAT positive. There was no statistically significant association between TrueNAT results and

Table 2: Comparison and statistical association between TrueNAT results and necrosis on cytology reports

TrueNAT result	Cytology reports s/o		Total		
	Granulomatous inflammation with necrosis	Granulomatous inflammation without necrosis			
Positive	33 (66%)	2 (4%)	35 (70%)	Chi-square = 9.317 $p = 0.0022$ Significant at $p < 0.01$	Sensitivity = 80.49% Specificity = 77.78%
Negative	8 (16%)	7 (14%)	15 (30%)		
Total	41 (82%)	9 (18%)	50 (100%)		

Table 3: Comparison and statistical association between TrueNAT results and granulomatous inflammation on cytology reports

TrueNAT result	Cytopathology results showing granulomatous inflammation		Total		
	Yes	No			
Positive	33 (66%)	2 (4%)	35 (70%)	Chi-square = 0.2702 $p = 0.6032$ Not significant at $p < 0.01$	Sensitivity = 70.21% Specificity = 33.33%
Negative	14 (28%)	1 (2%)	15 (30%)		
Total	47 (94%)	3 (30%)	50 (100%)		

AFB results in diagnosing TB in patients with cervical lymphadenitis (Chi-square = 0.2848, $p = 0.593595$, not significant at $p < 0.01$). The sensitivity and specificity of the TrueNAT assay for detecting AFB on the FNA sample compared to the ZN staining method for AFB were 17.14 and 93.33%, respectively (Table 4). The smear quality, staining method, technician expertise, and scanty bacilli in the FNA samples are responsible for the relatively lower sensitivity and higher specificity rates in ZN staining, which ultimately help to decide to start the anti-TB treatment. In the study by Goyal,⁸ AFB by ZN staining of the cervical lymph node aspirate samples showed a sensitivity and specificity of 45.45 and 100%, respectively, with an AFB positivity rate of 39.2%. In a study by Habous et al.,¹⁵ the sensitivity was 53.85, and specificity was 100% for AFB staining. The positivity rate of AFB was 30.43%. The sensitivity and specificity of GeneXpert assay for detecting AFB on the FNA sample compared to the ZN staining method for AFB were 76.92 and 100%, respectively. The GeneXpert positivity was 43.47%. In the study by Bankar et al.,¹⁶ Mukhida et al.,⁶ and Sharma et al.,¹² the AFB positivity rate for the ZN staining method was 17.14, 4.13, and 20% respectively. Haridas et al.¹⁰ demonstrated that Xpert MTB/RIF assay had 100% sensitivity in smear-positive samples while 71.83% in smear-negative samples.

In our study, 16 (32%) patients had comorbidities. The most common comorbidity was diabetes mellitus in 25% of patients, followed by hypertension (18.75%) and hypothyroidism (12.50%). Nine out of 16 patients (56.25%) were TrueNAT positive, and 7 (43.75%) were TrueNAT negative. There was no statistically significant association

between the TrueNAT results and the patient's comorbidities (Chi-square = 0.09, $p = 0.95$, and not significant at $p < 0.01$). Studies done by Purohit et al.,⁴ Fantahun et al.,¹⁷ Mohiuddin et al.,¹⁸ and Kunoor et al.¹⁹ also reported diabetes mellitus as a common comorbidity in patients with cervical lymphadenitis.

Ultrasound examination of the neck in the study participants showed right-sided lymphadenopathy in 28 (56%) patients, left-sided lymphadenopathy in 16 (32%) patients, and involvement of both right and left sides in 6 (12%) patients. A total of 35 (70%) patients had necrosis of the lymph node on the USG of the neck, of which 26 (74.29%) were TrueNAT positive and 9 (25.71%) were TrueNAT negative. The sensitivity and specificity of TrueNAT compared with necrosis in cervical lymph nodes on the USG of the neck were 74.29 and 33.33%, respectively, but no statistically significant association was observed (Chi-square = 0.043, $p = 0.8366$, and not significant at $p < 0.01$) (Table 5).

In our study, six (12%) had lung lesions on chest X-ray, of which three patients were female and had a history of previous pulmonary TB. Studies done by Kamal et al.,⁵ Mukhida et al.,⁶ and Jha et al.¹¹ observed lung lesions on chest X-ray in 3.1, 7.5, and 16% of patients, respectively.

In our study, the TrueNAT assay identified all specimens as rifampicin-sensitive. However, the sensitivity and specificity of the TrueNAT assay in detecting rifampicin resistance were not attempted because it requires comparison with the liquid culture method, a gold-standard method, for diagnosing TB. A study conducted by Haridas et al.¹⁰ did not detect any rifampicin-

resistant case in this study on Xpert MTB/RIF assay.

Limitation

In our institute, there is no laboratory facility available to carryout culture and drug sensitivity testing for comparison, which is the gold standard for diagnosis.

CONCLUSION

The present study supports the TrueNAT assay as a reliable reverse transcription polymerase chain reaction-based test for the rapid diagnosis of lymph node TB. It can be used as an adjunctive test to conventional cytological examination, smear microscopy, and ultrasonic evaluation of necrotic cervical lymphadenopathy for the diagnosis of lymph node TB. The sensitivity and specificity of NAAT for detecting *M. tuberculosis* increase whenever there is granulomatous necrosis on cytology of the lymph node and USG neck showing findings of necrotic lymph nodes.

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Table 4: Comparison and the statistical association between FNA and AFB positivity by ZN staining and TrueNAT results

TrueNAT result	FNA/AFB result		Total		
	Positive	Negative			
Positive	6 (12%)	29 (58%)	35 (70%)	Chi-square = 0.2848 $p = 0.593595$ Not significant at $p < 0.01$	Sensitivity = 17.14% Specificity = 93.33%
Negative	1 (2%)	14 (28%)	15 (30%)		
Total	7 (14%)	43 (86%)	50 (100%)		

Table 5: Comparison and statistical association between TrueNAT result and necrotic lymph node on USG neck

TrueNAT result	USG neck showing necrotic lymph nodes		Total		
	Yes	No			
Positive	26 (52%)	10 (20%)	36 (72%)	Chi-square = 0.043 $p = 0.8366$ Not significant at $p < 0.01$	Sensitivity = 74.29% Specificity = 33.33%
Negative	9 (18%)	5 (10%)	14 (28%)		
Total	35 (70%)	15 (30%)	50 (100%)		

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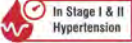


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Dynamics of Antibody Response to Covishield Vaccine after 6 Months: A Longitudinal Prospective Study



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ABSTRACT

Objectives: To study the dynamics of antibody responses in the real world up to 6 months following two Covishield vaccination doses and evaluate its correlation with age.

Materials and methods: From March 2021 to February 2022, a prospective, longitudinal study of healthcare workers (HCWs) from a dedicated COVID-19 hospital was conducted. Institutional Ethics Committee permission was obtained. HCWs were divided into two groups. The first group consisted of individuals who had received the first dose of the COVID-19 vaccine, with at least 3 weeks elapsed since the dose, and who had not received the second dose until the initial blood sample for antibody testing was obtained. The second group consisted of individuals who had received both COVID-19 doses and had at least 2 weeks between the administration of the second dose and the collection of the first sample for antibody testing. In March 2021, after undergoing phlebotomy for serum collection, the participants responded to the survey. Electrochemiluminescence immunoassay (ECLIA) was used to perform a quantitative test for antibodies to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) protein receptor domain [receptor binding domain (RBD)]. The test used had a 98.8% sensitivity and a 99.9% specificity. If the antibody titer was 0.80 U/mL or higher, it was deemed positive; if it was lower, it was deemed negative. Two follow-ups were conducted for both groups, 3 and 6 months following the first sample collection. During both follow-up visits, a blood sample was obtained for testing the amount of antibody response, and the history of COVID-19 disease following the initial sample was taken.

Results: Every HCW had received the Covishield vaccination. After the vaccine's first dosage, 61 HCWs in the first group underwent antibody testing. The information about the 43 HCWs in the first group who attended the two follow-ups is as follows. There were 14 (32.6%) nurses and 5 (11.6%) doctors among the 43 HCWs. The age range was 21–55 years, with the median [interquartile range (IQR)] age being 26 (22–40) years and 20 (60.5%) being females. The vaccination series had a median (IQR) of 34 (29–49) days between doses. There was a statistically significant difference in immunoglobulin G (IgG) levels of the three samples, $\chi^2 = 13.579$, $p = 0.001$. Median (IQR) IgG levels of the three samples at 1 month after the first dose, 3 and 6 months after the second dose were 8511 (51–15400) U/mL, 1471 (249–5050) U/mL, and 978 (220–2854) U/mL, respectively. The antibody titer was negative for two HCWs in the first sample, positive in the rest of the samples, and positive in all samples in both follow-ups. In the second group, following two COVID-19 dosages, a total of 65 HCWs had tested positive for antibodies. The information of the 56 HCWs in group II who attended both follow-ups is as follows. Of the 56 HCWs, 15 (26.8%) were doctors, 27 (48.2%) were nurses, and 14 (25%) were others. The age range was 20–64 years, with a median (IQR) of 29.5 (22–37.7) and 31 (55.3%) female participants. The vaccination series had a median (IQR) interval of 32 (29–35) days between doses. There was a statistically significant difference in IgG levels of the three samples, $\chi^2 = 31.107$, $p < 0.0001$. Median (IQR) IgG levels of the three samples at 20 days, 3.8 months, and 7 months after the second dose were 2377.5, 1345.5, and 1257 U/mL, respectively. Spearman's rank order correlation was used to assess the association between IgG level and age in both groups. The relationship between IgG levels and age was weakly correlated and not statistically significant.

Conclusion: There is a waning of antibody titer over time postimmunization. A lower antibody titer can be a contributing factor for infections that emerge later. IgG levels postvaccination do not differ according to age.

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus-caused coronavirus illness (COVID-19) has impacted 760 million people and has caused 6.8 million deaths all over the world.¹ Antibodies are proteins produced by the body's immune system after you have been infected or

vaccinated with a disease agent.² Vaccination is the safe way for acquiring herd immunity. Safe and effective vaccines available equitably are the game-changing tool in controlling the worldwide COVID-19 pandemic.³ In India, the COVID-19 vaccination commenced on 16th January 2021, with two vaccines—AZD1222-ChAdOx1-S (Covishield)

and BBV152 (Covaxin).⁴ Later other vaccines like Sputnik V, and Corbavax were added. To date, India has given 2.2 billion doses and >95 crore Indians are fully vaccinated.⁵ Covishield contributes to most (79.3%) of this vaccination.⁵ The immune response following COVID-19 vaccination can be evaluated by measuring the antibodies. A person's total amount of antibodies can be assessed using methods like the enzyme-linked immunosorbent assay (ELISA), and certain neutralizing antibodies can be tested for viral neutralization assays.⁶

Though phase 3 data from randomized controlled trials have found Covishield and Covaxin safe and effective, the real-world data about the antibody response following Covishield vaccines is limited. After 6 months of two doses of the ChAdOx1 nCoV-19 coronavirus vaccine (recombinant) (Covishield), we examined the dynamics of antibody responses and assessed how they are correlated with age.

MATERIALS AND METHODS

Study Design

The present prospective, single-center, longitudinal study was carried out on healthcare workers (HCWs) from a dedicated COVID-19 hospital (DCH) in a metropolitan city in India.

Study Period

The research was carried out between March 2021 and February 2022.

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Sampling

The following two groups of HCWs were taken:

- First group: Individuals who had received the first dose of the COVID-19 vaccine, with at least 3 weeks elapsed since the dose, and had not received the second dose until the initial blood sample for antibody testing was obtained.
- Second group: Individuals who have received both COVID-19 doses and have had at least 2 weeks between the administration of the second dose and the collection of the first sample for antibody testing.

Inclusion Criteria

Healthcare workers included doctors, nurses, security personnel, and other staff members employed by this DCH. Participants in the study who had received the COVID-19 vaccination were also included.

Study Procedure

The first sample for antibody testing was obtained from the participants in March 2021 after they underwent phlebotomy for serum collection and completed the survey. Using the "Elecsys anti-SARS-CoV-2" electrochemiluminescence immunoassay (ECLIA), a quantitative test for antibodies to the SARS-CoV-2 spike (S) protein receptor domain [receptor binding domain (RBD)] was conducted. This test's specificity was 99.9% (CI: 99.9–100) and sensitivity was 98.8% (CI: 98.1–99.3). If the antibody titer was 0.80 U/mL or higher, it was deemed positive; if it was lower, it was deemed negative.

Follow-up

Two follow-ups were conducted for both groups, 3 and 6 months following the first sample collection. During both follow-up visits, a blood sample was obtained for testing the amount of antibody response and the history of COVID-19 disease following the initial sample, and that of the second COVID-19 vaccine for the first group was taken.

Statistical Analysis

Microsoft Excel version 2010 was used for data entry, and the Statistical Package for the Social Sciences (SPSS) 16 software (SPSS Inc., Chicago, Illinois, United States of America) package was used for statistical analysis. The data were examined for normality, and for nonparametric data, relevant statistical tests such as the Wilcoxon signed-rank test, Fischer's exact test, and Chi-squared test were employed. Two-sided tests were also included. Continuous data were shown as the median [interquartile range (IQR)], while categorical data were shown as numbers.

RESULTS

Every HCW had received the Covishield vaccination. After the vaccine's first dosage, 61 HCWs in the first group underwent antibody testing. The information about the 43 HCWs in the first group who attended the two follow-ups is as follows—there were 14 (32.6%) nurses and 5 (11.6%) doctors among the 43 HCWs. The age range was 21–55 years, with the median (IQR) age being 26 (22–40) years, and 20 (60.5%) were females. The vaccination series had a median (IQR) of 34 (29–49) days between doses.

There was a statistically significant difference in immunoglobulin G (IgG) levels of the three samples, $\chi^2 = 13.579$, $p = 0.001$. Median (IQR) IgG levels of the three samples at 1 month after the first dose, 3 and 6 months after the second dose were 8511 (51–15400) U/mL, 1471 (249–5050) U/mL, and 978 (220–2854) U/mL, respectively as shown in Figure 1. The antibody titer was negative for two HCWs in the first sample, positive in the rest of all samples, and positive in all samples in both follow-ups. Between the first dose and the first sample, the period of time [median (IQR)] was 31 (28–38) days, with a range of 26–58 days. Between the second dose and the second sample, the period of time [median (IQR)] was 92 (83–101) days, with a range of 58–121 days. Between the second dose and the third sample, the period of time [median

(IQR)] was 183 (176–190) days, with a range of 144–212 days.

A *post hoc* analysis using Wilcoxon signed-rank tests was carried out, and a level of significance of $p < 0.017$ was found by using a Bonferroni correction. IgG levels decreased statistically significantly from the first to the second sample ($Z = -3.598$, $p < 0.0001$), from the second to the third sample ($Z = -4.633$, $p < 0.0001$), and from the first to the third sample ($Z = -3.574$, $p < 0.0001$). A history of COVID-19 was present in six HCWs before the first sample collection, two between the first and second samples, and none between the second and third samples. All these COVID-19 infections were mild.

The association between the age of 43 HCWs and their IgG level at 1 month following the first dose and 3 and 6 months following the second dose was examined using Spearman's rank order correlation (Table 1). Age and IgG levels had a weak correlation that was not statistically significant [$(r_s = 0.033$, $p = 0.836$), $(r_s = 0.055$, $p = 0.724$), $(r_s = -0.026$, $p = 0.866$) respectively].

In the second group, following two COVID-19 dosages, a total of 65 HCWs had tested positive for antibodies. The information of the 56 HCWs in group two who attended both follow-ups is as follows. Of the 56 HCWs, 15 (26.8%) were doctors, 27 (48.2%) were nurses, and 14 (25%) were

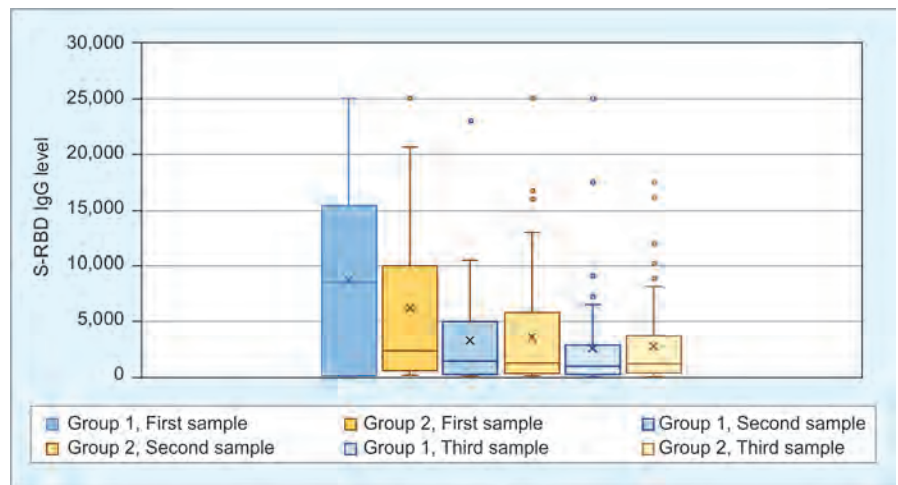


Fig. 1: Antibody response postvaccination

Table 1: Spearman's rank order correlation between age and IgG in group I

			IgG, 1 month after the first dose	IgG, 3 months after the second dose	IgG, 6 months after the second dose
Spearman's rho	Age	Correlation coefficient (r_s)	0.033	0.055	-0.26
		Significance (two-tailed)	0.836	0.724	0.866
		N	43	43	43

others. The age range was 20–64 years, with a median (IQR) of 29.5 (22–37.7) and 31 (55.3%) female participants. The vaccination series had a median (IQR) interval of 32 (29–35) days between doses. There was a statistically significant difference in IgG levels of the three samples, $\chi^2 = 31.107$, $p < 0.0001$. Median (IQR) IgG levels of the three samples at 20 days, 3.8 months, and 7 months after the second dose were 2377.5, 1345.5, and 1257 U/mL, respectively. The antibody titer was positive in all samples during the first and in both follow-up samples.

Between the second dosage and the first sample, the period of time [median (IQR)] was 19.6 (17–23) days, with a range of 15–25 days. Between the second dose and the second sample, the period of time [median (IQR)] was 114 (109–118) days, with a range of 98–144 days. Between the second dosage and the third sample, the period of time [median (IQR)] was 207 (202–212) days, with a range of 186–245 days.

Aposthoc analysis using Wilcoxon signed-rank tests was carried out, and a level of significance of $p < 0.017$ was found by using a Bonferroni correction. There was a statistically significant reduction in IgG levels from the first to the second sample ($Z = -3.646$, $p < 0.0001$), from the second to the third sample ($Z = -3.450$, $p < 0.001$), and from the first to the third sample ($Z = -3.336$, $p < 0.001$). A history of COVID-19 was present in 10 HCWs before the first sample collection, four HCWs between the first and second samples, and one HCW between the second and third samples. All these COVID-19 infections were mild.

The association between the age of 56 HCWs and their IgG levels at 20 days, 3.8 months, and 7 months following the second dosage was ascertained using Spearman's rank order correlation (Table 2). Age and IgG levels had a weak correlation that was not statistically significant [$(r_s = 0.148, p = 0.277)$, $(r_s = 0.161, p = 0.236)$, $(r_s = -0.147, p = 0.279)$, respectively].

DISCUSSION

Though the antibody titer was highest after the first dose, two HCWs had negative titers after the first dose. The antibody titers decreased subsequently in both groups but did not become negative until 6 months. Given that not all vaccine-induced short-lived plasmablasts develop into long-lived plasma cells, a drop in antibody titer is expected to occur.^{7–9}

Table 2: Spearman's rank order correlation between age and IgG in group I

		IgG, 1 month after the first dose	IgG, 3 months after the second dose	IgG, 6 months after the second dose
Spearman's rho	Age	0.148	0.161	–0.147
	Correlation coefficient (r_s)			
	Significance (two-tailed)	0.277	0.236	0.279
	N	56	56	56

In a longitudinal prospective study post Pfizer-BioNTech (BNT162b2) vaccination, the antibody levels had fallen after 12 weeks and 6 months.⁷ This finding was similar to our study. Also in this study, the IgG response was significantly inversely correlated with age.⁷ In our study, there was a weak correlation between the age of vaccinated individuals and IgG levels, which was not significant. Also, in a longitudinal cohort study in 2021 from Odisha in HCWs with a complete dose of vaccines, there were no obvious statistically significant variations in antibody titers with respect to comorbidities, gender, or age.⁸

Quantitative anti-spike antibodies were serially measured at 3-week, 3-, and 6-month intervals following the completion of the second dosage of Covishield and Covaxin in a longitudinal research involving 481 HCWs.⁹ With both vaccinations, the seropositivity rate was 5.6 times lower at 6 months.⁹ This finding was similar to our study. In this research study, the second dosage of the vaccine did not significantly increase the titer of spike antibodies in comparison to the first dose.⁹ In our study the antibody titer was highest after the first dose, but two HCWs had negative titers after the first dose.

A significant decrease in antibody levels was also observed after 6 months following the second of two Covishield vaccination doses in 122 HCWs in India, according to a prospective longitudinal research.¹⁰ The only significant factor influencing antibody levels at 6 months was a past history of COVID-19.¹⁰ In another longitudinal cohort study of HCWs post BNT162b2 vaccination from Israel, lower antibody concentrations were associated with male sex, older age, immunosuppression, diabetes, hypertension, heart disease, and autoimmune diseases.¹¹ The limitation of this study is that we have not measured cell-mediated immunity.

CONCLUSION

There is a waning of antibody titer over time postimmunization. A lower antibody titer can be the contributing factor for infections that

emerge later. IgG levels postvaccination do not differ as per age.

ACKNOWLEDGMENT

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Hypomagnesemia in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Background: Recent research has shown that low serum levels of magnesium are often linked to both microvascular and macrovascular complications in individuals with diabetes mellitus. Hence, monitoring of serum magnesium levels is needed in diabetic patients. Furthermore, the addition of magnesium through supplementation may present a novel therapeutic strategy for mitigating vascular complications in individuals with diabetes.

Objectives: To assess the prevalence of hypomagnesemia in type 2 diabetes mellitus patients and to assess the association between hypomagnesemia and microvascular complications of diabetes mellitus in a tertiary care hospital in North Kerala.

Materials and methods: An analytical cross-sectional study was conducted at a tertiary care hospital involving 230 diabetic patients receiving outpatient and inpatient care in the Department of Internal Medicine at Government Medical College, Kozhikode, Kerala. The study took place from January 2018 to December 2018, during which serum magnesium levels were assessed and analyzed in relation to the patients' microvascular complications and glycemic control.

Results: We observed that 19.13% of the participants had hypomagnesemia. This condition was found to be more common among older individuals with diabetes, as indicated by a p -value of 0.022. However, there were no significant differences in serum magnesium levels based on gender (p -value 0.18), body mass index (BMI) (p -value 0.223), or the duration of diabetes (p -value 0.36). The prevalence of diabetic retinopathy, diabetic neuropathy, and diabetic nephropathy was higher in diabetics with hypomagnesemia than their counterparts with normal magnesium, with a p -value of 0.001, 0.001, and 0.001, respectively. There was a significant negative correlation obtained between serum magnesium and glycated hemoglobin (HbA1C) values (Pearson coefficient = -0.240 and p -value = <0.01) and fasting blood sugar (FBS) values (Pearson coefficient = -0.265 and p -value = <0.01).

Conclusion: Hypomagnesemia is negatively correlated with HbA1C and FBS but not related to duration of diabetes and gender. The prevalence of microvascular complications was higher among the diabetics with hypomagnesemia.

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INTRODUCTION

India is often referred to as the diabetes capital of the world, having the highest percentage of diabetes cases globally. The total number of people with diabetes has been projected to rise from 171 million in 2000 to 366 million in 2030.¹ Globally, an estimated 422 million adults had diabetes in 2014 compared to 108 million in 1980. The global prevalence of diabetes has doubled, from 4.7 to 8.5% in the adult population from 1980.² The number of people with diabetes in India increased from 26.0 million in 1990 to 65.0 million in 2016. Hypomagnesemia is frequently observed in individuals with type 2 diabetes mellitus. Overall prevalence of hypomagnesemia in type 2 diabetes mellitus varies from 13.5 to 47.7%.³ In a study conducted in North Kerala in 2013, hypomagnesemia was seen in 15.7% of the participants among patients with type 2 diabetes.⁴ Various studies conducted across India and the world showed that the prevalence of hypomagnesemia (Jain et al. –32%,⁵ Chhatrapati Shivaji Subharti Hospital

–34%,⁶ Saini et al.⁷ –25–39%, Wälti et al.⁸ –37.6%, Mohan et al.⁹ –35%) varied from 25 to 39%. A higher occurrence of magnesium deficiency has been observed in individuals with type 2 diabetes mellitus, particularly among those who have poorly controlled blood sugar levels, a longer history of the disease, and the existence of chronic micro- and macrovascular complications.¹⁰ Hypomagnesemia has been linked to poor glycemic control and a higher occurrence of retinopathy, neuropathy, nephropathy, and macrovascular complications in diabetes mellitus.¹⁰ Therefore, it is advisable to regularly assess the magnesium levels in all type 2 diabetic patients.¹¹ Oral magnesium supplements can help to correct magnesium deficiencies, enhance insulin sensitivity, reduce oxidative stress, and mitigate systemic inflammation. Magnesium supplementation presents a promising new approach to reducing vascular complications in diabetes patients.¹² This study was designed to find out the prevalence of hypomagnesemia in type 2 diabetes mellitus patients in a tertiary

care hospital in North Kerala and its influence on microvascular complications of diabetes mellitus.

MATERIALS AND METHODS

An analytical cross-sectional study was conducted at a tertiary care hospital involving 230 diabetic patients receiving outpatient and inpatient care in the Department of Internal Medicine at Government Medical College, Kozhikode, Kerala between January 2018 to December 2018. The ethics clearance from the Institutional Ethics Committee (IEC) was obtained prior to start of study (GMCKKD/RP 2018/IEC/11). The study included diagnosed cases of type 2 diabetes mellitus of ≥ 5 years duration. All patients with other comorbidities like hypertension, chronic liver disease, coronary artery disease, chronic kidney disease of other causes, patients on drugs known to affect magnesium levels like aminoglycosides, amphotericin, cyclosporine, digoxin and diuretics, proton-pump inhibitors, magnesium supplementation and magnesium-containing antacids were excluded from the study. Patients with acute or chronic diarrheal/malabsorption states, thyroid or adrenal dysfunction, pregnant/lactating women, history of chronic alcohol use, sepsis, and patients not consenting for blood sampling were also excluded from the study.

A total of 230 diabetic patients (115 males and 115 females), after assessing for eligibility as per the inclusion and exclusion criteria, were included in the study. Before the study, all patients were informed about the study, and informed written consent was duly taken. All participants were evaluated by detailed history, including age, gender, duration of diabetes, and current use of medication. Blood pressure, height, and weight were taken. Body mass index (BMI) was calculated, and patients were classified according to the World Health Organization (WHO) Asian BMI classification

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(18.5–22.99 = normal, ≤ 18.5 = underweight, 23–24.99 = overweight, ≥ 25 = obese). To diagnose diabetic retinopathy, fundus examination was done by an ophthalmologist, and findings were noted; patients were classified into four groups (normal/ nonproliferative diabetic retinopathy/proliferative diabetic retinopathy/macular edema) based on fundus findings according to International Clinical Diabetic Retinopathy Disease Severity Scale. To diagnose diabetic nephropathy, urine albumin-to-creatinine ratio (ACR) was used, and patients with urine ACR < 30 mg/gm of creatinine was normal, and 3–300 mg/gm of creatinine was microalbuminuria and > 300 mg/gm of creatinine was macroalbuminuria according to American Diabetic Association guidelines. To diagnose diabetic neuropathy, detailed medical history and neurological examination, pinprick sensation test, perception with monofilaments, vibration and position, and reflexes were performed in all patients, and scores were calculated using the Michigan Neuropathy screening instrument. Autonomic neuropathy was not included in this study. Routine investigations [complete blood count (CBC), renal function test (RFT), liver function test (LFT)], electrocardiogram (ECG), serum magnesium levels, fasting blood sugar (FBS), postprandial blood sugar (PPBS), glycated hemoglobin (HbA1C), urine routine, and urine ACR were done in all patients. Normal serum magnesium level was taken as 1.5–2.3 mg/dL (Calmagite dye method—test principle). Data assessment was done by using Statistical Package for the Social Sciences (SPSS) software. Microsoft Word and Excel were used to generate tables and charts.

RESULTS

Of the total 230 patients in our study, 115 patients were males and 115 were females. The basic characteristics of the study population are given in Table 1. The mean age of the study population was 62.63 years (± 11.211). The prevalence of hypomagnesemia in our study was 19.13% (44) among the diabetic patients, with a mean magnesium value of 1.87 mg/dL (± 0.373). Among the patients with hypomagnesemia, 41% (18) were males and 60% (26) were females. There was no significant difference between gender and magnesium levels (p -value 0.18). The mean duration of diabetes was 11.21 years (± 5.368), and the mean BMI was 23.2 kg/m² (± 3.052). No significant association was found between duration of diabetes and BMI with hypomagnesemia, with p -values of 0.36 and 0.22, respectively. In our study, out of 230 patients, 50% of patients had nonproliferative diabetic retinopathy, 4.3% had proliferative diabetic retinopathy, and

2.2% had macular edema. In our study, out of 230 patients, 49.1% (113) had signs of diabetic neuropathy as indicated by score ≥ 2 using the Michigan Neuropathy screening instrument. In our study, out of 230 patients, 37% (85) had microalbuminuria, and 36% (83) had macroalbuminuria. The prevalence of diabetic retinopathy, diabetic neuropathy, and diabetic nephropathy were higher in diabetics with hypomagnesemia with the p -value of 0.001, 0.001, and 0.001, respectively. The mean HbA1C value was 9.23% (± 1.84). A significant negative correlation was observed between serum magnesium and HbA1C values, as indicated by a Pearson coefficient of -0.240 and a p -value of < 0.01 . This suggests that as serum magnesium levels decrease, HbA1C levels tend to increase (Fig. 1). A significant negative correlation was found between serum magnesium and FBS values, with a Pearson coefficient -0.265 and a p -value of < 0.01 . This indicates that as serum magnesium levels decrease, FBS levels tend to increase (Fig. 2). Although there existed a weak negative correlation between PPBS and serum magnesium, p -value was not statistically significant (Pearson coefficient = -0.078 , p -value = 0.239). Hypomagnesemia and complications of diabetes mellitus among study population is given in Table 2.

Table 1: Demographic and clinical details of study population

Variables	Mean ($\pm$ standard deviation)
Mean age	62.63 years (± 11.211)
Sex (male:female)	115:115
Duration of diabetes (mean)	11.21 years (± 5.368)
BMI (mean)	23.2 kg/m ² (± 3.052)
Systolic blood pressure (mean)	130.67 mm Hg (± 12.523)
Diastolic blood pressure (mean)	82.37 mm Hg (± 6.683)
FBS (mean)	176.94 mg/dL (± 66.235)
Postprandial blood sugar (mean)	202.27 mg/dL (± 85.872)
HbA1C (mean)	9.23% (± 1.843)

Table 2: Hypomagnesemia and complications of diabetes mellitus among study population

Variables	Number (%)
Serum magnesium (mean)	1.87 mg/dL (± 0.373)
Hypomagnesemia	44 (19.13%)
Diabetic retinopathy	130 (56.52%)
Diabetic neuropathy	113 (49.13%)
Diabetic nephropathy	168 (73.04%)

DISCUSSION

Type 2 diabetes has become a worldwide epidemic, with a rising incidence over the past decade. It has been observed that hypomagnesemia occurs more frequently in individuals with type 2 diabetes when compared to those without diabetes.³ According to the study conducted by Pham et al.,³ overall prevalence of hypomagnesemia in type 2 diabetes mellitus varied from 13.5 to 47.7%. In our study, we found that 19.13% of diabetic patients had hypomagnesemia, which was similar to a study conducted by Mohammed et al. in North Kerala, who observed a prevalence of 15.7% for hypomagnesemia among participants with type 2 diabetes.⁴ The higher prevalence obtained in this study might be due to larger

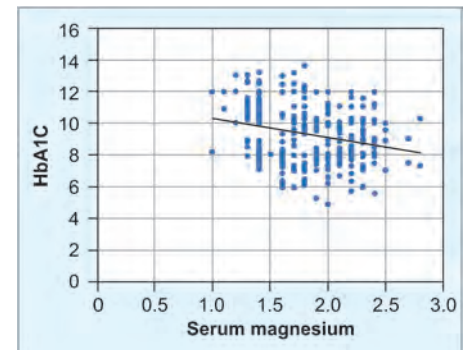


Fig. 1: Scatter diagram showing negative correlation between serum magnesium and HbA1C values (Pearson coefficient = -0.240 and p -value = < 0.01)

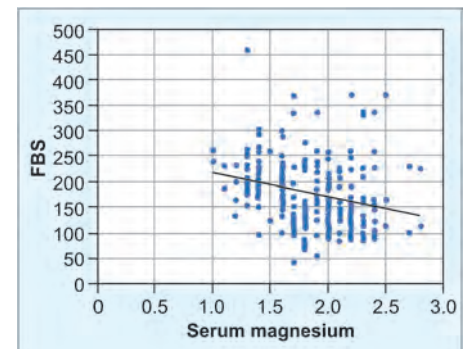


Fig. 2: Scatter diagram showing negative correlation between serum magnesium and FBS values (Pearson coefficient = -0.265 and p -value = < 0.01)

Table 3: Comparison of various parameters with serum magnesium

Variables	Hypomagnesemia (N = 44)	Normomagnesemia (N = 186)	p-value
Mean age	66.1136 years (± 11.150)	61.8065 years (± 11.095)	0.022
Diabetic retinopathy	43 (97.73%)	87 (46.77%)	0.001
Diabetic neuropathy	39 (88.64%)	74 (39.78%)	0.001
Diabetic nephropathy	42 (95.45%)	126 (67.74%)	0.001
HbA1C (>7%)	44 (100%)	170 (91.39%)	<0.01
FBS (mean)	215.863 mg/dL (± 55.271)	167.736 mg/dL (± 65.381)	0.001

sample size in our study compared to the study mentioned above. A study conducted by Dasgupta et al. from Assam reported hypomagnesemia in only 11% of diabetics. The lower incidence of hypomagnesemia in their study was attributed to stricter exclusion criteria followed in the study.¹³ Studies done by Mishra et al.¹⁴ and Nasri et al.¹⁵ showed significant negative correlation depicting that as the age increases, plasma magnesium level decreases. This was in concordance with our study, which showed that diabetics with hypomagnesemia [66.11 (± 11.15) years] were older compared to diabetics with normomagnesemia [61.81 (± 11.09) years] (p -value of 0.022). Although there existed mild negative correlation between age and serum magnesium, but it was not statistically significant (Pearson coefficient = -0.0107 and p -value = 0.106). We did not observe a significant difference in serum magnesium levels between males and females, as indicated by a p -value of 0.18. Furthermore, there was no significant association between the duration of diabetes and serum magnesium levels, with a p -value of 0.36. However, studies done by Wälti et al.⁸ and Mishra et al.¹⁴ showed inverse correlation between duration of diabetes and serum magnesium. Hypomagnesemia has been reported in patients with diabetic retinopathy, with lower magnesium levels predicting a greater risk of severe diabetic retinopathy. Of the diabetic patients with hypomagnesemia [19.13% (44)], 97.73% (43) patients had diabetic retinopathy compared to 46.77% (87) diabetic patients with normal magnesium ($n = 186$), indicating that prevalence of diabetic retinopathy was higher in diabetics with hypomagnesemia than their counterparts with normal magnesium (p -value = 0.001). This was comparable to the study conducted by Dasgupta et al.,¹³ where they demonstrated higher prevalence of retinopathy in the hypomagnesemia group (64 vs 45.8%). This was also comparable to study done by Fuji et al.,¹⁶ where a marked depletion in plasma and erythrocyte magnesium levels in diabetic patients with advanced retinopathy was established. Hypomagnesemia has been reported in patients with diabetic neuropathy. Of the diabetic patients with

hypomagnesemia [19.13% (44)], 88.64% (39) patients had diabetic neuropathy compared to 39.78% (74) diabetic patients with normal magnesium ($n = 186$), indicating that prevalence of diabetic neuropathy was higher in diabetics with hypomagnesemia than their counterparts with normal magnesium (p -value = 0.001). This was comparable to the study conducted by De Lorde Lima et al.,¹⁷ where they demonstrated higher prevalence of neuropathy in the hypomagnesemia group. Hypomagnesemia has been reported in patients with diabetic nephropathy, with lower magnesium levels predicting a greater risk of severe diabetic nephropathy. Of diabetic patients with hypomagnesemia [19.13% (44)], 95.45% (42) patients had diabetic nephropathy compared to 67.74% (126) diabetic patients with normal magnesium ($n = 186$), indicating that prevalence of diabetic nephropathy was higher in diabetics with hypomagnesemia than their counterparts with normal magnesium (p -value = 0.001). This was comparable to the study conducted by Sajjan et al.,¹⁸ where they established significant differences in serum magnesium and diabetic nephropathy in diabetic patients. The mean HbA1C value was 9.23% (± 1.84). A significant negative correlation was observed between serum magnesium and HbA1C values, as indicated by a Pearson coefficient of -0.240 and a p -value of <0.01 . This suggests that as serum magnesium levels decrease, HbA1C levels tend to increase. This was in comparison to the study done by Mohammed et al.,⁴ Mishra et al.,¹⁴ and Sharma et al.¹⁹ In our study, no significant difference was found between BMI and serum magnesium levels (p -value = 0.223). The mean FBS of diabetic patients with hypomagnesemia and normomagnesemia were 215.86 (± 55.27) mg% and 167.74 (± 65.38) mg%, respectively. A significant negative correlation was found between serum magnesium and FBS values, with a Pearson coefficient of -0.265 and a p -value of <0.01 . This indicates that as serum magnesium levels decrease, FBS levels tend to increase. This was in comparison to the study done by Mohammed et al.,⁴ Mishra et al.,¹⁴ and Sharma et al.¹⁹ The mean PPBS was 202.27 $\pm$ 85.87 mg/dL. There existed a significant difference between PPBS and

serum magnesium levels with p -value of 0.021. There existed a weak negative correlation, but p -value was not significant (Pearson coefficient = -0.078 , p -value = 0.239). Comparison of various parameters with serum magnesium is given in Table 3.

This study included a large sample with representation from a varied population. This study was aimed at establishing the relationship between plasma magnesium levels and microvascular complications in diabetics. However, we acknowledge that intra-erythrocyte magnesium and urinary magnesium are relatively more sensitive methods to assess magnesium deficiency than plasma magnesium. Hypomagnesemia is also found to be associated with macrovascular complications like myocardial infarction.²⁰ However, we did not attempt to study the effect of magnesium levels on macrovascular complications. Few studies have demonstrated favorable effect on lipid profile²¹ and blood glucose¹² levels with oral magnesium supplementation. Follow-up studies are recommended with large sample size and supplementing magnesium either prophylactically to look for delay in complications of diabetes mellitus or by therapeutically correcting magnesium for deficient people and to look for glycemic control.

CONCLUSION

Hypomagnesemia is associated with poor glycemic control among diabetic patients. The prevalence of microvascular complications was higher among hypomagnesemic diabetics. Magnesium could be checked as a routine investigation for all uncontrolled diabetic patients.

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Prevalence and Association of Risk Factors According to Liver Steatosis and Fibrosis Stages among Nonalcoholic Fatty Liver Disease Patients with Type 2 Diabetes Mellitus in India: A Cross-sectional Study

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) and nonalcoholic fatty liver disease (NAFLD) are linked to the global diabetes epidemic, leading to increased disease progression and adverse health outcomes. The renaming of NAFLD to metabolic dysfunction-associated steatotic liver disease (MASLD) at the 2023 European Association for the Study of the Liver Congress highlights the complex relationship between metabolic disorders and liver health. Taking this into consideration, we aimed this study to identify prevalence and risk factors associated with the stages of NAFLD in individuals with T2DM in the Indian population.

Materials and methods: This observational, cross-sectional study was conducted on 1,521 T2DM patients at Dr Panikar's Speciality Care Centre, Mumbai, between September 1, 2022 and October 31, 2022. Demographic parameters such as age, gender, height, weight, and anthropometric parameters such as body mass index (BMI) and waist circumference were measured. Liver fibrosis and steatosis stages were identified by vibration-controlled transient elastography (VCTE) using FibroScan®.

Results: The prevalence of liver steatosis was 75.1% among the 1,521 diabetes cases [S0 (24.9%), S1 (15.1%), S2 (24%), and S3 (36%)], whereas the prevalence of liver fibrosis was 28.0% [F0 (72%), F1 (19%), F2 (5%), F3 (1.5%), and F4 (3.4%)]. The S1 ($p = 0.012$), S3 ($p = 0.001$), F1 ($p = 0.001$), and F2 ($p = 0.001$) grades showed significant gender-related changes, demonstrating a positive connection. Furthermore, waist circumference was associated with disease severity in both liver steatosis and fibrosis stages ($p = 0.001$), but BMI was solely associated with the degree of steatosis ($p = 0.001$). The mean age differences between these categories, however, did not reach statistical significance (p -values of 0.149 and 0.078, respectively, for the steatosis and fibrosis grades).

Conclusion: The study reveals a high prevalence of NAFLD (steatosis and fibrosis) in T2DM patients, increasing the risk of advanced fibrosis. In T2DM patients with risk factors including waist circumference and BMI, appropriate screening and intervention are required.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is highly prevalent among type 2 diabetes mellitus (T2DM) patients in India, with up to 70% affected.¹⁻³ The synergy between T2DM and NAFLD accelerates disease progression and increases health risks. The alarming rise of T2DM in India contributes to the global diabetes epidemic, with NAFLD emerging as a parallel health challenge. The coexistence of these conditions poses management challenges and elevates the risk of adverse outcomes,²⁻⁴ emphasizing the need for integrated approaches to prevention and treatment in the Indian healthcare system.

The well-established link between T2DM and NAFLD, in which people with T2DM have a higher prevalence of NAFLD, highlights the complex interplay between metabolic disorders and liver health.^{3,5,6} This observation prompted a significant paradigm shift at the

2023 European Association for the Study of the Liver (EASL) Congress, when the term "metabolic dysfunction-associated steatotic liver disease" (MASLD) was coined to replace "nonalcoholic fatty liver disease" (NAFLD). The EASL, La Asociación Latinoamericana para el Estudio del Hígado (ALEH), and the American Association for the Study of Liver Diseases (AASLD) announced the renaming of NAFLD to MASLD in June 2023. The rationale for this change was to offer a diagnosis for the most common chronic liver disease in the world while also establishing a supportive and nonstigmatizing nomenclature. Over 30% of people worldwide are afflicted by this condition. Additionally, a wider range of liver conditions linked to metabolic dysfunction is covered by the new term, including nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver (NAFL).⁷

Demographic and anthropometric analysis, a method focused on examining parameters related to body composition, dimensions, and structure, plays a pivotal role in comprehending the factors that contribute to the development and advancement of NAFLD within the subset of individuals who have T2DM. By assessing measurements such as body mass index (BMI), waist circumference (WC), and age, anthropometric analysis helps discern patterns that can shed light on the underlying mechanisms linking these two complex health conditions. Hence, in light of the existing knowledge gaps and the evident interconnection between T2DM and NAFLD, the cross-sectional study endeavors to address this dearth of information by investigating the prevalence and risk factors associated with NAFLD specifically within the context of T2DM patients in India.

MATERIALS AND METHODS

Study Design and Patients

This is a prospective, observational, cross-sectional study conducted at Dr Panikar's Speciality Care Centre, Mumbai, Maharashtra,

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between September 1, 2022 and October 31, 2022 among patients with T2DM attending the diabetes clinic. Patients over 18 years of age who provided written informed consent were included in the study. The individuals exhibiting excessive daily alcohol intake, defined as ≥ 30 gm in men and ≥ 20 gm in women, were excluded in alignment with the diagnostic requirements for NAFLD. Furthermore, participants with secondary hepatic steatosis attributed to specific causes—namely, pregnancy, misuse of steatogenic drugs (including amiodarone, tamoxifen, methotrexate, corticosteroids, and estrogen), and severe malnutrition—were not included. The presence of a positive hepatitis B surface antigen or hepatitis C viral antibody also warranted exclusion. Other chronic liver diseases, encompassing autoimmune hepatitis, hemochromatosis, Wilson's disease, primary biliary cirrhosis, and drug-induced hepatitis, constituted additional grounds for exclusion. Lastly, instances of measurement failure or unreliable outcomes during vibration-controlled transient elastography (VCTE) evaluation, such as those stemming from ascites, cholestasis, acute exacerbation, or hepatitis flare with alanine aminotransferase (ALT) >5 times baseline, an interquartile range to median ratio (IQR/M) surpassing 30%, or a success rate falling below 60%, led to participant exclusion.

Data Collection

Demographic information, along with BMI and WC, were recorded. Using a FibroScan® device, VCTE was conducted under fasting conditions for over 4 hours, following the manufacturer's guidelines. A FibroScan® result was deemed reliable when it comprised 10 or more valid measurements and was expressed in kilopascals (kPa). Successful readings were characterized by a success rate exceeding 60% and an IQR/M of 0.3 or less among the 10 measurements. The controlled attenuation parameter (CAP) was used to determine the extent of hepatic steatosis, and the results were reported in decibels per meter (dB/m). CAP values for S0, no steatosis (<237 dB/m), S1 ranged from 237.0 to 259.0 dB/m, from 259.0 to 291.0 dB/m for S2, and from 291.0 to 400.0 dB/m for S3.⁸ Cutoff values for fibrosis diagnosis were <5.5 for fibrosis stage F0 (no fibrosis), 5.5–8.0 for F1 (mild fibrosis), 8.0–10.0 for F2 (moderate fibrosis), 11.0–16.0 for F3 (severe fibrosis), and >16.0 for F4 (cirrhosis).⁹

Ethical Approval

In view of the nature of the study, all procedures were performed as part of routine care. Therefore, ethical approval was not applied for any Ethics Committee. Informed

consent was obtained from all participants prior to their inclusion in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki and all applicable laws and regulations. All data collected from the diabetes clinic OPD were kept confidential and were used only for research purposes.

Statistical Analysis

Results are expressed as mean $\pm$ standard deviation or number and percentage as appropriate for qualitative and quantitative variables. The statistical analysis was performed at 95% confidence intervals with p -value <0.05 considered to be significant. The statistical package SPSS, version 24.0, (SPSS Inc., Chicago, Ill., USA) software was used to analyze the data.

RESULTS

A total of 1,521 patients were enrolled in this study. The prevalence of liver steatosis was 75.1% among the 1,521 diabetes cases [S0 (24.9%), S1 (15.1%), S2 (24%), and S3 (36%)], whereas the prevalence of liver fibrosis was 28.0% [F0 (72%), F1 (19%), F2 (5%), F3 (1.5%), and F4 (3.4%)].

The overall mean age of the participants was 53.24 ± 11.33 years, height was 1.19 ± 0.72 m, weight was 71.78 ± 17.59 kg, WC measurement was 97.65 ± 30.36 cm, and BMI was 19.07 ± 13.60 kg/m². There were 52.8% male participants in the study (Table 1). Among different grades of steatosis and fibrosis, S3 (36%) and F0 (74%) and F1 (19%) were found most common in this study population (Figs 1 and 2).

There was no significant difference in mean age between the different grades of liver steatosis (p -value = 0.149) and fibrosis (p -value = 0.078), implying that age may not be a significant differentiator between these grades. Steatosis analysis shows that grades S1 and S2 have higher mean ages, implying an age-related aspect in disease progression. Similarly, cirrhosis analysis shows

that advanced fibrosis stages (F3 and F4) have higher mean ages, implying an age-related trend (Table 2).

The study reveals possible gender differences in the distribution of liver steatosis and fibrosis grades. Grade S0 has a nearly equal gender distribution, with males accounting for 52.1% of cases and females accounting for 47.9% ($p = 0.244$). In contrast, there is a significant gender disparity in grade S1. Females have a significantly

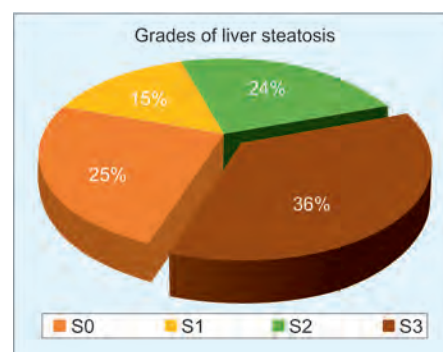


Fig. 1: Grade-wise distribution of liver steatosis in the study population

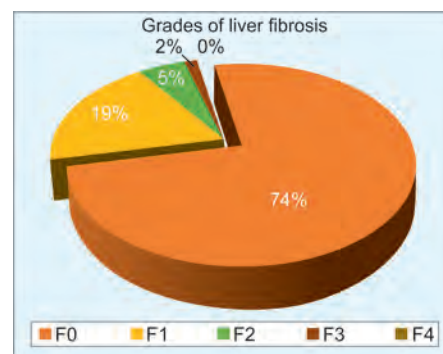


Fig. 2: Grade-wise distribution of liver fibrosis in the study population

Table 2: Association of age with different grades of liver steatosis and liver fibrosis

Grades	No. of cases	Age (year) (mean $\pm$ SD)	p-value ^a
Steatosis (N = 1,521)			
S0	378	52.90 $\pm$ 12.91	0.149
S1	231	54.25 $\pm$ 10.79	
S2	365	53.92 $\pm$ 10.24	
S3	547	52.58 $\pm$ 11.08	
Fibrosis (N = 1,516)			
F0	1,092	52.86 $\pm$ 11.51	0.078
F1	274	54.34 $\pm$ 10.68	
F2	76	52.68 $\pm$ 10.58	
F3	23	56.00 $\pm$ 10.18	
F4	51	56.00 $\pm$ 11.57	

* p -value <0.05 is considered to be statistically significant

Table 1: Demographic details of study participants (N = 1,521)

Variables	Mean $\pm$ SD
Age (year)	53.24 $\pm$ 11.33
Height (m)	1.19 $\pm$ 0.72
Weight (kg)	71.78 $\pm$ 17.59
WC (cm)	97.65 $\pm$ 30.36
BMI (kg/m ²)	19.07 $\pm$ 13.60
Gender	
Male, n (%)	804 (52.8%)
Female, n (%)	719 (47.2%)

higher proportion of cases (55.8%) than males (44.2%) (p -value = 0.012). Cases in grade S2 are almost evenly divided between genders, with 50.7% males and 49.3% females (p = 0.711). Surprisingly, there is a significant gender disparity in grade S3. Males account for a significantly higher percentage of cases (58.1%) than females (41.9%) (p -value = 0.001) (Table 3, Fig. 3).

Further investigation reveals distinct gender patterns within different fibrosis grades. Notably, gender disparities exist in grades F1 and F2, emphasizing gender's potential role in influencing fibrosis progression in those stages. Gender appears to play a lesser role in the distribution of fibrosis in grades F0, F3, and F4 (Table 3, Fig. 4).

A consistent pattern emerges in both steatosis and fibrosis, as disease severity increases, mean WC tends to increase. This pattern emphasizes the potential role of abdominal adiposity in the progression of liver diseases. Notably, the results of this study also support the relationship between WC and disease severity grade in both liver steatosis (p -value = 0.001) and liver fibrosis (p -value = 0.001). This relationship is consistent with our understanding of the impact of central obesity on liver health (Table 4).

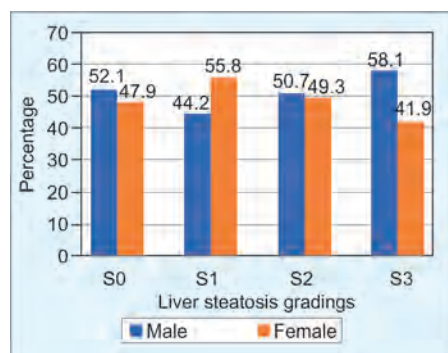


Fig. 3: Gender-wise distribution of study participants among different grades of liver steatosis

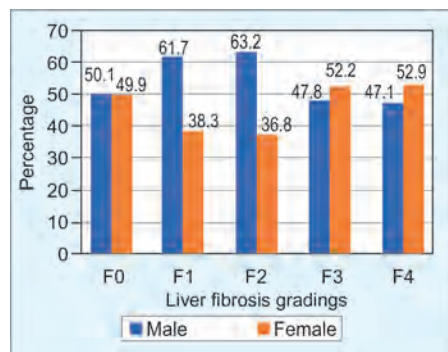


Fig. 4: Gender-wise distribution of study participants among different grades of liver fibrosis

In both steatosis and fibrosis evaluations, a consistent trend emerges in which increased disease grades are associated with elevated mean BMI. The high p -value (p = 0.001) in the steatosis analysis suggests that BMI could be an accurate predictor of disease severity

in the context of steatosis. The absence of significance (p > 0.05) in the fibrosis analysis, on the other hand, suggests a more intricate interplay between BMI and fibrosis, indicating a nuanced relationship that goes beyond a simple association (Table 5).

Table 3: Association of gender with different grades of liver steatosis and liver fibrosis

Grades	Steatosis (N = 1,521)				p-value*
	Male (n = 802)		Female (n = 719)		
	No. of cases	%	No. of cases	%	
S0	197	52.1	181	47.9	0.244
S1	102	44.2	129	55.8	0.012
S2	185	50.7	180	49.3	0.711
S3	318	58.1	229	41.9	0.001
Grades	Fibrosis (N = 1,516)				p-value
	Male (n = 799)		Female (n = 717)		
	No. of cases	%	No. of cases	%	
F0	547	50.1	545	49.9	0.932
F1	169	61.7	105	38.3	0.001
F2	48	63.2	28	36.8	0.001
F3	11	47.8	12	52.2	0.768
F4	24	47.1	27	52.9	0.552

* p -value < 0.05 is considered to be statistically significant

Table 4: Association of WC with different grades of liver steatosis and liver fibrosis

Grades	No. of cases	WC (cm) (mean $\pm$ SD)	<i>p</i> -value*
Steatosis (N = 1,521)			
S0	272	90.97 $\pm$ 10.83	0.001
S1	147	95.39 $\pm$ 10.61	0.001
S2	246	98.27 $\pm$ 09.51	0.001
S3	374	100.38 $\pm$ 11.04	0.001
Fibrosis (N = 1,037)			
F0	746	95.14 $\pm$ 10.56	0.001
F1	186	99.36 $\pm$ 11.59	0.001
F2	55	103.13 $\pm$ 12.36	0.001
F3	17	99.71 $\pm$ 13.27	0.001
F4	33	104.55 $\pm$ 11.81	0.001

* p -value < 0.05 is considered to be statistically significant

Table 5: Association between mean BMI and liver steatosis and fibrosis severity

Grades	No. of cases	Mean BMI	<i>p</i> -value*
Steatosis (N = 1,032)			
S0	263	25.62 $\pm$ 4.66	0.001
S1	150	27.40 $\pm$ 4.10	0.001
S2	249	28.42 $\pm$ 4.51	0.001
S3	370	29.48 $\pm$ 5.93	0.001
Fibrosis (N = 1,030)			
F0	736	27.45 $\pm$ 5.31	>0.05
F1	188	28.69 $\pm$ 5.03	>0.05
F2	54	29.96 $\pm$ 4.99	>0.05
F3	16	28.89 $\pm$ 5.65	>0.05
F4	36	29.96 $\pm$ 4.55	>0.05

* p -value < 0.05 is considered to be statistically significant

DISCUSSION

The findings presented in this study shed light on the intricate relationship between liver steatosis, fibrosis severity, and associated factors among diabetes patients. The study included 1,521 individuals, of which 75.1% exhibited liver steatosis and 28.0% showed signs of fibrosis. The analysis provides valuable insights into disease progression, age-related variations, gender-related patterns, and the role of anthropometric measures such as WC and BMI. Notably, the analysis of mean ages across steatosis and fibrosis grades underscores a consistent trend, although statistical assessments reveal that the differences in mean age among these grades are not significant. Nevertheless, subtle trends become apparent, indicating potential age-related factors in the advancement of the disease. These findings echo recent studies that have similarly explored age-related trends in liver disease progression, underscoring the intricate interplay between age and disease severity. A study involving 380 diabetes patients, for instance, documented that 72.6% of the participants exhibited liver steatosis, accompanied by a mean age of 55.22 ± 10.88 years and a mean BMI of 29 kg/m^2 . Notably, this study focused on exploring the association between type 2 diabetes status and the prevalence of liver steatosis and fibrosis among individuals aged ≥ 40 years.¹⁰ While the study did not specifically mention the prevalence of liver fibrosis, it is worthwhile to note that other independent studies have identified age as a pivotal factor that can influence the development of liver fibrosis in diabetes patients.^{6,11}

The study's exploration of gender-related variations within liver steatosis and fibrosis grades in diabetes patients reveals intriguing patterns. While the distribution in certain grades does not display statistical significance, such as in grade S0 and F0 (as they denote the absence of disease), other grades exhibit significant gender disparities. In particular, grades S1 and S3 and fibrosis grades F1 and F2 show substantial gender-related differences. There is limited information on the association of gender-related variations within liver steatosis and fibrosis grades in diabetes patients. However, some studies have found that gender differences are prominent in NAFLD, and different factors are associated with liver status in males as compared to females.¹²

The investigation into anthropometric measures, namely WC and BMI, unveils

significant associations with liver disease severity. The significant p -value ($p = 0.001$) observed in the steatosis analysis provides valuable insights into the potential role of BMI as an indicator of disease severity within the context of steatosis. This significance suggests that higher BMI values are associated with more severe steatosis grades, possibly reflecting the contribution of excess adiposity to lipid accumulation in the liver. The observation is in line with a study that identified a correlation between increasing BMI and higher NAFLD prevalence, along with elevated steatosis levels among individuals with overweight and diabetes compared to those without diabetes.¹³ Another study found that hepatic steatosis in patients with T2DM is associated with more significant BMI.¹⁴

As per the present study, WC is associated with liver steatosis in T2DM patients. The observation is in alignment with a study, in which waist-to-calf circumference ratio (WCR) is an independent predictor of hepatic steatosis and fibrosis in patients with type 2 diabetes.¹⁵ Another study found that increased central obesity, measured by WC, was the strongest factor associated with steatosis.¹⁶ The accumulation of visceral fat is believed to contribute to insulin resistance and inflammation, both of which play crucial roles in the development and progression of liver steatosis.

Conversely, the absence of significance ($p > 0.05$) in the fibrosis analysis highlights a more complex interplay between BMI and fibrosis. The nuanced relationship suggests that factors beyond simple adiposity might be at play in influencing fibrosis severity. This aligns with recent research indicating that fibrosis progression is influenced by multiple factors, including genetics, metabolic health, inflammation, and oxidative stress.¹⁷ While obesity is a recognized risk factor for fibrosis, its impact might be mediated by other variables such as a body shape index (ABSI) and waist-to-height ratio (WHtR) that warrant further investigation.

The present study's comprehensive analysis emphasizes the interplay between liver steatosis, liver fibrosis severity, and various contributing factors among diabetes patients. The findings underscore the importance of understanding these complex dynamics for effective disease management. However, as with any study, limitations must be acknowledged, including potential selection bias and the need for further longitudinal investigations to establish causal relationships. Nonetheless, this study contributes to the evolving

understanding of liver health in the context of diabetes and its associated factors.

CONCLUSION

In conclusion, the study shows the high incidence of hepatic steatosis (75.1%) and fibrosis (28.0%) in patients with type 2 diabetes. Further, age, gender, WC, and BMI are all associated with the severity of liver steatosis and fibrosis in T2DM patients. While age and gender play minor roles, WC and BMI emerge as significant predictors of disease severity. Given the multifaceted nature of these associations, these findings highlight the need for a comprehensive approach to assessing and managing liver health in T2DM patients.

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Determination of Sample Size for Different Clinical Study Designs



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ABSTRACT

Aim: This study illustrates parameters, procedures, and calculations for the statistical determination of sample size for different clinical study designs.

Materials and methods: In any research process, the sample size is an important consideration for the implementation of the planned study. From time to time, literature on sample size has been documented in the medical literature. However, the situations covered under them lack comprehensiveness in terms of different study designs, demonstration of calculations, and overreliance on statistical software.

Results: The present study provides various facets of sample size determination, such as prerequisite parameters, mathematical formulation, and calculations for clinical study designs [descriptive studies, randomized controlled trials (RCT), correlational studies, comparison of multiple outcomes, survival analysis, sensitivity, and specificity], which will be quite useful.

Conclusion: This communication will be a good education and learning source for medical professionals to pick and choose a specific scenario and estimate the sample size.

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INTRODUCTION

The most pertinent question in every clinical research is, "how many samples should be studied to answer the primary outcome of interest?" Irrespective of the scientific approaches adopted, epidemiological, genetic, imaging, high-throughput, and omics studies, the determination of the sample size is of paramount importance. The research results are interpreted based on the sample studied. Hence, having a system of statistically determined sample size can't be overemphasized. Usually, statisticians, epidemiologists, and research methodologists are the professionals who discuss the finer nuances of the requirement for sample size. Unfortunately, many medical settings are devoid of these professionals. Consequently, professionals in medical settings (DM/MD/MS/Mch) face difficulty in arriving at the appropriate sample size.

In addition to possible outcomes of interest and design of the study, other factors, such as manpower, availability of funds, settings, etc., are vital in the determination of sample size. Therefore, the requirements of sample size constitute broadly the statistical and non-statistical parameters. The statistical parameters are instrumental in providing the essential quantitative parameters, and non-statistical parameters direct the implementation of the planned clinical study. The synchronization of these two factors plays a vital role in arriving at the precise

estimate of the population characteristics based on the sample studied.

Scientific communications, in the form of journal articles¹⁻³ and books^{4,5} covering various aspects of determination of the sample size, is not uncommon. However, the journal articles are mostly statistically oriented,⁶⁻⁸ and the contents of books become quite technically oriented. Such statistical jargon and books, although complete from the theoretical and applied statistics, arrive at the most relevant section in journals or books like searching for a needle in the haystacks. Therefore, succinct information regarding aspects of statistically determining the sample size is vital. With this consideration, we attempt to demonstrate the procedure for the determination of sample size through common clinical examples. In this communication, we also provide in brief the essential statistical parameters that are prerequisites. This communication also strikes a balance between the statistical and clinical parameters and thus will help the resident to communicate more effectively with their professional colleagues.

DETERMINE SAMPLE SIZE

The two main approaches to sample size calculation are:

- Hypothesis-based: Here, we involve "power" or β -error to ensure a significant finding is easy to approach and widely available.

- Confidence interval methods: This method involves precision estimation to ensure a conclusive clinical finding as it directly estimates the magnitude of the effect. However, its formulation is difficult and not widely available.

Steps involved for sample size calculation in clinical research:

- Identify the primary outcome.
- Determine and assess the effect's magnitude and variability, which will serve as the foundation for the study's conclusion.
- Determine the statistical technique that will be applied to determine the primary effect size.
- Determine the sample size.
- Provide enough facts to provide explicability when describing the sample size calculation process.

Basic Essential Parameters for Estimation of Sample Size

The sample size is calculated using a formula mostly derived based on the objective of estimation or comparison by adopting a specific study design of the study. However, the formula is composed of various components, which are required to make sure that the sample is sufficient to achieve a level of precision. Sampling is one of the important components that will be taken into consideration while calculating the sampling size for any study, but in the present study, the discussion of sampling methodology or different sampling mechanisms was not the objective.

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We have given an explanation of basic parameters for sample size that are generally considered essential parameters for the calculation of sample size, namely:

- α (type I error): Denoting the probability of falsely rejecting the null hypothesis (H_0) and detecting a statistically significant difference when the groups are not different, that is, the chance of a false-positive result. For example, let us consider that a certain medication is being tested for lowering the blood pressure among the study subjects. The estimated blood pressure with the standard medication and the newly tested medication may be the same, and we may falsely reject this hypothesis and deduce that the mean decrease with the newer medication is significantly greater than that of the existing medication. This is a false claim. The type I error is also known as the significance level and is specified at the planning stage of the study as $\alpha = 10$ or 5 or 1%. The standard value of Z_α for one- or two-sided tests has been tabulated below (Table 1).
- β (type II error): Denoting the probability of falsely accepting H_0 and not detecting a statistically significant difference when a specified difference between the groups exists, that is, the chance of a false-negative result. For example, a test for a disease may report a negative result when the patient is infected. This is a type II error because we accept the conclusion of the test as negative, even though it is incorrect. Antigen tests for coronavirus disease of 2019 (COVID-19) may report a negative result when an individual is COVID-19 positive.
- Power ($1 - \beta$): Denoting the probability of correctly rejecting H_0 and detecting a

statistically significant difference when a specified difference between the groups exists. The standard value of Z_β has been tabulated below (Table 2).

- Effect size or minimal clinically relevant difference (d): Magnitude of the difference between the actual value of the tested parameter and groups that the investigator considers biologically plausible and clinically relevant and specified by the null hypothesis. Effect size is derived using the mean differences and standard deviation (SD). The "effect size" quantifies the magnitude of the planned intervention, and the higher the value, the better the intervention. It is quite clear from the above formula that if the effect size is small, the required sample size will increase, and if the effect size is large, the required sample size will be small. Usually, the range of (<0.5), ($0.5-0.8$), and (>0.8) is considered a small, moderate, and large effect size. There are different measures of effect size such as odds ratio $[(a \times d)/(b \times c)]$, standardized mean difference $[(\mu_1 - \mu_2)/\sigma]$, correlation coefficient $[p_{xy} = \text{Cov}(x,y)/(\sigma_x \times \sigma_y)]$ etc. These values are calculated based on the experimental results.

General Formula

The choice of mathematical formula for estimating the sample size depends upon the research question. Hence, the form varies under different scenarios. Conceptually, the general formula for the determination of the sample size can be understood as embedding three main factors, namely:

- The ratio of the case: control/exposure: nonexposure/intervention: placebo ($r/r+1$).
- Statistical parameters consisting of Z score (Z_α, Z_β).
- Effect size $[(\epsilon/\sigma)]$.

$$n = \left(\frac{r+1}{r} \right) \frac{(Z_{\alpha/2} + Z_\beta)^2}{(\epsilon/\sigma)^2}$$

Here, r denotes the prefixed case-to-control allocation ratio, α denotes the significance level, $(1 - \beta)$ denotes the achievable power level, ϵ denotes the difference between the means, and σ denotes SD. A detailed description of sample size calculation under different study designs has been presented in Table 3.

CALCULATION OF SAMPLE SIZE

1. To test whether there is a difference between continuous outcomes of the new and standard or reference drug (test for equality).

Example: Study to determine if a drug significantly reduces blood sugar levels (posttreatment vs pretreatment analysis).

Here,

μ_1 : Mean blood glucose level after taking standard drug = 160 mg/dL

μ_2 : Mean blood glucose level after taking new drug = 140 mg/dL

σ : SD of treatment blood glucose levels = 40 mg/dL

ϵ : Difference between the blood glucose levels after taking new and standard drugs = 20 mg/dL

The required sample size for the two-sided alternative to achieve power $(1 - \beta) = 80\%$ ($Z_\beta = 0.84$) at the $\alpha = 5\%$ level (two-sided) ($Z_{\alpha/2} = 0.96$) of significance can be calculated as:

$$r = 1:1, n = n_{\text{cases}} = n_{\text{controls}}$$

$$= \left(\frac{r+1}{r} \right) \frac{(Z_{\alpha/2} + Z_\beta)^2 \sigma^2}{(\epsilon)^2} \\ = \left(\frac{1+1}{1} \right) \frac{(1.96 + 0.84)^2 (40)^2}{(20)^2} \approx 2 \times 31 \approx 62$$

$$r = 1:3, n_{\text{cases}}$$

$$= \left(\frac{3+1}{3} \right) \frac{(1.96 + 0.84)^2 (40)^2}{(20)^2} \approx 1.33 \times 31 \approx 41$$

$$n_{\text{controls}} = r \times n_{\text{cases}} = 123$$

Hence, the total sample size required for planning this study is a ratio of 1:1, which is $62 + 62 = 124$, while the ratio of 1:3 is $41 + 123 = 164$.

2. To test whether there is a difference between proportions of outcome due to the new drug and the standard or reference drug (test for equality).

Example: The study was planned to determine a change in the percentage of posttreatment recovery from urinary tract infection cases.

Here,

p_1 : New drug posttreatment recovery rate from urinary tract infection rate = 65%.

p_2 : Standard or reference drug posttreatment recovery rate from urinary tract infection rate = 85%.

ϵ : Difference drug response = 20%.

The required sample size at a 5% level of significance $Z_{\alpha/2} = 1.96$ and at 80% power $Z_\beta = 0.84$ can be calculated as:

$$r = 1:1, n = n_{\text{cases}} = n_{\text{controls}}$$

$$= \frac{(Z_{\alpha/2} + Z_\beta)^2 \left[\frac{p_1(1-p_1)}{r} + p_2(1-p_2) \right]}{(\epsilon)^2} \\ = \frac{(2.8)^2 [(0.65 \times 0.35) + (0.85 \times 0.15)]}{(0.2)^2} \approx 70$$

Table 1: Inverse Z table for the standard normal distribution

α	Z_α	$Z_{1-\alpha}$	$Z_{\alpha/2}$	$Z_{1-\alpha/2}$
0.010	-2.33	2.33	-2.58	2.58
0.025	-1.96	1.96	-2.24	2.24
0.050	-1.64	1.64	-1.96	1.96
0.100	-1.28	1.28	-1.64	1.64

Note: Due to symmetric nature of standard normal, the values of Z_α and $Z_{\alpha/2}$ are negative. In usual practice, we use the values of $Z_{1-\alpha}$ and $Z_{1-\alpha/2}$, which are positive values

Table 2: Standard normal variate ($Z_{1-\beta}$) corresponding to different values of power ($1 - \beta$)

Power	$Z_{1-\beta}$
0.80	0.84
0.90	1.28
0.95	1.65
0.99	2.33

Table 3: Study design based sample size calculation formulae

Study design	Formula
Test for equality (continuous outcomes)	$n = n_{cases} = n_{controls} = \left(\frac{r+1}{r} \right) \frac{(Z_{\alpha/2} + Z_{\beta})^2 \sigma^2}{(\varepsilon)^2}$ μ_1: Mean of continuous outcome of the placebo control or an active control drug μ_2: Mean of continuous outcome of the new or test drug σ: SD of the continuous outcome of the standard or reference drug $\varepsilon = (\mu_2 - \mu_1)$ denotes the difference between the means of new and placebo (control) drug Assumption: σ is known r: Ratio of allocation of case to control (prefixed)
Test for equality (proportions of outcome)	$n = n_{cases} = n_{controls} = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \left[\frac{p_1(1-p_1)}{r} + p_2(1-p_2) \right]}{(\varepsilon)^2}$ p_1: Proportion of response due to the new drug p_2: Proportion of response due to standard or reference drug $\sigma = \left(\sqrt{\frac{p_1(1-p_1)}{r} + p_2(1-p_2)} \right)$ – pooled $\varepsilon = (p_1 - p_2)$ – difference between the proportions of response due to new and standard drugs Let population sizes (N's) be small relative to n $f_1 = \frac{N_1 - n}{N_1 - 1}$ and $f_2 = \frac{N_2 - n}{N_2 - 1}$
Test for equality (proportions of outcome) (finite population)	$n = n_{cases} = n_{controls} = \left(Z_{\alpha/2} + Z_{\beta} \right)^2 \frac{(f_1 p_1 (1-p_1) + f_2 p_2 (1-p_2))}{(p_1 - p_2)^2}$
RCT: test for noninferiority/superiority (continuous outcomes)	$n = n_{cases} = n_{controls} = \left(\frac{r+1}{r} \right) \frac{(Z_{\alpha} + Z_{\beta})^2 \sigma^2}{(\varepsilon - \delta)^2}$ Superiority trials ($\delta > 0$) Noninferiority trials ($\delta < 0$) μ_1: Mean of continuous outcome of the placebo control or an active control drug μ_2: Mean of continuous outcome of the new or test drug σ: SD of the continuous outcome of the placebo control or an active control drug $\varepsilon = (\mu_2 - \mu_1)$ – difference between the means of new and placebo control drug responses δ: Clinically meaningful difference, (largest change from the reference value that is trivial) Assumption: σ is known
RCT: test for noninferiority/superiority (proportions of outcome)	$n = n_{cases} = n_{controls} = \frac{(Z_{\alpha} + Z_{\beta})^2 \left[\frac{p_1(1-p_1)}{r} + p_2(1-p_2) \right]}{(\varepsilon - \delta)^2}$ p_1: Proportion of response due to the placebo or standard or reference drug p_2: Proportion of response due to the new drug $\varepsilon = (p_2 - p_1)$ – difference between the proportions of responses due to new and standard drug $\sigma = \left(\sqrt{\frac{p_1(1-p_1)}{r} + p_2(1-p_2)} \right)$ – pooled δ: Clinically meaningful difference, (largest change from the reference value that is trivial)
RCT: test for equivalence (continuous outcomes)	$n = n_{cases} = n_{controls} = \left(\frac{r+1}{r} \right) \frac{(Z_{\alpha} + Z_{\beta/2})^2 \sigma^2}{(\delta - \varepsilon)^2}$ μ_1: Mean of continuous outcome of the placebo control or an active control drug μ_2: Mean of continuous outcome of the new or test drug σ: SD of the continuous outcome of the placebo control or an active control drug $\varepsilon = (\mu_2 - \mu_1)$ – difference between the means of new and placebo control drug responses δ: Clinically meaningful difference, (largest change from the reference value that is trivial) Assume: σ^2 is known

Contd...

RCT: test for equivalence
(proportions of outcome)

$$n_{cases} = n_{controls} = \frac{(Z_{\alpha} + Z_{\beta/2})^2 \left[\frac{p_1(1-p_1)}{r} + p_2(1-p_2) \right]}{(\delta - |\varepsilon|)^2}$$

p_1 : Proportion of response due to the placebo or standard or reference drug

p_2 : Proportion of response due to the new drug

$$\sigma = \left(\sqrt{\frac{p_1(1-p_1)}{r} + p_2(1-p_2)} \right) - \text{pooled}$$

$\varepsilon = (p_2 - p_1)$ – difference between the proportions of responses due to new and standard drug

δ : Clinically meaningful difference, described as the largest change from the reference value that is trivial

Odds ratio: case control

$$n_{cases} = n_{controls} = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \left[\frac{1}{r p_T(1-p_T)} + \frac{1}{p_C(1-p_C)} \right]}{[\log(OR)]^2}$$

p_T : Proportion of patients who experienced outcomes due to new drug

$$O_T = \left(\frac{p_T}{1-p_T} \right) - \text{Odd due to new or test drug}$$

p_C : Proportion of patients experienced outcomes due to placebo control drug

$$O_C = \left(\frac{p_C}{1-p_C} \right) - \text{Odd due to placebo control or an active control drug}$$

$$OR = \frac{O_T}{O_C} = \text{Odds ratio between the test new drug and the control}$$

Multiple proportions

$$n = \delta_{\alpha,\beta} \left[\sum_{k=1}^r \frac{(p_k - p_{k,0})^2}{p_{k,0}} \right]^{-1}$$

p_k : Proportion patients with response value k ($k = 1 \dots, r$) due to new or test drug

$p_{k,0}$: Proportion patients with response value k due to placebo control or an active control drug

$\delta_{\alpha,\beta}$: A noncentral Chi-square random variable

Test for equality of hazard ratio

$$\sigma^2(\lambda_i) = \lambda_i^2 \left(1 + \frac{e^{-\lambda_i T} - e^{-\lambda_i(T-T_0)}}{\lambda_i T_0} \right)^{-1}$$

λ_1 : Hazard rates due to a placebo control or an active control drug

λ_2 : Hazard rates due to a new or test drug

$\sigma(\lambda_1)$: SD of placebo control or an active control drug

$\sigma(\lambda_2)$: SD of a new or test drug

$\varepsilon = (\lambda_1 - \lambda_2)$: Difference between the hazard rates of control and new drug responses

Correlation between two
continuous variables

$$n = \left(\frac{z_{\alpha/2} + z_{\beta}}{C(r)} \right)^2 + 3$$

ρ : Correlation among variables mentioned in literature or standard reference

r : Assumed sample correlation

$$C(r) = \frac{1}{2} \ln \left(\frac{1+r}{1-r} \right), \text{ where } \ln(\cdot) \text{ refers the natural logarithmic value}$$

Validity of a diagnostic test
(sensitivity and specificity analysis)

$$n_{sensitivity} = \frac{(Z_{\alpha/2})^2 S_N(1-S_N)}{(L)^2(\pi)}$$

$$n_{specificity} = \frac{(Z_{\alpha/2})^2 S_P(1-S_P)}{(L)^2(1-\pi)}$$

S_N : anticipated sensitivity, S_P : anticipated specificity,

L : absolute precision desired on either side of sensitivity or specificity.

π : assumed prevalence of a disease

$$r=1:3, n_{\text{cases}} = \frac{(2.8)^2 \left[\frac{0.65 \times 0.35}{3} + 0.85 \times 0.15 \right]}{(0.2)^2} \approx 40$$

$$n_{\text{controls}} = r \times n_{\text{cases}} = 120$$

Hence, the total sample size required for planning this study is a ratio of 1:1, which is 70 + 70 = 140, while the ratio of 1:3 is 40 + 120 = 160.

3. Randomized clinical trials: The problem of testing differences between the continuous outcome of the new drug and the standard drug (test for noninferiority/superiority).

Example: A placebo-controlled trial to determine if a drug reduces weight.

In an investigation of a new drug or intervention for a particular disease, a randomized controlled trial (RCT) can be conducted to investigate if the new treatment is superior to a standard reference or placebo drug.

When a new drug or treatment is compared with an established or standard drug with the objective of demonstrating that the new treatment is equivalent to a gold standard on average under an acceptable superiority margin, it is called a noninferiority situation. For certain trials, the objective, therefore, is not to demonstrate that a new treatment is superior to a placebo or equivalent to an established treatment but rather to demonstrate that a given treatment is clinically not inferior or no worse compared with another.

Superiority trials (if $\delta > 0$, the rejection of the null hypothesis indicates superiority over the reference value).

Here,

μ_1 : Mean body weight after medication from the placebo = 70 kg

μ_2 : Mean body weight after medication from new drug = 65 kg

σ : SD of weight after medication of placebo = 5 kg

ϵ : Difference between the means of new drug and placebo = 5 kg

δ : 2 kg

The required sample size at $\alpha = 5\%$ (one-sided), level of significance $Z_\alpha = 1.64$, and at $1 - \beta = 80\%$, power $Z_\beta = 0.84$ can be calculated as:

$$r=1:1, n = n_{\text{cases}} = n_{\text{controls}} = \left(\frac{r+1}{r} \right) \frac{(Z_\alpha + Z_\beta)^2 \sigma^2}{(\epsilon - \delta)^2} \\ = \left(\frac{1+1}{1} \right) \frac{(2.48)^2 (5)^2}{(5-2)^2} = 2 \times 17.08 \approx 34$$

$$r=1:3, n_{\text{cases}} = \left(\frac{3+1}{3} \right) \frac{(2.48)^2 (5)^2}{(5-2)^2} \\ = 1.33 \times 17.08 \approx 23$$

$$n_{\text{controls}} = r \times n_{\text{cases}} = 69$$

Hence, the total sample size required for planning this study is a ratio of 1:1, which is 34 + 34 = 68, while the ratio of 1:3 is 23 + 69 = 92.

Noninferiority trials (if $\delta > 0$, the rejection of the null hypothesis indicates noninferiority over the reference value).

Example: Study to determine if a new drug is noninferior to the standard drug in reducing weight.

Here,

μ_1 : Mean body weight after medication from standard drug = 70 kg.

μ_2 : Mean body weight after medication from new drug = 68 kg.

σ : SD of body weight after medication of the placebo = 5 kg.

ϵ : Difference between the means of new and standard drug responses = 2 kg

$\delta = -2$ kg.

The required sample size at $\alpha = 5\%$ (one-sided), level of significance $Z_\alpha = 1.64$, and at $1 - \beta = 80\%$, power $Z_\beta = 0.84$ can be calculated for:

$$r=1:1, n = n_{\text{cases}} = n_{\text{controls}} = \left(\frac{r+1}{r} \right) \frac{(Z_\alpha + Z_\beta)^2 \sigma^2}{(\epsilon - \delta)^2} \\ = \left(\frac{1+1}{1} \right) \frac{(1.64 + 0.84)^2 (5)^2}{(2 - (-2))^2} = 2 \times 9.61 \approx 19$$

$$r=1:3, n_{\text{cases}} = \left(\frac{3+1}{3} \right) \frac{(1.64 + 0.84)^2 (5)^2}{(2 - (-2))^2} \\ = 1.33 \times 9.61 \approx 13$$

$$n_{\text{controls}} = r \times n_{\text{cases}} = 39$$

Hence, the total sample size required for planning this study is a ratio of 1:1 is 19 + 19 = 38, while the ratio of 1:3 is 13 + 39 = 52.

4. Randomized clinical trials (RCT): To test differences among proportions of responses due to new and standard or reference drugs (test for noninferiority/superiority).

Superiority trials (If $\delta > 0$, the rejection of the null hypothesis indicates superiority over the reference value)

Example: Study to determine if a new drug reduces mortality after myocardial infarction as compared to a placebo (or standard drug).

Here,

p_1 : Proportion of reduction mortality after myocardial infarction after treatment from placebo = 55%

p_2 : Proportion of reduction mortality after myocardial infarction after treatment from new drug = 65%

ϵ : Difference between the new drug and placebo percentages = 10%

$\delta = 1\%$.

The required sample at $\alpha = 5\%$ (one-sided), level of significance $Z_\alpha = 1.64$, and at $1 - \beta = 80\%$, power $Z_\beta = 0.84$ can be calculated for:

$$r=1:1, n = n_{\text{cases}} = n_{\text{controls}} \\ = \frac{(Z_\alpha + Z_\beta)^2 \left[\frac{p_1(1-p_1)}{r} + p_2(1-p_2) \right]}{(\epsilon - \delta)^2} \\ = \frac{(2.84)^2 \left[0.55 \times 0.45 + 0.65 \times 0.35 \right]}{(0.1 - 0.01)^2} \approx 361$$

$$r=1:3, n_{\text{cases}} \\ = \frac{(1.96 + 0.84)^2 \left[\frac{0.65 \times 0.35}{3} + 0.65 \times 0.35 \right]}{(0.1 - 0.01)^2} \approx 235$$

$$n_{\text{controls}} = r \times n_{\text{cases}} = 705$$

Hence, the total sample size required for planning this study is a ratio of 1:1, which is 361 + 361 = 722, while the ratio of 1:3 is 235 + 705 = 940.

Noninferiority trials (If $\delta > 0$, the rejection of the null hypothesis indicates noninferiority over the reference value.)

Example: Study to determine if a new drug is noninferior in reducing mortality after myocardial infarction as compared to the standard drug.

Here,

p_1 : Proportion of reduction in mortality after myocardial infarction after treatment from placebo = 55%.

p_2 : Proportion of reduction mortality after myocardial infarction after treatment from new drug = 65%.

ϵ : Difference between the new drug and placebo percentages = 10%.

$\delta = -1\%$.

The required sample size for the two-sided alternative to achieve a power $(1 - \beta) = 80\%$ ($Z_\beta = 0.84$) at the $\alpha = 5\%$ level (one-sided) ($Z_\alpha = 1.64$) of significance can be calculated as:

$$r=1:1, n_{\text{cases}} = n_{\text{controls}} \\ = \frac{(Z_\alpha + Z_\beta)^2 \left[\frac{p_1(1-p_1)}{r} + p_2(1-p_2) \right]}{(\epsilon - \delta)^2} \\ = \frac{(2.48)^2 \left[0.55 \times 0.45 + 0.65 \times 0.35 \right]}{(0.1 + 0.01)^2} \approx 939$$

$$r = 1:3, n_{\text{cases}}$$

$$= \frac{(2.84)^2 \left[\frac{0.65 \times 0.35}{3} + 0.65 \times 0.35 \right]}{(0.1 + 0.01)^2} \approx 940$$

$$n_{\text{controls}} = r \times n_{\text{cases}} = 2820$$

Hence, the total sample size required for planning this study is a ratio of 1:1 is 939 + 939 = 1878, while the ratio of 1:3 is 939 + 2820 = 3759.

5. Randomized clinical trials (RCT): The problem of testing whether the mean response of the two drugs is concluded to be equivalent (test for equivalence).

Example: Study to determine if a new drug reduces blood glucose level to the same extent as the standard drug.

Here,

μ_1 : Mean blood glucose level after medication from standard drug = 140 mg/dL.

μ_2 : Mean blood glucose level after medication from new drug = 130 mg/dL.

σ : SD of blood glucose level after medication of the standard drug = 10 mg/dL.

ε : True mean difference = 5 mg/dL.

$\delta = 5$

The required sample size for the two-sided alternative to achieve power $(1 - \beta) = 80\%$ ($Z_{\beta/2} = 1.28$) at the $\alpha = 5\%$ level (one-sided) ($Z_{\alpha} = 1.64$) level of significance can be calculated as:

$$r = 1:1, n_{\text{cases}} = n_{\text{controls}}$$

$$= \left(\frac{r+1}{r} \right) \frac{(Z_{\alpha} + Z_{\beta/2})^2 \sigma^2}{(\delta - |\varepsilon|)^2}$$

$$= \left(\frac{1+1}{1} \right) \frac{(2.48)^2 (10)^2}{(5-10)^2} = 2 \times 136.4 \approx 274$$

$$n_{\text{cases}} = \left(\frac{3+1}{3} \right) \frac{(1.64 + 1.28)^2 (10)^2}{(5-10)^2}$$

$$= 1.33 \times 136.4 \approx 181$$

$$n_{\text{controls}} = r \times n_{\text{cases}} = 544$$

Hence, the total sample size required for planning this study is a ratio of 1:1, which is 274 + 274 = 548, while the ratio of 1:3 is 181 + 544 = 735.

6. Randomized clinical trials (RCT): The problem of testing whether the proportion of responses due to a new drug is equivalent to a gold standard

or reference drug responses (test for equivalence).

Example: Study to determine if a new drug produces remissions in acute leukemia in a similar proportion of patients as the standard drug.

Here,

p_1 : Standard drug response rate to treat acute leukemia = 30%.

p_2 : New drug response rate to treat acute leukemia = 15%.

ε : Difference drug response = 5%.

δ : Believed difference in responder rate = 20.

The required sample size for the two-sided alternative to achieve a power $(1 - \beta) = 80\%$ ($Z_{\beta/2} = 1.28$) at the $\alpha = 5\%$ level (one-sided) ($Z_{\alpha} = 1.64$) level of significance can be calculated as:

$$r = 1:1, n_{\text{cases}} = n_{\text{controls}}$$

$$\frac{(Z_{\alpha} + Z_{\beta/2})^2 \left[\frac{p_1(1-p_1)}{r} + p_2(1-p_2) \right]}{(\delta - |\varepsilon|)^2}$$

$$= \frac{(2.48)^2 (0.3 \times 0.7 + 0.15 \times 0.85)}{(0.2 - 0.05)^2} \approx 128$$

$$r = 1:3, n_{\text{cases}}$$

$$\frac{(Z_{\alpha} + Z_{\beta/2})^2 \left[\frac{p_1(1-p_1)}{r} + p_2(1-p_2) \right]}{(\delta - |\varepsilon|)^2}$$

$$= \frac{(1.64 + 1.28)^2 \left(\frac{0.3 \times 0.7}{3} + 0.15 \times 0.85 \right)}{(0.2 - 0.05)^2} \approx 75$$

$$n_{\text{controls}} = r \times n_{\text{cases}} = 225$$

Hence, the total sample size required for planning this study in the ratio of 1:1 is 128 + 128 = 256, while for the ratio of 1:3 is 75 + 225 = 300.

7. Randomized clinical trials (RCT): To investigate the relative effect (e.g., risk or benefit) of the treatments for the disease under study (odds ratio-case control).

Example: A case-control study to determine if smoking is a risk factor for cancer of the stomach.

Here,

p_T : Proportion of cases who smoke = 60%.

p_C : Proportion of controls who smoke = 40%.

$$OR = \frac{0.6(1-0.4)}{(1-0.6)0.4} = 2.25$$

The required sample size for the two-sided alternative to achieve a power $(1 - \beta) = 80\%$ ($Z_{\beta} = 0.84$) at the $\alpha = 5\%$ level of significance ($Z_{\alpha/2} = 1.96$) can be calculated as:

$$r = 1:1, n_{\text{cases}} = n_{\text{controls}}$$

$$= \frac{(Z_{\alpha/2} + Z_{\beta})^2 \left[\frac{1}{r p_T (1-p_T)} + \frac{1}{p_C (1-p_C)} \right]}{[\log(OR)]^2}$$

$$= \frac{(2.84)^2 \left[\frac{1}{1 \times 0.4(1-0.4)} + \frac{1}{0.6(1-0.6)} \right]}{[\log(2.25)]^2} \approx 100$$

$$r = 1:3, n_{\text{cases}} = \frac{(Z_{\alpha/2} + Z_{\beta})^2 (2.84)^2}{[\log(OR)]^2 [\log(2.25)]^2}$$

$$\times \left[\frac{1}{3 \times 0.4(1-0.4)} + \frac{1}{0.6(1-0.6)} \right] \approx 66$$

$$n_{\text{controls}} = r \times n_{\text{cases}} = 198$$

Hence, the total sample size required for planning this study in the ratio of 1:1 is 100 + 100 = 200, while for the ratio of 1:3 is 66 + 198 = 364.

8. Multiple proportions: To study the distribution of categorical responses that are nonbinary under a new drug with some reference distribution, which may be obtained from historical (control) data (tests for goodness-of-fit).

Example: Study to determine if a new drug (vs placebo or standard drug) favorably affects outcome after stroke (full recovery, partial recovery, and death).

Here,

Let outcomes: full recovery (p_1), partial recovery (p_2), and death (p_3).

Under standard drug: (p_1, p_2, p_3) = (0.50, 0.30, 0.20).

Under new drug: ($p_{1,0}, p_{2,0}, p_{3,0}$) = (0.60, 0.30, 0.10).

The required sample size for the two-sided alternative to achieve power $(1 - \beta) = 80\%$ at the $\alpha = 5\%$ level of significance, and $\delta_{\alpha,\beta} = 9.634$ can be calculated as:

$$n = \delta_{\alpha,\beta} \left[\sum_{k=1}^r \frac{(p_k - p_{k,0})^2}{p_{k,0}} \right]^{-1} = 9.634$$

$$\times \left[\frac{(p_1 - p_{1,0})^2}{p_{1,0}} + \frac{(p_2 - p_{2,0})^2}{p_{2,0}} + \frac{(p_3 - p_{3,0})^2}{p_{3,0}} \right]^{-1}$$

$$= 9.634 \left[\frac{(0.5 - 0.6)^2}{0.6} + \frac{(0.3 - 0.3)^2}{0.3} + \frac{(0.2 - 0.1)^2}{0.1} \right]^{-1} \approx 82$$

Hence, the total sample size required for planning this study is a ratio of 1:1, which is 82 + 82 = 164, while the ratio of 1:3 is 82 + 246 = 328.

The study design involving testing of multiple proportions is sophisticated and beyond the scope of further illustration in the present communication. Interested readers may refer to the work by Zhang et al., 2018 for a more detailed account of different aspects of multiple proportions.⁹

9. Survival: To compare two drugs or treatments by comparing either hazard rates or the median survival times (test for equality of Hazard Ratio).

Example: A placebo-controlled RCT to determine if a new drug improves survival in heart failure.

Let the survival functions between treatment groups be derived under an exponential model; under this assumption,

Here,

λ_1 : Hazard rates due to a placebo = 0.75

λ_2 : Hazard rates due to a new drug = 0.25

$\sigma(\lambda_1)$: SD of placebo = 1.97

$\sigma(\lambda_2)$: SD of a new drug = 0.94

T : Duration of trial = 3 years

T_0 : Accrual time = 1

The required sample size for the two-sided alternative to achieve power $(1 - \beta)$ (at 80%, $Z_\beta = 0.84$) at the α level of significance [at $\alpha = 5\%$ (two-sided) $Z_{\alpha/2} = 1.96$] can be calculated for situations that may desirable to have an unequal treatment allocation, that is, $n_{\text{controls}}/n_{\text{cases}} = r$, for some r , then $n_{\text{controls}} = rn_{\text{cases}}$

$$n_{\text{cases}} = \frac{(Z_{\alpha/2} + Z_\beta)^2}{(\lambda_1 - \lambda_2)^2} \left[\frac{\sigma^2(\lambda_1)}{r} + \sigma^2(\lambda_2) \right]$$

$$r = 1:1, n_{\text{cases}} = \frac{(1.96 + 0.84)^2}{(0.75 - 0.25)^2} [1.97 + 0.94] \approx 91$$

Hence, the total sample size required for planning this study is a ratio of 1:1, which is $82 + 82 = 164$, while the ratio of 1:3 is $82 + 246 = 328$.

In clinical settings, survival analysis stands at the upper hierarchical level of analytical methods. Here, we have demonstrated with only one example, and a more thorough description for the determination of sample size involving the application of techniques

of survival analysis can be found in the work by Schoenfeld and David in 1983.¹⁰

10. Correlation: To detect a significant correlation between two continuous variables.

Example: Study to determine the correlation between blood homocysteine and sugar levels.

Here,

r : Correlation reported among blood homocysteine and blood sugar level = 0.3.

The required sample size at $\alpha = 5\%$ (two-sided) level of significance, $Z_{\alpha/2} = 1.96$, and at $1 - \beta = 80\%$ power $Z_\beta = 0.84$ can be calculated as:

$$n = \left(\frac{Z_{\alpha/2} + Z_\beta}{C(r)} \right)^2 + 3 = \left(\frac{1.96 + 0.84}{0.31} \right)^2 + 3 \approx 85$$

11. Sensitivity and specificity analysis: To measure the inherent validity of a diagnostic test against a gold standard.

Example: Study the sensitivity and specificity of newly diagnosed procedure of glaucoma.

Here,

S_N : Sensitivity of newly diagnosed procedure of glaucoma = 0.8.

S_P : Specificity newly diagnosed procedure of glaucoma = 0.8.

L : Absolute precision = 10%

π = Assumed prevalence of a disease = 0.2

Required sample size at $\alpha = 5\%$ (two-sided) level of significance $Z_{\alpha/2} = 1.96$ can be calculated as:

$$n_{\text{sensitivity}} = \frac{(Z_{\alpha/2})^2 S_N (1 - S_N)}{(L)^2 (\pi)} = \frac{(1.96)^2 [(0.8 \times 0.2)]}{(0.1)^2 (0.2)} \approx 307$$

$$n_{\text{specificity}} = \frac{(Z_{\alpha/2})^2 S_P (1 - S_P)}{(L)^2 (1 - \pi)} = \frac{(1.96)^2 [(0.8 \times 0.2)]}{(0.1)^2 (1 - 0.2)} \approx 77$$

In studies involving prospective diagnostic accuracy, the work by Li and Fine is more comprehensive.¹¹

CONCLUSION

The present communication illustrates determining sample size for different clinical designs.¹⁻³ We have attempted to provide a systematic approach for arriving at the required sample size^{4,12} with the aid of various parameters and statistical formulas. Although different software for the calculation of sample size exists, this communication demonstrates the finer nuances in a stepwise manner. Interested readers may find it useful to work on their own through simple Excel spreadsheets based on specific clinical study designs.

COMPETING INTERESTS

The authors declared no competing interests for this communication.

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Normative Cognitive Scores in Western India, Stratified by Age, Rurality, Cognitive Domains, and Psychiatric Comorbidity

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ABSTRACT

Background and objectives: Indian ethnic and educational diversities necessitate obtaining normative cognitive data in different populations. We aimed to evaluate cognitive scores using a Marathi translation of the Kolkata cognitive battery (KCB) and to study the association of KCB components with depression and sociodemographic variables.

Materials and methods: We studied 2,651 individuals aged ≥ 40 years without preexisting neuropsychiatric conditions from urban (Mumbai) and rural districts of Maharashtra. For each component of KCB, the lowest 10th percentile score was used to define cognitive impairment.

Results: We studied 1,435 (54%) rural and 1,216 (46%) urban residents equally divided by gender (1,316 women and 1,335 men), average age 54 years. KCB scores were significantly lower with female sex, older age, illiteracy, and depression. The largest effect sizes attributable to these factors were in the domains of calculation (gender), visuoconstructional ability (VCA) (rurality), and verbal fluency (VF) (depression). Scores remained significantly lower in rural residents after controlling for age, sex, and education, particularly for VCA, immediate recall, and calculation.

Conclusion: This Marathi KCB, having been validated on large urban as well as rural samples, may be used to study cognition in Marathi-speaking populations with appropriate cutoffs tailored to the degree of urbanization of the population.

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BACKGROUND

There are few community-based studies on cognition in India, especially in rural areas. Ethnic, sociocultural, educational, and linguistic diversities in India make it necessary to obtain normative data on cognition in different populations. Tripathi and Tiwari have reported objective cognitive dysfunction in the areas of "orientation," "concentration," and "functioning/self-care" in normally aging older adults in urban Lucknow.¹ Gambhir et al., in a rural study of elderly, found a dementia prevalence of 2.7% and suggested that Hindi Mental State Examination (HMSE) score of 17 should be used as the cutoff for the illiterate population.² Ganguli et al. described a battery of cognitive tests that were developed for screening an illiterate elderly rural Hindi-speaking population based on their research conducted in Ballabgarh district in Haryana.³ Further, Banerjee et al.⁴ and Das et al.⁵ have obtained normative data for cognitive functions in a Bengali urban population utilizing the Kolkata cognitive battery (KCB) screening.

The mini-mental state examination (MMSE) and the HMSE, although popular and easy to administer, suffer from a lack of sensitivity to early dementia, especially of the subcortical variety.⁶ We aimed to

evaluate cognitive scores using the KCB, in an age-stratified manner, in Maharashtrian rural and urban communities and evolve cutoff scores based on individual test scores within the KCB as a step toward refining its sensitivity and specificity as a screening instrument to detect cognitive impairment in the specific population under study. Further, we aimed to compare differences in individual test scores classed according to different sociodemographic variables as well as Geriatric Depression Scale (GDS)⁷ scores and, finally, compare our sample's scores with those of the Kolkata and Ballabgarh study populations.

MATERIALS AND METHODS

Study Design

The KCB has been validated in urban populations by Das et al.,⁵ and the Hindi cognitive battery from which it was derived has been validated in the rural setting by Ganguli et al.³ In the first part of this study, the partially modified Hindi cognitive screening battery used by Ganguli et al. was translated into Marathi and again back-translated to Hindi by two independent bilingual translators. The GDS was also translated into Marathi and back-translated into Hindi. Field

testing on 40 persons was done initially for both KCB and GDS to ensure inter- and intra-investigator reliability, and the test was scored by the chief investigator and a qualified psychologist each time. Intrarater reliability was 1, and interrater reliability was over 0.9 for both KCB and GDS. Qualified psychologists and final-year residents in psychiatry training were trained in the administration of the translated KCB and GDS test by the chief investigator and a consultant psychiatrist.

In the second part, a cross-sectional interview-based survey was conducted in urban, semi-urban, and rural areas of Maharashtra.

Setting

The study was conducted in the villages of Vaitarna (Wada taluka, Thane district, population 671 as per 2011 census), Birwadi (Shahapur taluka, Thane district, population 3,415), and Pen taluka (Raigad district, population 37,852) over a period of 16 months from March 2015 to July 2016. These areas were chosen considering that they are the setting of ongoing primary healthcare projects under the community health department of the parent hospital, which made it feasible to obtain information on household numbers, size, and the number

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of people over 40 years of age in these areas. The urban areas in Mumbai included Kumbharwada in Dharavi, Kalachowki, and Antop Hill areas.

Data Collection

All persons aged 40 and over and residing in the study areas were invited to take part in the survey. We excluded persons with known mental retardation, previous stroke, any known psychiatric illness, or those reported by family to have previously diagnosed dementia or significant memory impairment impeding daily activities. Healthy individuals who met these criteria and consented to take part in the study comprised the final sample.

Trained personnel first recorded all epidemiological and demographic data for the consenting respondents and then administered the KCB. We used the KCB version validated by Ganguli et al., as it had questions on the post office, district, village, and block relevant to a rural community.³

The Marathi KCB was validated by readministering 30% of the cognition tasks from each of the eight domains of the KCB on 40 randomly chosen study participants by a second field researcher for interrater and by the same researcher after a gap of 6 weeks for intrarater reliability. Test administration and scoring were supervised by the chief investigator.

Our primary outcome measure was the age-stratified KCB score. Data collected on completed years of schooling was classified into educational categories, namely, illiterate, primary (1–5 years), secondary (6–12 years), and graduation level (13 years and above).

Cutoff Scores

For screening a large population, operational cutoff points are essential to differentiate between the cognitively impaired and the unimpaired groups.⁸ Following the precedent set by Das et al.,⁵ we chose the lowest 10th percentile score as the cutoff point to identify the significantly cognitively impaired 10th of the population. In GDS, scores range from 0 to 30. The higher scores indicate undetected depression. We chose the 90th percentile as the operational cutoff point to identify respondents with masked depression.

Statistical Methods

The data was analyzed using the appropriate Statistical Package for the Social Sciences and JASP (Jeffreys's Amazing Statistics Program, an open source statistical package developed by University of Amsterdam).^{9,10} Values were expressed in frequencies as well as percentages in relevant rows. Spearman rank correlation coefficients were calculated to determine intra- and interobserver reliability. Analysis of

variance (ANOVA) was used to compare means between groups. Kruskal–Wallis *H* test was used to analyze overall differences between age-groups and educational classes, and the Mann–Whitney *U* test was used to compare the two genders, urban and rural groups, groups with and without masked depression, and to compare each of the subgroups in age and education with the other subgroups.

The study was cleared by the Institutional Ethics Committee of Lokmanya Tilak Municipal Medical College and General Hospital (LTMGH), Mumbai, Maharashtra, India.

RESULTS

Demographic Profile

We screened 2,752 persons over 40 years of age; we excluded 19 persons with known intellectual developmental disorder, 31 with possible previous stroke, 36 with previous psychiatric illness, and 15 persons reported by family to have previously diagnosed dementia or significant memory impairment impeding daily activities. Our final sample size was 2,651 individuals who satisfied the inclusion and exclusion criteria and consented to participate in an interview. Their sociodemographic characteristics are summarized in Table 1. Among these participants, 1,435 (54%) were from rural localities, while 1,216 (46%) belonged to urban localities. The study group was equally divided with respect to gender, comprising 1,335 men and 1,316 women. However, in the younger age-groups (<60 years), men outnumbered women, and this trend was reversed for the older age-groups. The mean age of the study participants was 54 years, and women were slightly older (mean 54.28 years) than men (mean 53.87 years), though this difference was not significant. Most of the participants were poorly educated. Out of 1,335 men, 752 (56.3%) had studied for 5 years or less, and among women, the corresponding proportion was significantly higher (1,001 of 1,316, 76.1%, $p < 0.01$). Correspondingly, men significantly outnumbered women in the groups with higher education. We also noted a significant gender difference in occupation, with most of the women participants reporting as housewives (1,108, 84.2% of 1,316) and most of the remainder in unskilled and semiskilled occupations. Among men, 516/1,335, that is, 38.4%, reported employment in unskilled vocations, followed by semiskilled and clerical work, respectively. We observed a significant downtrend in mean years of education with increasing age (Table 1). We observed a significant difference in scores between rural and urban subsets of the study sample. The urban residents were

significantly younger and had significantly higher years of education than the rural residents (Table 1). While the study sample comprised roughly equal numbers of men and women with no significant difference in their mean age, the two gender groups differed notably in education, with men on average having 6.5 years of schooling compared to 4.7 years for women (Table 1).

Test Scores and Validation

Individual test scores with mean, median, standard deviation (SD), interquartile range, and 10th and 90th percentile scores are recorded in Table 2. Spearman rank correlation coefficients for both inter- and intrarater reliability were high for each test, ranging from 0.92 to 1.0. The score range for each domain spanned from zero to the maximum attainable score, except in the case of immediate recall, in which the maximum score attained was 28 out of 30.

Gender

The individual test scores refined by gender, shown in Table 3, highlight a significant difference in the mean scores, with women scoring lower than men on each test. The 90th percentile scores were higher for men in tests of verbal fluency (VF), immediate recall, visuoconstructional ability (VCA), and delayed recognition, and the 10th percentile scores were higher for MMSE, VCA, and delayed recognition. The difference in test scores attributable to gender, that is, effect size, ranged from 5 to 20%, with the largest effect size observed for test 4 calculation.

Rural vs Urban Residence

The individual test scores for rural and urban subsets, shown in Table 4, demonstrate higher mean scores in each test for the urban subset. Around 10th percentile scores were higher for urban residents in all tests except delayed word lists, and 90th percentile scores were also higher in four of the eight tests. Effect size ranged from 10 to 47%, with the largest difference observed for test 6, VCA, followed by test 5, immediate recall.

Presence vs Absence of Depression

In our study sample, the 90th percentile score for GDS was 17, which we used as the operational cutoff to identify masked depression. We observed significantly lower mean scores on all tests among the respondents who scored 17 and above on the GDS (Table 5). The largest effect size, up to 18%, was seen in test 3, MSE, and test 1, VF.

Table 6 shows the comparison of mean scores between different educational groups. Significant differences were observed in all tests between the illiterate group and every

Table 1: Demographic characteristics

Variables	Sex					Mean age in years ($\pm$ SD)	Mean years of education ($\pm$ SD)
						M 53.9 ($\pm$ 10.3)	M 6.5 ($\pm$ 4.3)
						F 54.3 ($\pm$ 10.5)	F 4.7 ($\pm$ 4.2)
						T 54.1 ($\pm$ 10.4)	T 5.6 ($\pm$ 4.3)
	Male		Female		Total		
	n	%	n	%	n		
Age-group (years)							
40–49	525	51.9	487	48.1	1012	44.2 ($\pm$ 2.9)	6.4 ($\pm$ 4.5)
50–59	441	52.6	398	47.4	839	53.5 ($\pm$ 2.7)	5.8 ($\pm$ 4.4)
60–69	232	43.3	304	56.7	536	63.2 ($\pm$ 2.7)	4.5 ($\pm$ 3.7)
70–79	116	55.2	94	44.8	210	73.1 ($\pm$ 3.0)	4.2 ($\pm$ 3.7)
80+	21	38.9	33	61.1	54	83.1 ($\pm$ 3.7)	4.4 ($\pm$ 3.6)
Total	1,335	50.4	1,316	49.6	2,651		
Educational level							
Illiterate	105	30.1	244	69.9	349	56.9 ($\pm$ 10.6)	0 (0)
Primary	647	46.1	757	53.9	1,404	54.5 ($\pm$ 10.7)	3.7 ($\pm$ 1.5)
Secondary	403	65.4	213	34.6	616	53.2 ($\pm$ 9.8)	9.0 ($\pm$ 4)
Graduate	180	63.8	102	36.2	282	50.2 ($\pm$ 8.1)	14.6 ($\pm$ 9)
Place of residence							
Rural	644	44.9	791	55.1	1435	55.1 ($\pm$ 10.8)	4.4 ($\pm$ 3.9)
Urban	691	56.8	525	43.2	1,216	52.8 ($\pm$ 9.8)	7.1 ($\pm$ 4.3)
Occupation							
Clerical	128	85.3	22	14.7	150		
Housewife	0	0	1,108	100	1,108		
Professional	71	76.3	22	23.7	93		
Retired	75	97.4	2	2.6	77		
Semiskilled	309	84.7	56	15.3	365		
Skilled	170	83.3	34	16.7	204		
Unemployed	66	94.3	4	5.7	70		
Unskilled	516	88.4	68	11.6	584		

F, female; M, male; T, total; significant difference noted in mean years of education across age-groups, mean age across educational groups, and mean age and years of education between urban and rural subgroups; p -value < 0.01 (ANOVA) for all

Table 2: Overview of test scores

KCB component tests	Maximum score	n	Range	Mean	SD	Median	Interquartile range	10th percentile score	90th percentile score
Test 1 VF	Non significant (NS)	2,651	0–32	11.86	5.35	12	7	5	20
Test 2 object naming	15	2,650	0–15	10.00	3.80	10	8	5	15
Test 3 MSE	30	2,635	0–30	24.56	5.31	26	8	17	30
Test 4 calculation	5	2,567	0–5	3.45	1.69	4	3	1	5
Test 5 immediate recall	30	2,651	0–28	12.01	5.89	12	8	4	20
Test 6 VCA	13	2,646	0–13	6.68	3.79	6	6	2	12
Test 7 delayed word list	10	2,623	0–10	4.77	2.14	5	2	2	7
Test 8 delayed recognition	20	2,637	0–20	8.57	4.36	9	6	2	14

other educational category, except for the comparison between the illiterate and primary education group for object naming and delayed recognition tests. Similarly, in the comparison between secondary education and graduate-

level groups, the difference was not significant for several tests, including immediate recall, VCA, and delayed recognition.

The comparison of means scores between age-groups is summarized in Table 7. Whereas,

between adjacent age bins, there was no significant difference in individual test scores (at both extremes of age-groups), significant differences were observed when the age-groups were sufficiently apart, typically

Table 3: Test scores sorted by gender and their comparison by Mann–Whitney *U* test

Parameters	Gender	n	Mean	SD	10th percentile score	90th percentile score	p-value	Effect size*	95% confidence interval for effect size	
									Lower	Upper
Test 1 VF	Men	1,335	12.36	5.4	5	20	<0.01	0.113	0.070	0.157
	Women	1,316	11.35	5.25	5	19				
Test 2 object naming	Men	1,335	10.16	3.62	5	15	<0.05	0.051	0.007	0.095
	Women	1,315	9.85	3.97	5	15				
Test 3 MSE	Men	1,324	25.17	5.21	17	30	<0.01	0.16	0.117	0.203
	Women	1,311	23.94	5.35	16	30				
Test 4 calculation	Men	1,282	3.74	1.6	1	5	<0.01	0.203	0.16	0.246
	Women	1,285	3.15	1.72	1	5				
Test 5 immediate recall	Men	1,335	12.75	5.92	4	20	<0.01	0.144	0.101	0.187
	Women	1,316	11.27	5.76	4	19				
Test 6 VCA	Men	1,332	7.13	3.76	2	12	<0.01	0.139	0.095	0.181
	Women	1,314	6.23	3.78	0	11				
Test 7 delayed word list	Men	1,319	4.93	2.07	2	7	<0.01	0.089	0.045	0.132
	Women	1,304	4.61	2.19	2	7				
Test 8 delayed recognition	Men	1,327	8.91	4.32	3	14	<0.01	0.085	0.041	0.129
	Women	1,310	8.22	4.35	2	13				

*, the Mann–Whitney *U* test, the effect size is given by the rank biserial correlation

Table 4: Test scores sorted by urban–rural residence and their comparison by Mann–Whitney *U* test

Parameters	Residence	n	Mean	SD	10th percentile score	90th percentile score	p-value	Effect size*	95% confidence interval for effect size	
									Lower	Upper
Test 1 VF	Rural	1,435	10.55	5.27	5	18	<0.01	−0.326	−0.365	−0.286
	Urban	1,216	13.41	5.02	7	20				
Test 2 object naming	Rural	1,434	9.68	4.25	4	15	<0.01	−0.109	−0.153	−0.065
	Urban	1,216	10.39	3.15	6	15				
Test 3 MSE	Rural	1,427	23.14	5.33	15	30	<0.01	−0.381	−0.419	−0.343
	Urban	1,208	26.23	4.78	19	30				
Test 4 calculation	Rural	1,424	2.94	1.73	0	5	<0.01	−0.378	−0.416	−0.339
	Urban	1,143	4.07	1.41	2	5				
Test 5 immediate recall	Rural	1,435	9.87	5.18	4	16	<0.01	−0.466	−0.5	−0.43
	Urban	1,216	14.54	5.66	7	22				
Test 6 VCA	Rural	1,432	5.27	3.43	0	10	<0.01	−0.472	−0.505	−0.437
	Urban	1,214	8.34	3.52	3	12				
Test 7 delayed word list	Rural	1,427	4.5	2.17	2	7	<0.01	−0.168	−0.211	−0.125
	Urban	1,196	5.09	2.06	2	7				
Test 8 delayed recognition	Rural	1,435	7.78	4.46	2	13	<0.01	−0.248	−0.289	−0.206
	Urban	1,202	9.51	4.06	4	14				

*, Mann–Whitney *U* test, the effect size is given by the rank biserial correlation

between the youngest two bins and the older bins.

Table 8 summarizes the comparison between the four educational classes at each age level. We observed that scores differed significantly between educational groups in the younger age levels across all tests, but with increasing age, differences ceased to be significant in the object naming and delayed word list domains.

DISCUSSION

The ethnic and educational diversity of the Indian population makes it necessary to obtain normative cognitive data for different regions. The most notable among the very few validated cognitive screening tools are those developed by Ganguli et al.³ for rural Hindi-speaking communities and the KCB by Das et al.⁵ We now attempt to

modify and tailor the KCB for Maharashtrian populations.

The GDS is designed such that high scores correlate with severe depression. Thus, the 90th percentile score of the GDS is used as the cutoff to screen individuals who are potentially clinically depressed. For our study sample, this cutoff is 17, which is lower than the accepted standard score of 22⁷ in rural communities (the cutoff in Das et al.'s sample⁵

Table 5: Test scores sorted by presence/absence of masked depression and their comparison by Mann–Whitney *U* test

Parameters	Depression [#]	n	Mean	SD	10th percentile score	90th percentile score	p-value	Effect size*	95% confidence interval for effect size	
									Lower	Upper
Test 1 VF	No	2,376	12.03	5.41	5	20	<0.01	0.173	0.102	0.242
	Yes	275	10.39	4.49	5	16				
Test 2 object naming	No	2,375	10.11	3.76	5	15	<0.01	0.141	0.07	0.211
	Yes	275	9.09	4.01	5	15				
Test 3 MSE	No	2,364	24.71	5.27	17	30	<0.01	0.187	0.116	0.256
	Yes	271	23.25	5.54	16	29				
Test 4 calculation	No	2,299	3.49	1.68	1	5	<0.01	0.152	0.08	0.222
	Yes	268	3.06	1.76	0	5				
Test 5 immediate recall	No	2,376	12.20	5.89	5	20	<0.01	0.165	0.094	0.234
	Yes	275	10.40	5.60	3	18				
Test 6 VCA	No	2,371	6.78	3.76	2	12	<0.01	0.135	0.063	0.205
	Yes	275	5.81	4.01	0	11				
Test 7 delayed word list	No	2,351	4.84	2.12	2	7	<0.01	0.159	0.087	0.228
	Yes	272	4.21	2.25	1	7				
Test 8 delayed recognition	No	2,362	8.68	4.33	3	14	<0.01	0.136	0.065	0.206
	Yes	275	7.59	4.58	2	12				

* , Mann–Whitney *U* test, effect size is given by the rank biserial correlation; [#] , presence of depression operationally defined as GDS score ≥ 17

Table 6: Test scores of each educational level compared with higher and lower levels using the Mann–Whitney *U* test

Parameters	Illiterate vs primary	Illiterate vs secondary	Illiterate vs graduate	Primary vs secondary	Primary vs graduate	Secondary vs graduate
Test 1 VF	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.05$
Test 2 object naming	NS	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$
Test 3 MSE	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$
Test 4 calculation	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$
Test 5 immediate recall	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	NS
Test 6 VCA	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	NS
Test 7 delayed word list	$p < 0.01$	$p < 0.01$	$p < 0.01$	NS	$p < 0.01$	$p < 0.01$
Test 8 delayed recognition	NS	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	NS

Table 7: Test scores of each age-group compared with older and younger groups using the Mann–Whitney *U* test

Parameters	40–49 vs 50–59	40–49 vs 60–69	40–49 vs 70–79	40–49 vs 80+	50–59 vs 60–69	50–59 vs 70–79	50–59 vs 80+	60–69 vs 70–79	60–69 vs 80+	70–79 vs 80+
Test 1 VF	NS	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	NS	NS	NS
Test 2 object naming	NS	$p < 0.01$	$p < 0.01$	NS	$p < 0.01$	$p < 0.01$	NS	NS	NS	NS
Test 3 MSE	NS	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$P < 0.05$	$p < 0.05$	NS
Test 4 calculation	NS	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	NS	NS	NS
Test 5 immediate recall	NS	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	NS	$p < 0.05$	NS
Test 6 VCA	NS	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	NS	NS
Test 7 delayed word list	NS	$p < 0.01$	$p < 0.01$	$p < 0.05$	$p < 0.01$	$p < 0.01$	NS	NS	NS	NS
Test 8 delayed recognition	NS	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p = 0.05$	NS	NS

was 21). Our camp-based methodology was dependent on respondents being sufficiently ambulatory and motivated to come to the screening site, which may have excluded the most depressed individuals with the uppermost range of GDS scores. However,

even this lower cutoff showed a significant association with low cognitive scores. While the depressed 10th of the study group had statistically significantly lower scores in each of the tests, the gap in mean scores was notably wide in the fields of immediate recall

and VF. Research indicates that depression affects cognitive performance in older as well as younger subjects, affecting the ability to complete complex tasks.¹¹ Sheline et al.,¹² studying the effect of late-life depression on cognitive performance, assessed five major

Table 8: Comparison between the four educational classes at each age bin, using the Kruskal–Wallis *H* test

Parameters	Within 40–49	Within 50–59	Within 60–69	Within 70–79	Within 80+
Test 1 VF	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$
Test 2 object naming	$p < 0.01$	$p < 0.01$	NS	NS	$p < 0.05$
Test 3 MSE	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$
Test 4 calculation	$p < 0.01$	$p < 0.01$	$p < 0.01$	NS	$p < 0.01$
Test 5 immediate recall	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.05$
Test 6 VCA	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	NS
Test 7 delayed word list	$p < 0.01$	$p < 0.01$	$p < 0.01$	NS	NS
Test 8 delayed recognition	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.05$

cognitive domains in patients with major depression and reported that changes in processing speed were found to most fully mediate the influence of predictor variables on all other cognitive domains.

Our study showed significantly poorer performance by women in each of the tests compared to men. While the largest gender-attributable score difference was observed in the testing calculation, the difference in VCA scores was striking, even in the lowest 10th percentile. The women were significantly less educated than men. Few among them (208/1316; 15.8%) had jobs outside the home, the majority being homemakers. The proportion of illiteracy was more than twice as high among women compared to men (F: 244/1316, 18.5%; M: 105/1335, 7.9%). The general awareness and comfort with writing and drawing among women may have been adversely affected as a result. Education, in particular literacy, has been shown to be associated with high cognition in the elderly.¹³ In a study of ethnically diverse elders, respondents with lower literacy levels had lower cognitive scores, this difference being attributed to poorer organization of visuospatial information, lack of previous exposure to stimuli, and difficulties with interpretation of the logical functions of language.¹⁴ Thus, it may be surmised that the observed differences in cognitive scores between men and women in our study are attributable to differences in their education levels.

Our study showed that test scores decreased (albeit not uniformly) with increasing age, with differences more pronounced between the youngest and oldest age-groups; no significant difference was observed comparing the scores of the moderately older or younger age-groups with each other. Das et al., in their Kolkata study, observed a similar pattern of significant differences in overall test scores, mainly when comparing the relatively younger age-groups (50–59) with elderly subjects aged above 70 years.⁵

The most remarkable finding of our study is the difference in test scores between the rural and urban subsets of the study group, particularly in the domains of VCA and immediate recall. Compared to rural, our urban respondents were significantly younger and better educated, with 50% of the urban dwellers having a secondary level or higher education vs only 21% of rural dwellers. The rural subset also had proportionately more women compared to the urban (R: 791/1435; 55.1% vs U: 525/1216; 43.2%). We noted a positive correlation of test scores with urban residence even after controlling for age, sex, and education, with the correlation coefficients being highest in the domains of VCA (0.323, $p < 0.01$), immediate recall (0.313, $p < 0.01$), and calculation (0.239, $p < 0.01$). The modern, fast-paced urban life, involving daily commutes, monetary calculations, workplace interactions, and a variety of cultural exchanges with different occupations and ethnicities, could have contributed to better general awareness, alertness, and mental processing speed, and subsequently higher test scores. Researchers from other countries have noted a similar rural–urban gap in cognitive scores, attributing it to educational disadvantage, selection through migration, and the existence of potentially modifiable risk factors other than lifestyle.^{15,16} There is thus considerable scope for further, larger studies of cognitive differences in urban and rural India, exploring factors, such as education, income, childhood illnesses, and substance use habits.

Ceiling Effect

Das et al.,⁵ in their study of cognitive scores in an urban elderly population, noticed possible ceiling effects in tests of object naming, calculation, MSE, and delayed recognition, which they attributed to the large number of literate subjects in an urban milieu. However, no such effect has been observed in the present study, either overall or in the urban subset of the participants group. This may be consequent to the difference in the

educational distribution of the two study sets, with two-thirds (501 of 745, 67%) of the Kolkata sample being educated at the secondary or higher level, compared to only a third of the present study group (898 of 2,651, 34%).

Limitations

A limitation of our study, which may have introduced a bias (in addition to the camp-based methodology, which may have excluded the severely depressed), is that many of our older subjects were unable to recall their exact age, and there may have been marginal misclassification of age bins.

CONCLUSION

We have presented and discussed the formulation and validation of a Marathi translation of the KCB. We found that cognitive scores declined with increasing age and poor education; however, our chief finding is the striking positive difference that an urban residential environment made to cognitive scores when other variables were comparable. This Marathi KCB, having been validated on a large sample of urban as well as rural residents, may be used to study cognition in Marathi-speaking populations with appropriate cutoffs tailored to the degree of urbanization of the locality.

Our study participants performed poorly in the domains of VF, object naming, and delayed recognition compared to the Ballabgarh and Kolkata study groups, with whom the original Hindi and Bengali cognitive testing instrument versions were validated. Further research is warranted to explore the factors leading to these differences. Women had poorer cognitive scores than men, which we surmise is due to their homebound lives, lesser education, and lower involvement in financial management.

FUNDING

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magnetic resonance imaging (MRI) volumetric studies," fully funded by the Cognitive Science Research Initiative 2012, Department of Science and Technology, Government of India.

DISCLAIMER

This manuscript has been published as a preprint on medRxiv (<https://www.medrxiv.org/content/10.1101/2022.03.22.22272678v1>) prior to its formal publication in the Journal of the Association of Physicians of India journal.

ETHICAL APPROVAL

The study was approved by the Human Research Institutional Ethics Committee, Lokmanya Tilak Municipal Medical College and General Hospital (LTMGH), Mumbai, Maharashtra, India.

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An Observational Study of Various Risk Factors and Etiological Profile in Patients with Lower Back Pain at Tertiary Care Center



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ABSTRACT

Objectives: The study aimed to analyze the risk factors and etiological profile of lower back pain (LBP) among patients attending a neurology outpatient department at a tertiary care center.

Materials and methods: A cross-sectional observational study was conducted, involving 170 patients, aged over 18, presenting with LBP between March and August 2023. Sociodemographic and lifestyle data were collected, and diagnostic investigations, including X-ray and magnetic resonance imaging (MRI), were performed. Patients were categorized into acute and chronic LBP groups for analysis.

Results: Age—acute LBP was more prevalent in younger patients (<35 years), while chronic LBP was predominant in older age-groups (≥55 years). Gender—females showed a higher prevalence of LBP compared to males, with chronic LBP more common among females. Triggering events—heavy weightlifting was a significant trigger for chronic LBP, while coughing/sneezing was common in acute LBP. Occupation—patients with physically exerting jobs were more prone to acute LBP, while chronic LBP was prevalent among homemakers and those with no work. Body mass index (BMI)—obesity and overweight were associated with chronic LBP. Medication—chronic LBP patients were more likely to be on medication compared to acute LBP patients. MRI findings—prolapsed intervertebral disk (PVD) was the most prevalent etiology, more common in chronic LBP patients. Other etiologies included vertebral fracture, tumor, tuberculosis, and various spinal conditions.

Conclusion: Lower back pain is a multifaceted condition influenced by age, gender, BMI, and lifestyle factors. Effective management and prevention strategies should consider these risk factors to improve patients' quality of life. A comprehensive approach is essential to address the complex etiology of LBP.

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INTRODUCTION

Lower back pain (LBP) is the leading cause of disability worldwide that had affected 619 million persons globally in 2020, and the number of cases is expected to rise to 843 million by 2050, primarily due to population growth and aging. It imposes a tremendous economic burden on both developed and developing countries. In the span of just a decade, from 2007 to 2017, LBP has emerged as a leading cause of years lived with disability (YLD). The data reveals a remarkable rise of 32 and 30% in YLD due to LBP among females and males, respectively, underlining its pressing public health implications.^{1,2}

Lower back pain is described as pain between the lower edge of the ribs and the buttock. People at any age can experience LBP. It is estimated that approximately 80% of the world population will experience an episode of incapacitating back pain at least once during their lifetime.³

Based on duration, LBP can be divided into acute (<6 weeks), subacute (6 weeks to <3 months), and chronic (>3 months). People with acute back pain are less likely to seek medical attention or be referred for treatment even though acute back pain frequently results from an actual or nearly actual tissue

injury or sprain. Chronic pain frequently persists even after an initial injury has healed.⁴

Risk factors of LBP are multifactorial and include physical factors, sociodemographic characteristics, lifestyle habits, and psychological factors. Sociodemographic factors have a great impact on LBP.⁵

Despite its prevalence, the exact etiology of LBP remains multifaceted and not fully understood. The present study was conducted to analyze the risk factors of LBP and etiological profile in patients presenting to neurology outpatient department (OPD).

MATERIALS AND METHODS

The present cross-sectional observational study was conducted in the Department of Neurology, SMS Medical College and Attached Group of Hospitals, Jaipur, India after the approval from ethical committee (845/MC/EC/2023) of the institute. A total of 170 patients were included in the study based on the following inclusion and exclusion criteria.

Inclusion Criteria

- Age >18 years.
- Patients who were presented with LBP from March 2023 to 2023.
- Given written consent to participate.

Exclusion Criteria

- Age <18 years.
- Patients with preexisting chronic neurological disorder such as old stroke, poliomyelitis, spastic disorders, or Parkinson's disease.
- Had a pacemaker or other electrical device.
- Refused consent to participate in study.

Methodology

After getting the consent from all the 170 patients, careful history, physical examination, and investigations were done. During history taking, patients were asked multiple domain questionnaire regarding sociodemographic factors and lifestyle pattern. Investigations included X-ray lumbosacral spine anteroposterior (AP) and lateral view and/or magnetic resonance imaging (MRI) of lower dorsal and lumbosacral spine.

After analyzing, the patients were divided into two groups to correlate various risk factors:

- Patients with acute LBP (≤6 weeks).
- Patients with chronic LBP (>3 months).

Sociodemographic data included factors such as age, sex, marital status, education, occupations, body mass index (BMI), type of bed mattress used, triggering events, smoking, physical activity, and the medications patients were taking for the LBP.

Degenerative X-ray spine is considered if there is evidence of vertebral body osteophytes, sclerotic (whiter than normal), thickened, and irregular vertebral body endplate surfaces, narrowing of the disk spaces due to reduced height of the intervertebral disks, and the disks themselves are not visible.

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Table 1: Pfirrmann PIVD grading

Pfirrmann grade for PIVD	Description
Grade 0	Focal disk herniation that does not hinder the nerve root
Grade I (contact)	Nerve root is in visible contact with the bulging or herniating disk material but remains in its normal location
Grade II (deviation)	Nerve root is displaced dorsally
Grade III (compression)	Nerve root is compressed between the disk material and the wall of the spinal canal

Magnetic resonance imaging of the spine was done to assess the etiology of the LBP. For prolapsed intervertebral disk (PIVD), Pfirrmann grading was done. The system incorporates four grades (Table 1).⁶

Statistical Analysis

Data were entered in MS Excel (Microsoft 365, Windows 11). Qualitative data were expressed in percentage or proportion, and quantitative data were presented as mean and standard deviation/median and interquartile range. Data were analyzed using Statistical Package for the Social Sciences (SPSS) software version 21. For quantitative variables, unpaired *t*-test was used as applicable, and for qualitative variables, the Chi-squared test was used. A *p*-value < 0.05 was considered significant.

RESULTS

Age

In the present study, 32.9% of patients were aged <35 years. Additionally, 47, 36, and 32% of patients were aged between 35 and 44, 45 and 54, and ≥55 years, respectively. Out of 170 patients, 112 (65.9%) had acute LBP, while 58 (34.1%) had chronic LBP. On comparing patients with acute and chronic pain, it was found that patients with acute LBP were younger than those with chronic backache. Specifically, 44.6% of the patients with acute LBP were <35 years old, while only 10.3% of patients with chronic LBP were of the same age-group. Similarly, 39.7% of patients with chronic LBP were aged ≥55 years (compared to 7.1% of patients with acute LBP), and this association was statistically significant (*p* < 0.001).

Sex

Out of 170 patients, 52.94% were females and 47.06% were males. Among females, 63.79%

had chronic LBP, while acute LBP was observed in 47.32%. In males, acute vs chronic LBP was observed in 52.68 vs 36.21% of patients, respectively. This association was statistically significant (*p* < 0.05).

Triggering Event

About 15.88% of patients had trauma, while 47.06% had heavy weightlifting as trigger events. Overall, coughing/sneezing/muscle strain as trigger events were seen in 18.82% of patients. In acute LBP, coughing, sneezing, and straining were seen in 21.43% of patients. About 45.54% of patients with chronic LBP had heavy weightlifting as a trigger event, and no triggering event was found in 14.29% of chronic LBP patients. This association was statistically significant (*p* < 0.05).

Occupation

It was observed that 16.47% of patients had no work, while 32.35, 12.35, 22.35, and 16.47% of patients worked as homemakers, office workers, jobs with physical exertion, and intense physical exertion, respectively. Patients with no work and homemakers mostly suffered from chronic LBP (16.47 and 32.35%, respectively), while acute LBP was mostly observed in patients who were physically exerting themselves. This association was statistically significant (*p* < 0.001).

Body Mass Index

Body mass index was in the normal range in 37.6% of patients. About 39.4 and 22.9% of patients were overweight and had obesity, respectively. We found that patients who had a BMI within the normal range had acute LBP (52.7 vs 8.6%), while those with a BMI >25 had chronic LBP (91.4 vs 47.3%). This association was statistically highly significant (*p* < 0.05).

Use of Medication

Out of 170 patients, 53.53% of patients were not on any medication, while 46.47% of patients were on medication in the form of nonsteroidal anti-inflammatory drugs ± gabapentin ± amitriptyline and local application. It was observed that 71.43% of patients with acute LBP were not on any medication, while 18.97% were taking medication. Chronic LBP patients were consuming medication either once a month (29.31%) or once a week (44.83%). This association was statistically significant (*p* < 0.05).

Others

About 83.3% of the patients were married. About 35.29% of the patients were illiterate, while 16.47, 14.12, 25.88, and 8.24% were educated till elementary, intermediate, secondary, and graduation levels, respectively.

About 80% of the patients had no extra physical activity/sports. About 65.88% of patients with LBP were using cotton mattresses. The rest were using either sponge (18.82%) or orthopedic mattresses (1.18%). About 14.12% of patients were not using any mattress. The habit of smoking was seen in 45.29% of patients. No significant association was seen between marital status, education, physical activity, type of mattress, and smoking (Tables 2 and 3 and Fig. 1).

Etiology

Magnetic resonance imaging of the lumbosacral spine showed PIVD in a total of 119 (70%) patients, while fractures (of the vertebral body/pars interarticularis) were seen in 13 (7.64%) patients. In nine (5.29%) patients, the etiology was a tumor, which included vertebral metastasis in three patients and primary spinal cord tumors in six patients (nerve sheath tumor and ependymoma). Tuberculosis of the spine and spondylolisthesis were seen in six (3.53%) and five (2.94%) patients, respectively (anterolisthesis in four of grade I and in one patient retrolisthesis of grade II). Failed back syndrome, fluorosis, and scoliosis were seen in two (1.18%) patients each. A hydatid cyst and spondyloarthritis were seen in one patient each. In 10 (5.88%) patients, the MRI spine was normal (Table 4).

Prolapsed intervertebral disk was the most prevalent cause in both acute (68.75%) and chronic (72.41%) LBP. Fracture and spondylolisthesis were seen in 12 (7.64%) and five (4.46%) patients with acute LBP, respectively. In 91% of patients, PIVD grade III was seen, followed by grade II (21%) and grade I (16%) (Table 5 and Fig. 2).

Prolapsed intervertebral disk was seen at the L4-L5 and L5-S1 levels in 85 (71.42%) patients, followed by the L3-L4 and L4-L5 levels in 22 (18.48%) patients. In the remaining 12 (10%) patients, multiple level PIVD was observed. Multiple level PIVD was seen in eight (66%) patients with chronic LBP.

DISCUSSION

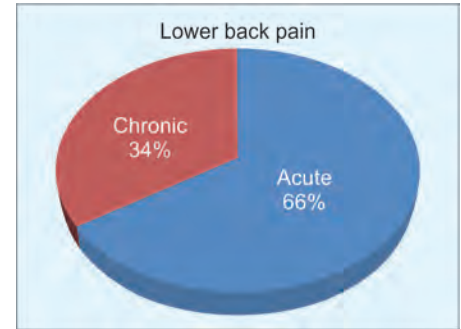
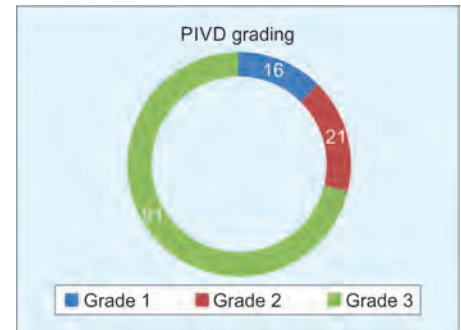
We found that growing age is significantly related to the chronicity of LBP while acute LBP was mostly observed in younger age-group. The results were like the study by Bener et al. in their study the age was one of the more common risk factors for LBP and the incidence was highest in the third decade.^{7,8} In their review, Wong et al. hypothesized that as people get older, the prevalence rates of severe and chronic LBP rise.⁹

Age-related decline in descending pain modulation pathway may be the cause of

Table 2: The various risk factors assessed in the present study

	Risk factors	Frequency (percentage)
Age	<35 years	56 (32.9)
	35–44 years	47 (27.6)
	45–54 years	36 (21.2)
	≥55 years	31 (18.2)
Sex	Male	80 (47.06%)
	Female	90 (52.94%)
Marriage	Married	142 (83.53%)
	Unmarried	28 (16.47%)
Education	Illiterate	60 (35.29%)
	Elementary	28 (16.47%)
	Intermediate	24 (14.12%)
	Secondary	44 (25.88%)
Triggering event	Graduate	14 (8.24%)
	Trauma	27 (15.88%)
	Coughing/sneezing/muscle strain	32 (18.82%)
	Heavy weightlifting	80 (47.06%)
Occupational	None	31 (18.24%)
	No work	28 (16.47%)
	Homemaker	55 (32.35%)
	Office	21 (12.35%)
BMI (kg/m ²)	Physical exertion	38 (22.35%)
	Intense physical exertion	28 (16.47%)
	Normal (<24.1)	64 (37.6%)
	Overweight (25–30)	67 (39.4%)
Physical activity	Obesity (>30)	39 (22.9%)
	No activity	136 (80.00%)
	Once a week	9 (5.29%)
	Twice a week	22 (12.94%)
Medication	≥3 times a week	3 (1.76%)
	None	91 (53.53%)
	Sporadic	14 (8.24%)
	Monthly	2 (11.76%)
Bed mattress	Weekly	40 (23.53%)
	Daily	5 (2.94%)
	Orthopedic	2 (1.18%)
	Sponge	32 (18.82%)
Smoking	Cotton	112 (65.88%)
	None	24 (14.12%)
	Present	79 (46.47%)
	Absent	91 (53.53%)

BMI, body mass index

**Fig. 1:** Distribution of patients according to duration of LBP**Fig. 2:** Distribution of patients with PIVD according to various grades

as well as poorer descending endogenous pain inhibitory regulation.¹²

In present study, females were more affected with LBP. Although few studies have found no significant differences in the prevalence of LBP between genders.¹³ The study by Bener et al. found that LBP was higher in women (67.7%) compared with men (51.6%). It was found in two studies that LBP symptoms were consistently more common among women.^{9,14}

Women continue to be the primary informal caregivers for the children and older people in Asian countries and this too is a factor in women's back pain syndromes. Hathorn et al. stated that the risk of LBP is higher among women because of the stress of hormonal changes, gynecological problems, and childbirth.¹⁵ In our region, the higher prevalence of LBP among females can be attributed to labor-intensive activities involving repetitive bending and lifting heavy weight such as fodder transportation and carrying irrigation sprinklers to farms. These activities increased strain on the lower back and contribute to a greater risk of discomfort and pain.

Also, in present study, majority of female had chronic LBP while male had acute LBP. According to Jiménez-Sánchez et al., women are two times as likely as

older people's increasing pain sensitivity. According to neuroimaging studies, as people age, their brains capacity to handle pain (the cingulate, insula, striatum, hippocampus, cerebellum, and prefrontal cortex) decreases noticeably.^{10,11} These results may point to age-related declines in inhibitory motor coordination in response to noxious stimuli,

Table 3: The association of various risk factors with LBP

Variables		LBP				p-value (Chi-square)	
		Acute (n = 112)		Chronic (n = 58)			Total
		N	%	N	%		
Age	<35 years	50	44.6%	6	10.3%	56	<0.001
	35–44 years	39	34.8%	8	13.8%	47	
	45–54 years	15	13.4%	21	36.2%	36	
	≥55 years	8	7.1%	23	39.7%	31	
Sex	Male	59	52.68%	21	36.21%	80	0.04
	Female	53	47.32%	37	63.79%	90	
Marital status	Married	90	80.36%	52	89.66%	142	0.08
	Unmarried	22	19.64%	6	10.34%	28	
Education	Illiterate	34	30.36%	26	44.83%	60	0.183
	Elementary	17	15.18%	11	18.97%	28	
	Intermediate	17	15.18%	7	12.07%	24	
	Secondary	32	28.57%	12	20.69%	44	
	Graduate	12	10.71%	2	3.45%	14	
Triggering event	Trauma	21	18.75%	6	10.34%	27	0.019
	Coughing/sneezing/muscle strain	24	21.43%	8	13.79%	32	
	Heavy weightlifting	51	45.54%	29	50.00%	80	
	Others	16	14.29%	15	25.86%	31	
Occupational	No work	10	8.93%	18	31.03%	28	<0.001
	Homemaker	32	28.57%	23	39.66%	55	
	Office	15	13.39%	6	10.34%	21	
	Physical exertion	36	32.14%	2	3.45%	38	
	Intense physical exertion	19	16.96%	9	15.52%	28	
BMI	<24.1	59	52.7%	5	8.6%	64	<0.001
	25–30	41	36.6%	26	44.8%	67	
	>30	12	10.7%	27	46.6%	39	
Physical Activity	No activity	87	77.68%	49	84.48%	136	0.68
	Once a week	6	5.36%	3	5.17%	9	
	Twice a week	17	15.18%	5	8.62%	22	
	≥3 times a week	2	1.79%	1	1.72%	3	
Use of medication	None	80	71.43%	11	18.97%	91	<0.001
	Sporadic	10	8.93%	4	6.90%	14	
	Monthly	3	2.68%	17	29.31%	20	
	Weekly	14	12.50%	26	44.83%	40	
	Daily	5	4.46%	0	0.00%	5	
Type of bed mattress	Ortho	0	0.00%	2	3.45%	2	0.119
	Sponge	22	19.64%	10	17.24%	32	
	Cotton	77	68.75%	35	60.34%	112	
	None	13	11.61%	11	18.97%	24	
Smoking	Present	56	50%	23	39.60%	79	0.06
	Absent	57	50.89%	34	58.62%	91	
Total		112	65.90%	58	100.00%	170	

BMI, body mass index

Table 4: Distribution of patients according to MRI findings

Investigations		Frequency	Percentage
MRI spine	PIVD	119	70.00%
	Tumor	9	5.29%
	Tuberculosis of spine	6	3.53%
	Failed back	2	1.18%
	Fracture	13	7.64%
	Fluorosis	2	1.18%
	Spondylolisthesis	5	2.94%
	Normal	10	5.88%
	Scoliosis	2	1.18%
	Hydrated cyst	1	0.59%
	Spondyloarthritis	1	0.59%
Total		170	100.00%

Table 5: Association of MRI findings with LBP

Variables		LBP					p-value (Chi-square)
		Acute		Chronic		Total	
		N	%	N	%		
MRI spine	PIVD	77	68.75%	42	72.41%	119	0.002
	Tumor	6	5.36%	3	5.17%	9	
	Tuberculosis of spine	6	5.36%	0	0.00%	6	
	Failed back syndrome	0	0.00%	2	3.45%	2	
	Fracture	12	10.71%	1	1.72%	13	
	Fluorosis	0	0.00%	2	3.45%	2	
	Spondylolisthesis	5	4.46%	0	0.00%	5	
	Normal	2	1.79%	8	13.79%	10	
	Scoliosis	2	1.79%	0	0.00%	2	
	Hydrated cyst	1	0.89%	0	0.00%	1	
	Spondyloarthritis	1	0.89%	0	0.00%	1	
Total		112	100.00%	58	100.00%	170	

males to develop chronic LBP.¹⁶ Complex biopsychosocial mechanisms, such as less effective pain habituation or diffuse noxious inhibitory control, genetic sensitivity, pain coping, and a higher vulnerability to develop temporal summation of chemically or mechanically evoked pain, may be responsible for the higher prevalence of chronic pain in females. In addition, women frequently have more concurrent chronic illnesses, such as osteoporosis, osteopenia, and osteoarthritis, which are known to increase the likelihood of developing chronic LBP and psychological distress in older adults.⁹

Most patients in the present study were either obese or overweight. The results were in accordance with studies conducted by Waddell et al. and Bener et al., which showed that obesity or higher BMI was associated with an increased occurrence of LBP. Generally, it is believed that people with a good state of physical fitness appear to have a lesser risk of chronic LBP.

We found that patients who had a BMI within the normal range, <24.1, had acute LBP (52.7 vs 8.6%), while those with a BMI >25 had chronic lower backache (47.3 vs 91.4%). This association was statistically highly significant.^{9,17}

In the present study, we found that coughing, sneezing, and muscular events were most commonly seen in acute LBP (21.43 vs 13.79%), while heavy weightlifting was a common event in chronic LBP. This association was statistically significant. Additionally, it was observed that patients with no work or homemakers mostly suffered from chronic LBP, while acute pain was mostly observed in patients who were physically exerting themselves. This association was statistically significant ($p < 0.001$).¹⁸

A prospective study with >1,500 participants revealed that prior occupational biomechanical exposure to bending/twisting

increased the odds of having persistent LBP in retired adults aged 58–67 years. Similarly, retired postal workers with LBP who were between the ages of 70 and 75 were noted to have regularly lifted heavy objects for >20 years.¹⁹

The present study revealed that PIVD was the most prevalent etiology in our patients, with 119 (70%) cases, occurring in both chronic and acute LBP, but was more common

in patients with chronic LBP. PIVD mostly affected the L4-L5 vertebral level, followed by the L5-S1 level and L3-L4. In terms of PIVD grade, most patients had grade III, followed by grade II and grade I (Fig. 3A to C). These results are in accordance with the study performed by Kaliya-Perumal et al., where the majority of patients were in grade III, followed by grade II and grade I.²⁰ After PIVD, fracture of the spine (7.64%), tumor (5.29%), and tuberculosis of the

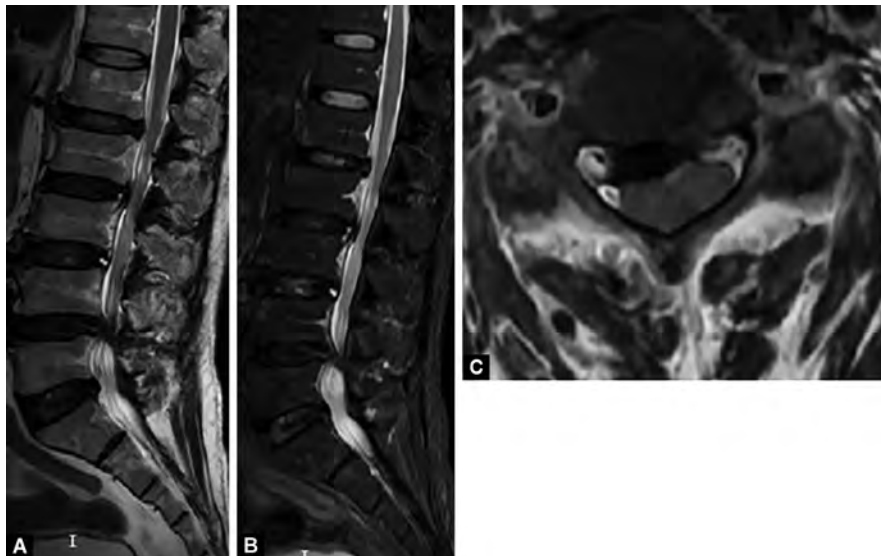
spine (3.53%) were observed. Other causes included sacralization of L5 (2.94%), fluorosis, failed back syndrome, and a hydatid cyst of the spine (Fig. 4A to F). MRI spine was normal in 10 (5.88%) patients.

CONCLUSION

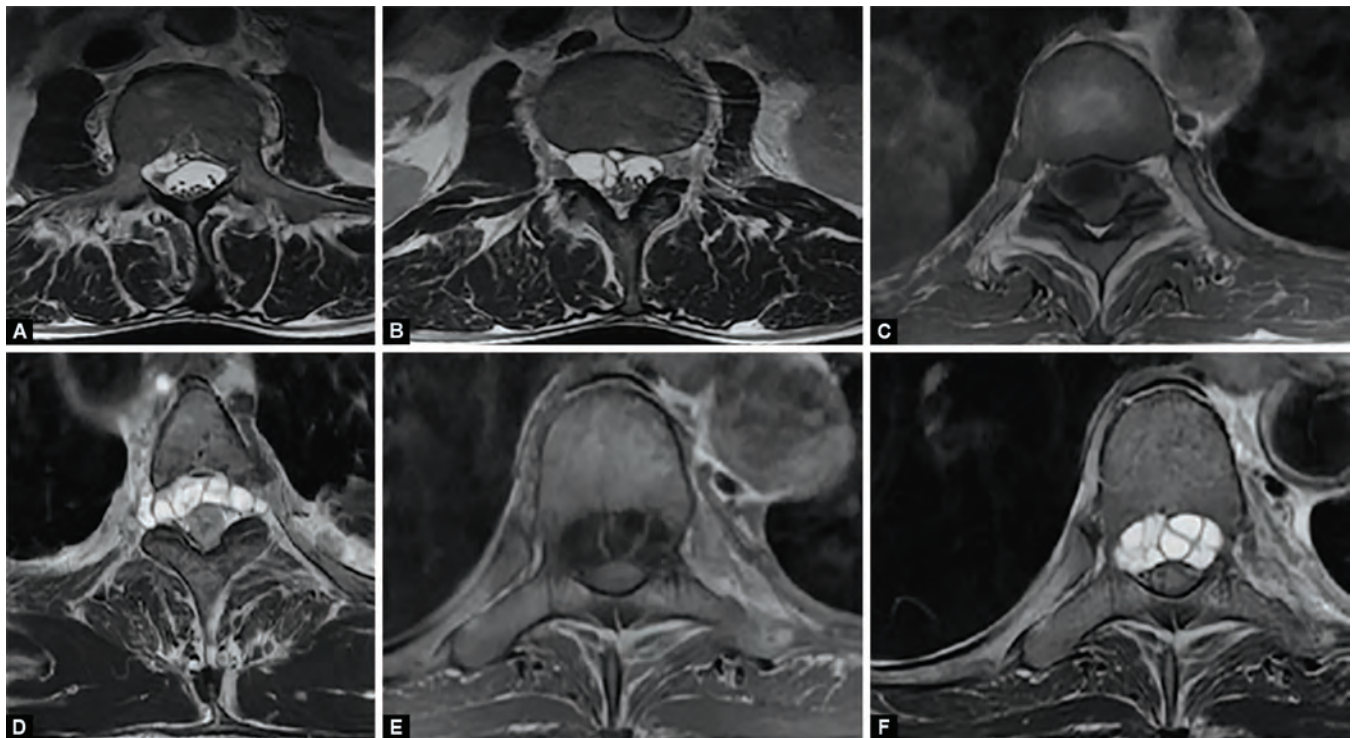
Lower back pain is a complex condition with a multitude of contributing factors, encompassing age, gender, sociodemographic, and lifestyle elements. Our analysis revealed that chronic LBP had various risk factors such as age, gender, BMI, and triggering events. Women were more likely to present with LBP than men. Chronic LBP was observed more frequently among older people and among those who were overweight. Coughing/sneezing were reported as triggering factors for acute LBP. Effective management and prevention strategies must consider this multifaceted etiology. A comprehensive approach that addresses these factors is essential to improve the quality of life for those affected by this condition.

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Figs 3A to C: Magnetic resonance imaging lumbosacral spine of patient with PIVD at multiple levels (grade III) in (A) T2 sagittal section, (B) T2 STIR sagittal section, and (C) T2 cross-sectional image



Figs 4A to F: Magnetic resonance imaging lumbosacral spine showing hydatid cyst in axial section of (A, B, D, and F) T2 and (C and E) T1 images

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Prediction of Micro- and Macrovascular Complications in Type 2 Diabetes Mellitus using Heart Rate Variability

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ABSTRACT

Objective: To explore the utility of heart rate variability (HRV), a noninvasive marker of cardiac autonomic activity, as a prescreening tool for the prediction of micro- and macrovascular complications in type 2 diabetes mellitus (T2DM).

Methods: Consenting type 2 diabetic patients of both genders between 30 and 70 years, without known micro- and macrovascular complications of diabetes, were enrolled. Patients with medications affecting the HRV were excluded. Prior to other screening tests, 15 minutes of resting electrocardiogram (ECG) (1 kHz) was recorded in enrolled patients, followed by an exercise stress test and assessment for nephropathy, retinopathy, and peripheral neuropathy. The patients with positive stress tests were referred for coronary angiography to confirm coronary artery disease. Based on screening test results, patients were grouped as Group I—T2DM without complications ($n = 31$) and Group II—T2DM with micro/macrovascular complications ($n = 29$), (total = 60).

Results: Group comparison and test for association were employed, and p -value of <0.05 was considered significant. Significantly reduced HRV (decreased standard deviation of NN interval) between groups and a strong association of HRV indices with complications of diabetes were observed. Logistic regression to classify complicated vs noncomplicated group was used, and an accuracy of 0.78 with 85% sensitivity, 74% specificity with area under the curve (AUC) of 0.83 was observed.

Conclusion: Significantly reduced HRV, stronger association with complications, and 85% sensitivity, 74% specificity, and 78% accuracy of classification make HRV indices a promising prescreening tool to predict micro- and macrovascular complications in type 2 diabetes.

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INTRODUCTION

Type 2 diabetes and its micro- and macrovascular complications seriously affect the patient's quality of life and place an immense burden on healthcare systems.^{1,2} If uncontrolled, diabetes progresses slowly to complications. Coronary artery disease (CAD) is a major complication of type 2 diabetes, and early detection of it is a real challenge. In most cases, the myocardial ischemia is silent since the patient is often unable to feel pain because of associated cardiac autonomic neuropathy (CAN).^{3,4} Prediction and timely referral for CAD screening is therefore crucial. In this context, the American Diabetes Association (ADA) has recommended screening guidelines.⁵ A screening protocol includes investigations for glycated hemoglobin (HbA1c) every 3 months and annual checks for lipid profile, nephropathy, retinopathy, peripheral and CAN.⁶ The rationale for including HbA1c is the observation that lowering HbA1c reduces the risk of micro- and macrovascular complications. Nonetheless, no consensus exists on optimal HbA1c cutoffs that actually reduce such risks.⁷ Furthermore, glycemic variability (short and long term) is shown

to be a better predictor of micro- and macrovascular complications of diabetes rather than the mean HbA1c level.⁸

Multiple invasive investigations recommended routinely for screening complications of diabetes affect the patient's compliance to these investigations. Moreover, if diabetes is associated with comorbidity such as hypertension, then assessing complication risk solely based on glycemic status is inadequate. It is, therefore, necessary to identify a biomarker that is simple to use, preferably noninvasive, and predicts the complications reliably.

Reduced heart rate variability (HRV), indicative of cardiac autonomic dysfunction, is associated with hypertension and type 2 diabetes mellitus (T2DM).⁹ Several studies [Hoorn study, Framingham study, Atherosclerosis Risk in Communities (ARIC) study] have documented progressive declines in HRV with concurrent increases in insulin resistance.^{10–12} The Toon Health Study in the Japanese adult population, using multivariate-adjusted logistic regression models, has shown a significant association of decreased SDNN (standard deviation of NN interval: an indicator of overall variability), RMSSD (root mean square of standard

deviation), HF (high-frequency component of FFT, the markers of cardiac parasympathetic modulation), and increased LF:HF ratio (a marker of sympathovagal balance) with increased homeostasis model assessment index for insulin resistance (HOMA-IR) and decreased Gutt's insulin sensitivity index (ISI).¹³ Moreover, HRV is shown to be reduced in patients with CAD without diabetes.¹⁴ In a 24-hour HRV study by Makimoto et al., the circadian vagal fluctuations, especially during the night, were found to be impaired (reduced) in patients with chronic kidney disease (CKD) without diabetes and are independent of age and comorbidities.¹⁵ To summarize, a reduced HRV is associated with metabolic disorder, type 2 diabetes, hypertension, as well as having an independent association with CAD and CKD. Accordingly, these observations support the "Neuroadrenergic Hypotheses of Hypertension" proposed by Grassi et al.¹⁶ stressing that progressive sympathetic overdrive (autonomic dysfunction) is an important factor that leads to progression of predisease state to clinically overt disease and then to its complications. Furthermore, in relation to diabetes, the oxidative stress caused by hyperglycemia and the underlying inflammatory state further impairs autonomic function, reducing HRV.¹⁷ In addition, an

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inverse association between glycemic variability and HRV (higher glycemic variability will reduce HRV) was observed.

In light of these observations, we investigated the utility of HRV as a prescreening tool for predicting complications in type 2 diabetes.

Objective: The objective of the present study was to explore the utility of HRV as a prescreening tool for predicting micro- and macrovascular complications in T2DM.

MATERIALS AND METHODS

Study Design

It was a cross-sectional observational study. The study was approved by the Institutional Ethics Committee with the Helsinki Declaration of 1975, as revised in 2000.

The sample size was estimated considering $\alpha = 0.05$, and statistical power at 80% and the large effect size (0.51) as proposed by Quintana,¹⁸ for HRV studies by modeling effect size distribution that requires a minimum of 21 participants per group. **Inclusion:** Consenting type 2 diabetes patients with disease duration greater than 1 year, between 30 and 70 years of age and of both genders without known micro- and macrovascular complications were enrolled during their visit to the outpatient department (OPD) at Smt. Kashibai Navale Medical College Pune between the period of January–June 2017 (total enrolled = 80). **Exclusion criteria:** Patients with a previous history of thyroid disorders, drugs affecting HRV (tricyclic antidepressants, β blockers and calcium channel blockers, ACE inhibitors) were excluded from the study. Out of 80 enrolled patients, the patients with arrhythmia or incomplete noisy electrocardiogram (ECG) records, or those unable to complete all screening tests were not considered for analysis ($n = 20$).

Cardiac Autonomic Reflex Test (CART) and Resting ECG

Standard CART protocol (30:15 ratio, deep breathing test (E:I ratio), orthostatic blood pressure and heart rate response) was employed. Additionally, 15 minutes of resting ECG sampled at 1 kHz (measurement using Chronovisor HRV-Dx made—Promorphosis Pvt. Ltd. Pune) was measured prior to other standard screening tests. The testing was done in a quiet room between 9 am to 12 pm of the day, and the patients were instructed to sit comfortably for 30 minutes prior to the test in the waiting area. The patients were asked to refrain from coffee and tea 3 hours prior to the test and strenuous exercise on the previous day. The patients were allowed to take their

routine oral hypoglycemic and insulin as per the schedule.

Other Screening Tests

All patients underwent routine clinical examination and were investigated for the presence of micro- and macrovascular complications using standard and established guidelines. In accordance, the patients were subjected to exercise stress test with multistage Bruce protocol or modified Bruce Protocol depending on the patient's condition. Those patients with positive stress test were subjected to coronary angiography for confirmation of CAD. All patients were also investigated for: (1) Presence of diabetic nephropathy (KDOQI guidelines),¹⁹ (2) diabetic retinopathy (ETDRS guidelines),²⁰ (3) diabetic peripheral neuropathy (clinically and suspected cases with nerve conduction study). Based on the results of screening tests, patients were categorized into two groups. Group I ($n = 31$) without complications (no retinopathy, nephropathy, peripheral neuropathy, and CAD) and Group II ($n = 29$) with mentioned complications. The presence or absence of CAN was excluded for segregating the patients into two groups, as apart from HRV, CAN was one of our study variables.

HRV Analysis

The HRV analysis was done as per the guidelines of the Task Force 1996.²¹ The HRV indices from time domain (SDNN—a marker of overall HRV) and frequency domain indices that included total power: measure of overall HRV, absolute low frequency power (LF ms^2) and normalized LF power (LF nu): measure of cardiac sympathetic/baroreflex modulation, absolute high frequency power (HF ms^2) and normalized HF power (HF nu): measure of cardiac parasympathetic modulation were computed from 5 minutes of resting ECG.

CART Analysis

As per the guidelines on assessment and interpretation of CAN by the Toronto panel,²² the detection and classification of severity of CAN was done. One positive cardiovagal

test as early or probable CAN, two positive cardiovagal tests as definite, and two positive cardiovagal tests with the presence of orthostatic hypotension as advanced CAN.

Statistical Analysis

Group comparison was done using the Mann–Whitney test (nonparametric), and association was tested by the Chi-square test using Epi Info 7 statistical software. A p -value of <0.05 was considered significant. Logistic regression was used to train the machine for classification (complication vs noncomplication in T2DM). Our dataset consists of 60 samples, and each sample is described by nine attributes, namely: gender, age, SDNN, total power, LF (ms^2), HF (ms^2), average heart rate, LF (nu), HF (nu). Every sample is labeled as either complicated or noncomplicated. In total, there are 31 cases of noncomplications and 29 cases of complications. We have divided our dataset into 70% training data and 30% test data. Thus, our training dataset consists of 42 samples, whereas our test dataset consists of 18 samples. We set up the problem as a classification problem, where our goal was to classify examples into either cases of complications or cases of noncomplication, based on the nine given attributes. We trained the data using a logistic regression classifier, and observed that the accuracy of classification on the training data was 0.81.

RESULTS

The demographic profile of all the patients is depicted in Table 1. Out of 60 patients that were included for analysis, there were 33.3% females ($n = 20$) and 66.6% males ($n = 40$). However, the age-group of both groups was comparable.

Out of 29 patients in group II, 13 patients were diagnosed with CAD.

The mean and standard deviation of all the parameters are depicted in Table 2.

A significant increase in average heart rate (90.1 ± 14 vs 76.7 ± 10 , p -value 0.0001), HbA1c (64 mmol/mol (8.4%) ± 1.5 vs 53 mmol/mol (7.5%) ± 1.6 , p -value 0.02) and significant reduction in SDNN (18.6 ± 10 vs 32.6 ± 12 ,

Table 1: Demographic profile

	Group I ($n = 31$) Type 2 diabetes without complication	Group II ($n = 29$) Type 2 diabetes with complication
Age	51.2 $\pm$ 11	54 $\pm$ 10
Autonomic neuropathy	23 (Early or probable CAN) 8 (No CAN)	16 (Early or probable CAN) 13 (Definite CAN)
Nephropathy	–	7 (stage 1–4, stage 2–2, stage 3–1)
Retinopathy	–	7
CAD	–	13
Peripheral Neuropathy	–	1

p -value 0.0001) LF (ms^2) (65 ± 116 vs 199.1 ± 221 , p -value 0.0001), HF (ms^2) (60.1 ± 93 vs 137.3 ± 127 , p -value 0.001) was observed in group II compared to group I. Though there was a marginal difference in breathing rate, however, the mean breathing rate in both the groups was greater than 8 breaths/min (significance of it is discussed in the discussion section). Results have shown a strong association of HRV indices [HF ms^2 , LF ms^2 , and SDNN (ms)] with type 2 diabetes with complications (odds ratio for group with complications) and with a longer duration of diabetes (Tables 3 and 4). On logistic regression, we observed that the accuracy of classification on the test data was 0.78. We obtained a specificity value of 0.74 and a sensitivity value of 0.85 on the test dataset, and with receiver operating characteristic (ROC) analysis, the area under the curve (AUC) value was 0.83 (Fig. 1).

DISCUSSION

HRV as Noninvasive Biomarker

Heart rate variability is the oscillations in successive RR intervals, generated by sinus

rhythm. HRV is a noninvasive prognostic marker of cardiac autonomic activity and provides information about two branches of the autonomic nervous system, namely, the sympathetic and parasympathetic divisions. The vagus (parasympathetic division) influences the cardiac pacemaker much more rapidly than sympathetic nerves; therefore, the shorter duration (5 minutes) beat-to-beat fluctuations are mainly modulated by the vagus. Greater the vagal influence, the greater the variability, indicating a healthier system. The progression from health to disorder is indicated by decreasing vagal influence, increasing sympathetic modulation, and reduced HRV.²³ Although cardiac autonomic dysfunction (determined by HRV) may be present even in prediabetic state, clinical CAN results much later in the disease course and is evident by abnormal CART.²⁴ Multiple studies have also demonstrated that autonomic dysfunction is associated with a variety of lifestyle disorders, such as type 2 diabetes, hypertension, obesity, metabolic syndrome, and cardiovascular disease. However, hyperglycemic state and the oxidative load

from the glycemic status and metabolic memory,²⁵ the autonomic dysfunction further exacerbates in type 2 diabetes.

HRV Methodological Considerations

As the objective of the present study was to examine the utility of HRV in predicting complications related to diabetes, we only included diabetic patients. A healthy or euglycemic control for the present study would have been irrelevant since many studies have already demonstrated progressive declines in HRV between diabetics and those with normal

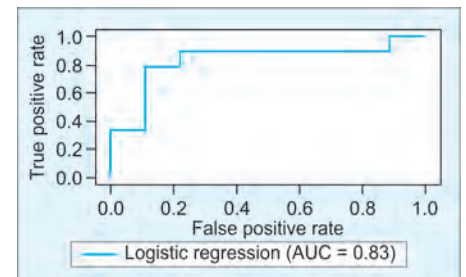


Fig. 1: Receiver operating characteristic analysis (AUC = 0.83)

Table 2: Mean SD and results of Mann–Whitney test

	Group I	Group II	Mann–Whitney test	
	Mean SD	Mean SD	H-score	p-value
Age	51.2 ± 11	54 ± 10	1.52	NS
Average heart rate/min	76.7 ± 10	90.1 ± 14	12.25	0.0001**
SDNN (ms)	32.6 ± 12	18.6 ± 10	18.41	0.0001**
Total power (ms^2)	672 ± 533	250.1 ± 358	17	0.000**
LF (ms^2)	199.1 ± 221	65 ± 116	16	0.0001**
HF (ms^2)	137.3 ± 127	60.1 ± 93	9.69	0.001**
LF (nu)	56.3 ± 18	52.6 ± 23	0.2	NS
HF (nu)	43.6 ± 18	47.4 ± 23	0.2	NS
LF/HF ratio	2.1 ± 2.7	1.8 ± 2	0.3	NS
Avg breathing rate/min	14.9 ± 3	16.6 ± 3	3.02	0.08
HbA1c	53 mmol/mol (7.5%) ± 1.6	64 mmol/mol (8.4%) ± 1.5	5.96	0.02*

*Significant; **Highly significant

Table 3: Association of HRV indices with complications

	Odds ratio	χ^2	p-value
HF (ms^2)/complications	7.6	12.1	0.0005**
LF (ms^2)/complications	8.5	8.4	0.003**
SDNN/complications	6.2	7.6	0.005**

**Highly significant

Table 4: Association of HRV indices with complications stratified for duration of diabetes

Parameters	Diabetes < 5 years			Diabetes > 5 years		
	Odds ratio	χ^2	p-value	Odds ratio	χ^2	p-value
HF (ms^2)	7.5	3.8	0.04	10	4.7	0.02*
LF (ms^2)	7.9	6.9	0.008	6.5	4.1	0.002**
SDNN (ms)	4.3	2.8	0.09	10	4.5	0.01*

*Significant; **Highly significant

blood sugar levels. As recommended by the Task Force, it is necessary to measure HRV for at least 5 minutes in order to get meaningful physiological interpretation. Therefore, the resting ECG was recorded for 15 minutes during which the patients could relax, and the last 5 minutes of recording were used for HRV analysis. The ECGs of all patients were recorded between 9 am and 12 pm on all days, to avoid circadian influences on HRV.

Glycemic Status and Complication

A significantly higher HbA1c in group I compared to group II (8.4 ± 1.5 vs 7.5 ± 1.6 , p -value 0.02) reflects poor glycemic status in patients with complications of diabetes. The results of our study are in accordance with those of various other studies.^{26,27}

Cardiac Autonomic Neuropathy Status in Two Groups

Out of 60 patients from both groups, 52 patients (86%) were having CAN. In a study conducted by Bhuyan et al.,²⁸ the prevalence of CAN observed was 70%. In the present study, all the patients in group II have autonomic neuropathy (55% early CAN and 44% definitive CAN) compared to group I where 74% have early CAN while 25% were not having clinical autonomic neuropathy. The findings are consistent with progressive deterioration of cardiac autonomic function due to complications of diabetes.

Overall Variability Between the Groups

In group I, significant reduction in overall variability indicated by reduced SDNN (ms) (18.6 ± 10 vs 32.6 ± 12 , p -value 0.0001) a time domain index, and reduced total power (ms^2) (250.1 ± 358 vs 672 ± 533 , p -value 0.000), a frequency domain index of HRV, was observed compared to group II. Both SDNN and TP (total power) are affected by average heart rate. As heart rate increases, variability will decrease. The average heart rate was significantly different (76.7 ± 10 vs 90.1 ± 14 , p -value 0.0001) between groups, though we ruled out other plausible explanations for this difference both clinically (viz., trait anxiety, stress, infection, etc.) and by laboratory investigation (viz., TSH, T3, T4 levels, etc.). The observed difference in average heart rate could therefore be attributed to progressive autonomic dysfunction reflected in differences in CART scores. These results suggest a progressive decline in HRV with micro- and macrovascular complications of diabetes. In a study by Khandoker et al.,²⁹ a significant difference in SDNN [22 (14–27) vs 19 (14.5–27.4)] was observed between noncomplicated vs T2DM with microvascular complications.

Cardiac Sympathetic/Baroreflex and Parasympathetic Modulation Between the Groups

Low frequency and high frequency are frequency domain indices of HRV, and are expressed either in absolute powers (LF and HF ms^2) or in normalized units as (LF and HF nu). LF reflects sympathetic/baroreflex and HF reflect parasympathetic modulation of cardiac autonomic activity. While the LF–HF ratio is a marker of sympathovagal balance. Breathing rate is known to affect frequency domain indices, especially if the breathing rate is less than 8 per minute, then it shifts the HF component of power spectrum into the LF component and results in an erroneous interpretation of parasympathetic modulation.³⁰ In the present study, we have measured post hoc breathing rate from ECG. In both the groups, the breathing rate was greater than 8 breaths per minute. Therefore, the assessed HF component reflects accurate parasympathetic modulation.

A significant reduction in absolute powers of both LF (65 ± 116 vs 199.1 ± 221 , p -value 0.0001) as well as HF (60.1 ± 93 vs 137.3 ± 127 , p -value 0.001) components was observed in group I compared to group II. This indicates progressive deterioration in both sympathetic/baroreflex sensitivity as well as parasympathetic modulation of the heart. In a study by Khandoker et al.,²⁹ a significant reduction in, LF ms^2 [225 (155–335) vs 205 (148–305)] and HF ms^2 [90 (69–128) vs 85.6 (73.3–136)] indices were observed between uncomplicated and T2DM with microvascular complications, respectively. Our study differs in a way that along with microvascular complications, we have also included macrovascular complication like CAD so as to cover complete spectrum of complications of diabetes. Similarly in a study conducted by Kudat,³¹ where 24 hour HRV was compared between DM with and without complications, a significant reduction in SDNN ms 29.5 ± 16.4 vs 46.2 ± 15.4 , LF 9.6 ± 7.6 vs 18.7 ± 7.3 , HF 5.5 ± 3.2 vs 9.8 ± 3.7 , and TP 16.7 ± 12.5 vs 30.0 ± 10.4 (absolute powers in ms) was observed. Since we observed significant differences even with a 5-minute HRV, we propose that the short duration HRV is a more convenient and feasible option for assessing autonomic dysfunction and its usefulness as a prescreening tool for type 2 diabetes complications.

Association of HRV Indices with Complications

We have used normal range for SDNN, LF, and HF indices (SDNN < 30 ms, LF <

193 ms^2 , HF < 82 ms^2) given by Nunan et al.³² to study the association of HRV indices with complication and duration of diabetes. As shown in Tables 3 and 4, a strong association between HRV indices (HF, LF, and SDNN) with complications and duration of diabetes was observed. The results highlight that the farther away the HRV indices are from the norms, the greater the risk of complication of diabetes. Similarly, the longer the duration of diabetes (>5 years), the greater is the risk of complication.

Heart Rate Variability and CAD

As in the present study, 13 out of 29 patients in group II (44%) had confirmed CAD, and HRV of this group is also significantly reduced compared to noncomplicated group, further strengthening the link between autonomic dysfunction and the process of atherosclerosis. Kotecha et al.³³ in a mixed comorbidity cohort had shown that 5 minutes of HRV can predict the obstructive CAD. It is the LF spectral power that was shown to be inversely related to the extent of CAD and a cutoff value of 250 ms^2 was identified as a strong independent predictor of obstructive disease in this clinical cohort.²⁷

Utility of HRV as a Prescreening Tool

To explore the utility of HRV indices as a prescreening tool, logistic regression analysis using nine feature sets (seven HRV indices, age, gender) was employed. It is a probabilistic statistical classification model, a simple but powerful linear algorithm for analyzing multidimensional data and generating predictions of clinical outcomes. Moreover, to find the optimal cutoff point with the highest sensitivity and specificity of LRA, a ROC curve was adopted. The AUC of the ROC is considered an effective measure of the performance of a screening test, with results ranging from 0.5 to 1.0, where larger values are indicative of better performance. In the present study with 85% sensitivity, 74% specificity and 78% accuracy of classification, and AUC of 0.83 with ROC analysis, the HRV indices have shown promising potential as a prescreening tool to predict micro- and macrovascular complications in type 2 diabetes, especially with an added advantage of being noninvasive and simple to measure.

LIMITATIONS

The HRV was measured under highly controlled conditions to minimize its inter- and intraindividual variations; therefore, extrapolation of results in real-world scenarios

(where HRV measurement conditions are more flexible) is a limitation.

CONCLUSION

Diabetes patients with complications have significantly lower HRV than those without complications. A strong correlation between HRV indices and complications of diabetes has been demonstrated, with 85% sensitivity, 74% specificity, and 78% accuracy. This makes HRV a promising prescreening tool to predict micro- and macrovascular complications in type 2 diabetes patients.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

- Heart rate variability is an established noninvasive prognostic marker of cardiac autonomic activity. Known association of type 2 diabetes and CAN. Progressive reduction in HRV from euglycemic state to clinically overt T2DM.
- Independent association of reduced HRV with CAD and CKD.

WHAT THIS STUDY ADDS?

- Within diabetic patients, there is a progressive reduction in overall variance, sympathetic/baroreflex modulation and parasympathetic modulation with complications. The association of reduced HRV is much stronger with complications and duration of type 2 diabetes.
- With ROC analysis, the HRV indices have shown potential utility as prescreening tool for classifying the presence of complications in patients with type 2 diabetes.

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Evaluation of Red Cell Distribution Width and Its Ratio to Total Serum Calcium as Predictors of Severity in Acute Pancreatitis



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ABSTRACT

Background: Acute pancreatitis (AP) is a potentially fatal condition that varies in its severity at presentation. It's crucial to recognize patients with a higher likelihood of severe outcomes to enhance their prognosis by promptly providing medical or endoscopic treatment and admitting them to a specialized intensive care unit (ICU). Despite the various scoring systems and methods, there is no reliable instrument to assess the severity of AP at its presentation. Red cell distribution width (RDW) and serum calcium levels are inexpensive markers readily available upon admission that can be used to anticipate the severity of AP.

Materials and methods: An observational cross-sectional study was carried out on 85 patients admitted to a referral hospital. The AP patients were categorized into two groups: those with mild AP (MAP) and those with moderately severe/severe AP (MSAP/SAP). RDW was assessed in all patients upon admission and at the 24-hour mark.

Results: Among the 85 AP patients, 55 were diagnosed with MAP, while 17 had MSAP and 13 had SAP. The mean serum calcium levels were notably lower in patients with MSAP/SAP compared to MAP. Additionally, the modified Marshall (MM) score, bedside index for severity in acute pancreatitis (BISAP) index, RDW at 0 hours and 24 hours, and RDW/total serum calcium (RDW/TSC) ratio were significantly higher in patients with MSAP/SAP than in MAP. The BISAP index, followed by MM, emerged as the most reliable predictors of severity, with RDW/TSC also showing strong predictive value. RDW/TSC demonstrated superior predictive ability for AP severity when compared to RDW measured at admission and at 24 hours. However, no individual parameter was identified as an independent significant predictor of AP.

Conclusion: Red cell distribution width and RDW/TSC ratio are comparable to BISAP index as predictors of severity in AP. They offer a cost-effective and readily accessible means to forecast AP severity upon admission, facilitating prompt intervention at the outset.

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INTRODUCTION

Acute pancreatitis (AP), a potentially life-threatening condition, manifests with varying degrees of severity. In developed nations, approximately 60–80% of AP cases stem from either gallstone disease or alcohol abuse.¹ It's imperative to promptly identify patients at elevated risk of severe or fatal AP to enhance prognosis through timely medical or endoscopic intervention and admission to a specialized intensive care unit (ICU).

Red cell distribution width (RDW) is a routine parameter of the complete blood count test that was initially used for differential diagnosis of anemia. In the presence of active inflammation due to oxidative stress and circulating inflammatory cytokines, there is reduction in red blood cell (RBC) survival and maturation. This results in the release of newer and larger RBC into the peripheral circulation and changing of membrane glycoproteins and ion channels of RBC with consequent morphological alteration which leads to an increase in RDW. Hypocalcemia

is a metabolic derangement commonly associated with AP more so in patients with severe AP (SAP). However, isolated total serum calcium (TSC) has not been established as direct marker of severity for AP severity, RDW/TSC ratio has been evaluated to be an excellent predictor of AP severity and a very good predictor of AP mortality.²

A recent study by Gravito-Soares et al.³ compared RDW and TSC at varying time points to Ranson, bedside index for severity in acute pancreatitis (BISAP), and MM scores, especially when evaluated at admission and within the initial 24 hours. RDW0h, alongside the RDW0h/TSC ratio, emerged as particularly strong indicators. RDW0h exceeding 13.0 and RDW0h/TSC surpassing 1.4 proved to be excellent predictors of AP severity, while RDW0h exceeding 14.0 and RDW0h/TSC surpassing 1.7 were identified as very good predictors of AP mortality.

Another study by Zhang et al.⁴ demonstrated that RDW exhibited superior prognostic capability in predicting mortality among SAP patients. When RDW surpassed

45.5, it demonstrated a sensitivity of 77.8% and a specificity of 70.8% in prognostic prediction. RDW emerged as an independent risk factor for forecasting mortality in SAP patients, as revealed by both multivariate logistic regression analysis and univariate analysis, akin to the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Sequential Organ Failure Assessment (SOFA) score.

The revised Atlanta classification⁵ is not suitable to differentiate moderately severe and severe pancreatitis in the first 48 hours of admission. Ranson score⁶ has been used but takes 48 hours to complete and therefore cannot be used at admission. Other scoring systems such as the SOFA have been developed but have only found to be useful in the intensive care setting and not for routine use in all patients presenting with AP. Other markers, such as tumor necrosis factor alpha (TNF- α), interleukin-6, interleukin-8, and procalcitonin, have been said to be able to predict the severity of AP, but these are not readily available and are expensive. An ideal marker/prognostic score should be simple, easily available at admission, economic, accurate, and quantitative.³

MATERIALS AND METHODS

This study was an observational cross-sectional investigation involving 85 AP patients admitted to the medicine and surgery wards at VMMC and Safdarjung Hospital, Delhi, spanning from December 2020 to June 2022. Each patient underwent comprehensive history-taking, clinical examination, and relevant diagnostic tests.

Acute pancreatitis was defined by the revised Atlanta criteria.⁵ Diagnosing a patient

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with AP, required two of the following three features:

- Abdominal pain consistent with AP, that is, acute onset, persistent, severe, epigastric pain often radiating to back.
- Serum lipase or amylase activity at least more than three times the upper limit of normal.
- Imaging showing characteristic findings of AP.

Inclusion Criteria

- All diagnosed cases of AP based on revised Atlanta classification.⁵
- Age >18 years.

Exclusion Criteria

- Patients on immunosuppressive therapy.
- Any infectious condition.
- Any malignancy.
- Chronic use of erythropoietin.
- Recent transfusion history.
- Pregnancy.

Statistical Analysis

The categorical variables were presented as counts and percentages (%), while quantitative data were expressed as means $\pm$ standard deviation (SD) and as median with interquartile range (25th and 75th percentiles). Normality of the data was assessed using the Kolmogorov–Smirnov test, and nonparametric tests were employed for nonnormally distributed data. The statistical analysis included:

- For quantitative variables not normally distributed, the Mann–Whitney *U* test was used, while the independent *t*-test was applied for normally distributed data to assess their association with severity according to the revised Atlanta classification.
- Chi-squared test was used to analyze the association of qualitative variables. Fisher's exact test was used if any cell had an expected value of <5.

- Receiver operating characteristic (ROC) curve analysis was conducted to determine the cutoff point for RDW, serum calcium, RDW/TSC ratio, BISAP, and modified Marshall (MM) for predicting SAP.
- Multivariate logistic regression was performed to identify significant risk factors for SAP.

Data entry was completed in Microsoft Excel, and the final analysis was carried out using Statistical Package for Social Sciences (SPSS) software, version 25.0, manufactured by IBM in Chicago, United States. A *p*-value of <0.05 was considered statistically significant.

RESULTS AND OBSERVATIONS

A total of 85 cases of AP were taken up for the study. The severity of cases based on revised Atlanta classification were mild in 55 (64.71%) of patients, moderate in 17 (20.00%), and was

severe in 13 out of 85 patients (15.29%). The patients were divided into two groups based on severity—mild AP (MAP) and moderately severe AP/SAP (MSAP/SAP)—and correlation was done between these two groups.

No significant association was seen between age, gender, etiology, hemoglobin, and platelet count with severity of AP (Table 1). There was a significant increase in the total leukocyte count (TLC), urea, and creatinine in the MSAP/SAP group compared with the MAP group. Serum calcium levels were significantly lower in the MSAP/SAP group when compared with the MAP group. RDW at 0 and 24 hours, RDW/TSC ratio, BISAP score, and MM score were also significantly higher in patients in the MSAP/SAP group than in the MAP group. Area under the receiver operating characteristic (AUROC) of RDW (%) (Table 2) at 0 hour was 0.794 (*p* < 0.0001) for a cutoff of >13 with sensitivity of 83.33%, specificity of 72.73%,

Table 1: Characteristics of patients with AP

Parameters	MAP (n = 55)	MSAP/SAP (n = 30)	p-value
Age	50.33 $\pm$ 10.43	53.43 $\pm$ 19.18	0.415
Males	34 (61.82%)	21 (70%)	55 (64.71%)
Hemoglobin (gm/dL)	13.17 $\pm$ 2.47	13.48 $\pm$ 2.81	0.343
TLC (cells/mm ³)	10247.27 $\pm$ 3629.04	14858.33 $\pm$ 7392.01	0.0004
Platelets (cells/mm ³)	209836.36 $\pm$ 88835.21	213333.33 $\pm$ 127027.1	0.541
Blood urea (mg/dL)	30.47 $\pm$ 12.61	100.07 $\pm$ 40.99	<0.0001
Serum creatinine (mg/dL)	0.72 $\pm$ 0.26	2.25 $\pm$ 0.99	<0.0001
Serum bilirubin (mg/dL)	1.61 $\pm$ 1.58	2.27 $\pm$ 2.15	0.631
SGOT (IU/L)	99.09 $\pm$ 68.5	89.2 $\pm$ 60.56	0.679
SGPT (IU/L)	209.16 $\pm$ 98.45	170.37 $\pm$ 119.3	0.064
ALP (IU/L)	204.04 $\pm$ 204.46	382.37 $\pm$ 236.37	<0.0001
RDW (%) at 0 hour	12.96 $\pm$ 1.39	15.3 $\pm$ 2.55	<0.0001
RDW (%) at 24 hours	12.47 $\pm$ 1.35	14.79 $\pm$ 2.16	<0.0001
Serum calcium (mg/dL)	9.09 $\pm$ 0.62	8.18 $\pm$ 0.57	<0.0001
RDW/TSC ratio	1.38 $\pm$ 0.2	1.83 $\pm$ 0.33	<0.0001
BISAP	0.62 $\pm$ 0.73	2.93 $\pm$ 0.87	<0.0001
MM	0.02 $\pm$ 0.13	2 $\pm$ 1.05	<0.0001

Table 2: Receiver operating characteristic curve of RDW, serum calcium, RDW/TSC ratio, BISAP, and MM for predicting SAP

SAP	RDW at 0 hour	RDW at 24 hours	Serum calcium (mg/dL)	RDW/TSC ratio	BISAP	MM
AUROC	0.794	0.821	0.87	0.884	0.968	0.932
SE	0.0598	0.05	0.0403	0.0437	0.0142	0.0322
95% CI	0.693–0.874	0.723–0.896	0.780–0.933	0.796–0.943	0.905–0.994	0.856–0.975
p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Cutoff	>13	>13	$\leq$ 8.7	>1.5	>1	>0
Sensitivity (95% CI)	83.33% (65.3–94.4%)	76.67% (57.7–90.1%)	83.33% (65.3–94.4%)	86.67% (69.3–96.2%)	96.67% (82.8–99.9%)	86.67% (69.3–96.2%)
Specificity (95% CI)	72.73% (59.0–83.9%)	83.64% (71.2–92.2%)	80% (67.0–89.6%)	83.64% (71.2–92.2%)	85.45% (73.3–93.5%)	98.18% (90.3–100.0%)
PPV (95% CI)	62.5% (45.8–77.3%)	71.9% (53.3–86.3%)	69.4% (51.9–83.7%)	74.3% (56.7–87.5%)	78.4% (61.8–90.2%)	96.3% (81.0–99.9%)
NPV (95% CI)	88.9% (75.9–96.3%)	86.8% (74.7–94.5%)	89.8% (77.8–96.6%)	92% (80.8–97.8%)	97.9% (88.9–99.9%)	93.1% (83.3–98.1%)
Diagnostic accuracy	76.47%	81.18%	81.18%	84.71%	89.41%	94.12%

positive predictive value (PPV) of 62.5%, negative predictive value (NPV) of 88.9%, and with diagnostic accuracy of 76.47%. AUROC of RDW at 24 hours was 0.821 ($p < 0.0001$) for a cutoff of >13 with a sensitivity of 76.67%, specificity of 83.64%, PPV of 71.9%, NPV of 86.8%, and a diagnostic accuracy of 81.18%. AUROC of serum calcium (mg/dL) was 0.870 ($p < 0.0001$) for a cutoff of ≤ 8.7 with a sensitivity of 83.33%, specificity of 80%, PPV of 69.4%, NPV of 89.8%, and diagnostic accuracy of 81.18%. AUROC for RDW/TSC was 0.884 ($p < 0.0001$) for a cutoff of >1.5 with a sensitivity of 86.67%, specificity of 83.64%, PPV of 74.3%, NPV of 92%, and diagnostic accuracy of 84.71%. AUROC for BISAP was 0.968 ($p < 0.0001$) for a cutoff of >1 with a sensitivity of 96.67%, specificity of 85.45%, PPV of 78.4%, NPV of 97.9%, and diagnostic accuracy of 89.4%. AUROC for MM score was 0.932 ($p < 0.0001$) for a cutoff of >0 with a sensitivity of 86.67%, specificity of 98.18%, PPV of 96.3%, NPV of 93.1%, and diagnostic accuracy of 94.12%. BISAP index followed by MM score were the best predictors of severity, followed by RDW/TSC ratio. Multivariate regression analysis showed that none of the variables included in our study was an independent significant risk factor for SAP.

DISCUSSION

In the present study on 85 patients of AP, there was no significant difference between the two groups regarding age. All patients above 70 years had MSAP/SAP. There was no significant association with age in studies by Zhang et al.,⁷ Gravito-Soares et al.,³ and Peng et al.⁸ However, age is an important implication in AP as advanced age is associated with more severe form of the disease and worse prognosis.

Our study did not show any gender predilection for SAP. Similar results were observed in studies by Peng et al.,⁸ Zhang et al.,⁷ and Karabuga et al.⁹ who did not find any gender differentiation in cases of MAP, MSAP, and SAP.

In our study, alcohol abuse was the most common cause of AP in male patients whereas gallstone pancreatitis was the most common in female patients. Majority of cases were of gallstone origin irrespective of gender in studies by Ye et al.¹⁰ and Gülen et al.¹¹

Mean TLC (cell/mm³) in our study was 10247.27 in MAP and 14858.33 in MSAP/SAP which was statistically significant ($p = 0.0004$). Similar results were seen in a study by Bedel et al.,¹² wherein mean TLC (per mm³) was 15.2 in nonsurvivors and 12.1 in survivors which was significantly higher in nonsurvivors ($p < 0.05$). Mean platelet count was 331.7

in nonsurvivors and 253.4 in survivors, respectively ($p < 0.05$).

In our study, mean urea in patients with MAP (mg/dL) was 30.47 and in MSAP was 100.07 which was statistically significant ($p < 0.0001$). Mean creatinine (mg/dL) in patients with MAP was 0.72 and in MSAP was 2.25 which was statistically significant ($p < 0.0001$). In a study by Zhang et al.,⁷ RDW values positively correlated with the patient blood urea nitrogen (BUN) ($p = 0.02$).

Mean bilirubin (mg/dL) in patients with MAP was 1.61 and 2.27 in patients with MSAP/SAP which was not significant ($p = 0.631$). Mean serum glutamic oxaloacetic transaminase (SGOT) (IU/L) was 99.09 in patients with MAP and 89.2 in patients with MSAP/SAP which was not significant ($p = 0.679$). Mean serum glutamic pyruvic transaminase (SGPT) in patients with MAP was 209.16 and 170.37 in patients with MSAP/SAP which was not significant. In a study by Zhang et al.,⁷ no significant correlation was seen between RDW and alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Red Cell Distribution Width

RDW0h

In our study, RDW was measured in all patients at admission. The median for MAP and MSAP/SAP was 13 and 15, respectively. The mean of RDW was found to be 12.96 in patients with MAP while it was 15.3 in patients with MSAP/SAP ($p = 0.001$). Significant association was seen in RDW (%) at 0 hour with severity ($p < 0.05$). Similar results were seen in studies by Gravito-Soares et al.,³ Han et al.,¹³ and Yao and Lv,¹⁴ wherein RDW was significantly higher in patients with MSAP/SAP when compared to MAP. They also observed that in all patients with AP, RDW correlated inversely with calcium, serum albumin, RBC count, and hemoglobin, and directly with age and LDH.

However, contrary results were seen in a study by Gülen et al.,¹¹ who observed that median RDW in mortality and nonmortality groups was found to be statistically nonsignificant ($p = 0.201$). In another study by Ye et al.,¹⁰ a regression analysis of RDW as a single predictive factor for severity of AP showed a regression coefficient of 0.177 ($p > 0.05$) with an odds ratio (OR) of 1.193 implying that RDW was not a prediction index of AP severity. However, they attributed this finding to the monocentric nature of the study, the limited sample size, and the regionalism of the case source.

In our study, ROC curve of RDW (Fig. 1) at 0 hour for predicting SAP was 0.794 with a sensitivity of 83.3% and specificity of 72.5% for a cutoff of >13 and PPV of 62.5% and NPV of 88.9%. Similarly, Gravito-Soares

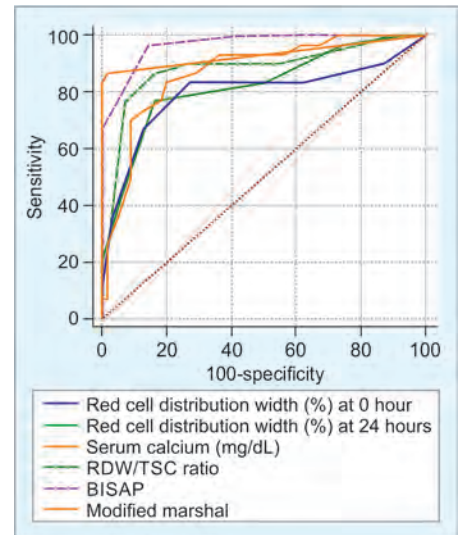


Fig. 1: Receiver operator characteristic curves

et al.³ suggested that RDW0h (AUROC: 0.960; $p > 0.001$) was a major predictor of SAP to a cutoff value of 13.0 (sensitivity—92.7%; specificity—84.3%). A study by Peng et al.⁸ also showed that for RDW cutoff for persistent organ failure in AP of 13.05%, area under the curve (AUC) was 0.791 (sensitivity—97.4%; specificity—55.8%) with a PPV of 0.411 and NPV 0.985 implying that RDW on admission is an independent prognostic factor for persistent organ failure in AP. Another study by Yao and Lv¹⁴ revealed that RDW had a sensitivity of 75% and specificity of 89.8% in predicting mortality and suggested that RDW levels were notably elevated in nonsurvivors of AP compared to both healthy individuals and survivors of AP patients. Similar results were also seen in a study by Zhang et al.⁷ The AUC for RDW was found to be 0.677 ($p < 0.000$). When RDW was combined with albumin, the AUC increased slightly to 0.693 [95% confidence interval (CI) 0.625–0.761, $p < 0.000$], surpassing the AUC of RDW alone. The optimal cutoff value for RDW to differentiate between MSAP and SAP was determined to be 13.55, with a sensitivity of 54.5% and specificity of 73.6%.

RDW24h

In our study, the mean $\pm$ SD of RDW at 24 hours following admission was 12.47 ± 1.35 and 14.79 ± 2.16 in patients with MAP and MSAP/SAP, respectively ($p < 0.001$). The median was 13 and 15 in MAP and MSAP/SAP, respectively. Significant association was seen in RDW (%) at 24 hours with severity ($p < 0.05$). The AUROC analysis of RDW 24 hours with severity of pancreatitis was 0.821 with a sensitivity of 76.67%, specificity of 83.64%, PPV of 71.9% and NPV of 86.8% for cutoff >13 . Study by Gravito-Soares et al.³ showed that RDW24h

(%) was 14.3 ± 1.9 and 12.8 ± 0.5 in patients in MAP and MSAP/SAP, respectively ($p < 0.001$). AUROC of RDW 24hrs with severity of AP was 0.848 ($p < 0.001$; cutoff 13.8) suggesting that RDW0h and RDW at 24 hours were excellent predictors of mortality in AP.

Total Serum Calcium

In our study, mean $\pm$ SD of serum calcium (mg/dL) in MAP was 9.09 ± 0.62 which was significantly higher compared to MSAP/SAP (8.18 ± 0.57) ($p < 0.0001$). Similar results were seen in a study by Yao and Lv,¹⁴ serum calcium (mmol/L) was found to be 2.11 ± 0.24 and 2.03 ± 0.19 in patients with MAP and MSAP/SAP, respectively ($p < 0.001$). AP with RDW $>13.3\%$ had lower levels of calcium and higher mortality (6/8). The nonsurvivors of AP had lower levels of calcium. Regression analysis of a study by Ye et al.¹⁰ showed that the regression coefficient of serum calcium was -5.706 ($p < 0.01$) with an OR of 0.003. Multifactor logistic regression analysis showed that serum calcium was an independent predictor of severity of AP.

In a study by Han et al.,¹³ TSC, in mmol/L was 2.12 ± 0.18 and 1.77 ± 0.24 in patients of MAP and MSAP/SAP, respectively ($p < 0.001$). The TSC in ICU patients was 1.85 while in non-ICU patients was 2.10 and in the survivors and nonsurvivors was 2.09 and 1.83, respectively. Above studies showed similar results comparable to our study.

In our study, AUROC analysis of calcium as a predictor of severity of AP was 0.870 for cutoff of ≤ 8.7 mg/dL with a sensitivity of 83.33%, specificity of 80%, PPV of 69.4%, NPV of 89.8%, and diagnostic accuracy of 80%.

Study by Han et al.¹³ showed that AUROC for TSC in AP patients of 0.773 in patients requiring ICU admission, and 0.809 in hospital deaths. The ROC AUCs for BISAP, serum calcium, and serum calcium and BISAP were 0.779, 0.797, and 0.852, respectively ($p < 0.01$) in the study by Ye et al.¹⁰

Red Cell Distribution Width/Total Serum Calcium Ratio

In our study, mean $\pm$ SD of RDW/TSC was 1.38 ± 0.2 and 1.83 ± 0.33 in patients with MAP and MSAP/SAP, respectively. The median RDW/TSC was 1.4 in patients with MAP and 1.8 in patients with MSAP/SAP ($p < 0.001$). Gravito-Soares et al.³ also showed a similar RDW/TSC of 1.8 ± 0.4 and 1.3 ± 0.1 in patients with MAP and MSAP/SAP, respectively ($p < 0.001$). A study by Bedel et al.¹² showed that RDW/TSC of 2.3 ± 0.5 and 1.7 ± 0.3 in nonsurvivors and survivors, respectively ($p < 0.001$). This was in concordance with our study.

Area under the receiver operating characteristic for RDW/TSC as predictor

of severity in AP was 0.884 for a cutoff of >1.5 ($p < 0.001$) with a sensitivity of 86.67%, specificity of 83.64%, PPV of 74.3%, NPV of 92%, and diagnostic accuracy of 84.71%. In study by Gravito-Soares et al.,³ AUROC of RDW/TSC was 0.973 for a cutoff of 1.4 ($p < 0.001$), with a sensitivity of 96.3% and specificity of 84.3% and stated that RDW0h/TSC >1.4 were excellent predictors for AP severity. Han et al.¹³ showed RDW/TSC AUROC of 0.824 for patients requiring ICU care, 0.768 in patients needing surgery and 0.855 inhospital deaths ($p < 0.001$). Bedel et al.¹² showed an RDW/TSC AUROC of 0.880 for a cutoff of >2.0 with a sensitivity of 91.9%, specificity of 81.1%, PPV of 82.9%, NPV of 91.1%, and diagnostic accuracy of 86.5%. These studies were in concordance with our results.

Bedside Index for Severity in Acute Pancreatitis

In our study, the mean BISAP index in patients with MAP was 0.62 ± 0.73 , while in patients with MSAP/SAP it was 2.93 ± 0.87 , which was significant ($p < 0.0001$). In a study by Gravito-Soares et al.,³ mean $\pm$ SD of BISAP for MSAP/SAP and MAP was 1.7 ± 0.9 and 1.0 ± 0.7 ($p < 0.001$), respectively. In a study by Ye et al.,¹⁰ the regression coefficient for BISAP as single factor of AP severity predictor was 1.373 [standard error (SE) 0.184] with OR of 3.948 ($p < 0.01$).

In our study, AUROC for BISAP as predictor of severity of AP was 0.968 for a cutoff of >1 , with a sensitivity of 96.67%, specificity of 85.45%, PPV of 78.4%, NPV of 97.9%, and diagnostic accuracy of 89.41%, showing that it was the best predictor of severity of AP. Gravito-Soares et al.³ showed an AUROC for BISAP to be 0.732 for a cutoff of >1.5 with a sensitivity and specificity of 57.3 and 55.1%, respectively.

Modified Marshall Score

In our study, mean MM score in patients with MAP was 0.02 ± 0.13 and 2 ± 1.05 in patients with MSAP/SAP which was statistically significant ($p < 0.0001$). In a study by Gravito-Soares et al.,³ mean MM score was 0.0 ± 0.0 in patients with MAP and 0.8 ± 0.7 in patients with MSAP/SAP ($p < 0.0001$).

Area under the receiver operating characteristic for MM score was 0.932 ($p < 0.0001$) for a cutoff of >0 with a sensitivity of 86.67%, specificity of 98.18%, PPV of 96.3%, NPV of 93.1%, and diagnostic accuracy of 94.12%. In a study by Gravito-Soares et al.,³ AUROC of MM score was 0.756 ($p < 0.001$) for a cutoff of 1.0 with a sensitivity of 51.2% and specificity of 100%.

Limitations of our Study

- In our study, number of subjects was small, therefore the statistical power of the study was low.

- There was no follow-up of subjects in our study; hence, the outcome could not be assessed.

In our study, BISAP index followed by MM Score were the best predictors of severity followed by RDW/TSC ratio. There is always a trade-off between sensitivity and specificity so we chose the variable with the maximum predictive value which in our study was BISAP index. RDW/TSC ratio was a better predictor of AP when compared to serum calcium and RDW at admission and at 24 hours. RDW at 24 hours was a better predictor of severity in AP than RDW at admission. On multivariate analysis, no individual parameter was an independent significant predictor of AP.

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Edema India: Executive Summary of Screening, Diagnosis, and Management of Edema



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ABSTRACT

The management of edema requires a systematic approach to screening, diagnosis, and treatment, with an essential initial assessment to differentiate between generalized and localized edema. The Association of Physicians of India (API) aimed to develop the first Indian Edema Consensus (Edema India), offering tailored recommendations for screening, diagnosing, and managing edema based on the insights from the expert panel. The panel suggested when evaluating edema symptoms, important factors to consider include the patient's current illness, medical history, risk factors, family history, and medications. Key diagnostic investigations for edema include complete blood count, cardiovascular imaging and markers, deep vein thrombosis (DVT) assessment, along with renal, hepatic, and thyroid function tests. Edema management involves a combination of pharmacologic and nonpharmacologic interventions, including limb elevation, physiotherapy, compression therapy, fluid removal, diuretics (loop diuretics: first-line therapy), and a sodium-restricted diet. The panel believed that educating patients could foster a preventive mindset, helping to prevent the worsening of edema.

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INTRODUCTION

The Association of Physicians of India (API) has pioneered the development of the first Indian Edema Consensus based on the recommendations of the expert panel that included cardiologists, physicians, diabetologists, endocrinologists, gastroenterologists, and nephrologists. This ground-breaking initiative offers comprehensive recommendations for the diagnosis and management of edema specifically tailored to the needs of Indian patients.

Edema is a common condition characterized by the accumulation of fluid in the interstitial space of body tissues. It can be caused by various systemic factors such as congestive heart failure, hepatic cirrhosis, renal disease, and thyroid disease, as well as local factors including lymphedema, deep vein thrombosis (DVT), and venous incompetence. The diagnosis and management of edema require a systematic approach and an initial assessment is crucial to determine whether the edema is generalized or localized, which helps tailor the differential diagnosis.

PATHOPHYSIOLOGY AND ETIOLOGY OF EDEMA

The two fundamental phases involved in edema development are^{1,2}:

- Changes in capillary hemodynamics that encourage seepage of fluid from the vascular compartment into the interstitium.
- Retention of salt and water by the kidneys via the renin-angiotensin-aldosterone system as a compensatory mechanism to regulate the target organ function.

Several common causes of edema include increase in capillary hydrostatic pressure, effective intravascular volume depletion that triggers a neurohumoral cascade, leading to renal vasoconstriction, changes in oncotic pressure, and a wide variety of medications that have the potential to induce edema (including anticancer, antihypertensive, antiparkinsonian, antipsychotics, anti-inflammatory, immunosuppressants, and cytokines) through various mechanisms, such as increased capillary permeability, vasodilatory edema, renal edema, and disruption of lymphatic drainage.³⁻⁶

Uncommon Conditions in Edema

- Myxedema: It occurs in hypothyroidism, although the exact pathophysiology is not well understood.
- Lymphedema: It is caused because of disruption of the lymphatic system leading to the accumulation of fluid in the interstitium.⁷

- Idiopathic edema is usually a diagnosis of exclusion, and is known to affect women of premenopausal age, causing edema in the upper and lower extremities and abdominal bloating with no apparent connection to the menstrual cycle.⁷

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Causes of Localized and Generalized Edema



HISTORY AND PHYSICAL EXAMINATION

Appropriate history and physical examination can help minimize unnecessary testing in patients. Initial attempts should focus on excluding major systemic causes to minimize complications and adverse outcomes. Several risk factors predispose a patient to a higher risk of edema and related complications.⁸ Identification of an underlying medical condition masquerading as edema can be challenging for clinicians, especially in patients with an existing chronic condition. The patients may present with localized or generalized edema and closely observing the signs and symptoms can help differentiate the underlying etiology.

Presenting Features of Edema and Its Causes

pitting edema. In edema of chronic venous obstruction, the skin is darkened, discolored,

and stained with multiple ulceration and nonpitting edema. In lymphedema, the skin has a tethered peau d'orange appearance and edema is commonly, but not always, unilateral. It is important to review serial body weight and urine output, measure jugular venous pressure, and examine feet for its involvement.

Evaluation of Patients with Edema Symptoms

Symptoms of edema include swelling of the whole body or localized swelling, breathlessness, puffiness of the face, and weight gain. Important factors to consider when evaluating patients with edema symptoms include details of the current illness (duration of edema, location, information about changes with position, dyspnea, oliguria or anuria, fatigue, pain, lethargy, fever, pregnancy

status, appetite changes, weight loss, etc.), history (previous episodes of peripheral edema, history of systemic or other diseases, comorbid conditions, malignancy, previous radiotherapy or surgery, venous incompetence, alcohol, smoking, etc.), risk factors and family history (DVT, alcohol history, heart failure), and medications. Physical examination helps rule out systemic causes of edema like heart failure, renal disease, hepatic disease, or thyroid disease. Tenderness indicates DVT or complex regional pain syndrome type 1, while lymphedema is typically nontender. Skin changes (temperature, color, texture) offer clues to the cause.^{1,10}

Methods to Quantitatively Assess Edema

Pitting edema assessment (based on the depth and duration of the indentation) can be done by pressing firmly with your thumb for at least 2 seconds on each extremity (over the dorsum of the foot, behind the medial malleolus, lower calf above the medial malleolus). The grading of edema is determined by pit depth (measured visually) and recovery time from grade 0 to 4. Volume measurements (with a water volumeter) and girth measurement (with a tape measure) is useful in ascites monitoring.

Wells' Score for Patients with Suspicion of Deep Vein Thrombosis

The Wells' score is the most widely used clinical decision tool for the diagnosis of



Signs of Edema

The earliest sign of edema is the concavity of the area between the medial malleolus and tendo-Achilles which is obliterated (Fig. 1).⁹ Other areas affected are the dorsum of the foot, the sacrum in bedridden patients, and edema of the upper limbs. In acute venous obstruction, skin is shiny with

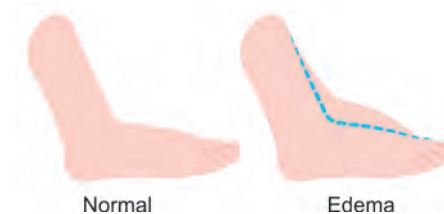


Fig. 1: Pedal edema

DVT. A clinician can avoid the necessity for an ultrasound to rule out DVT by risk stratifying to low risk (Wells' Score ≤ 2) and a negative D-dimer. The Wells' score helps stratify patients' pretest probability for DVT¹¹⁻¹³.

- Two (if score >2 DVT likely or if score <2 DVT unlikely).

- Three groups (high likelihood of DVT if >3; moderate likelihood if 1–2; low likelihood if ≤0).

Indian recommendation for screening

- Careful history and examination are the mainstay of appropriate diagnosis and subsequent management.
- In case of suspicion of DVT, one should risk stratify the patient using the clinical probability Wells' score.
- Edema grading scale can help differentiate between pitting and nonpitting edema and aid in identifying the etiology of edema.
- May consider to administer a simple self-evaluation test to evaluate for the risk of serious systemic causes of edema.

INVESTIGATIONS IN EDEMA

Commonly Used Laboratory Tests and Imaging Tests

- Complete blood count should be done for all edema patients.¹⁴
- Cardiac causes/congestive cardiac failure: Echocardiography, N-terminal pro-B-type natriuretic peptide (NT-proBNP)/B-type natriuretic peptide (BNP) measurement.
- Renal disease: Renal function tests including serum creatinine, urinalysis. Urine microalbuminuria and urine albumin–creatinine ratio, ultrasonography abdomen and pelvis.
- Hepatic disease: Liver function tests and serum albumin levels.
- Deep vein thrombosis (unilateral edema): D-dimer and lower limb venous Doppler.
- Venous insufficiency: Lower limb venous Doppler.
- Endocrine/metabolic disorders: Thyroid functions, uric acid.

Causes of Edema, Suggestive Features of the History and Recommended Investigations

MANAGEMENT OF EDEMA

Management of edema can be divided into two major groups, treatment of edema due to local causes and systemic causes.¹⁴ Nonpharmacologic measures are useful chiefly to treat edema due to local causes, in addition to etiological treatment. While treatment of edema due to systemic diseases according to the severity of peripheral edema is focused on general measures like diuretics, salt restriction to avoid fluid retention, and specific treatment of underlying etiology.

Edema Due to Local Causes

Nonpharmacologic Treatments

A variety of nonpharmacological interventions are frequently employed in practice to address edema. These interventions include limb elevation, compression techniques, massage therapy, and ice application.¹⁵

Recommendations on the use of nonpharmacological methods

- Limb elevation is routinely recommended in all patients with edema, except in case of fluid overload.
- Physiotherapy massages should be done by trained physical therapist only.
- Compression is routinely recommended for all patients of edema.
- The combination of limb elevation and compression therapy are recommended where possible.
- Ice application may be suggested in case acute onset of edema, severe congestive edema, presence of cellulitis.

Specific Treatment Based on the Etiology

Treatment of lymphedema varies depending on etiology and stage.¹⁶

Chronic lymphedema can be managed with limb elevation, avoiding dependent positioning for a prolonged period, weight reduction, skin care to maintain good hygiene, and avoidance of skin infection/injury, and avoiding tight-fitting clothing to prevent limb constriction.¹⁷ Physical therapy such as decongestive lymphatic therapy and manual lymph drainage which mobilizes lymph in patients with moderate-to-severe lymphedema.¹⁶ Compression therapy such as compression bandaging, compression garments, and intermittent pneumatic compression helps in drainage, but they may cause skin irritation and increase the risk of infection.¹⁷ Diuretics have no role in the management of lymphedema.¹ Filariasis is a common cause of asymmetrical unilateral or bilateral nonpitting edema in India. Diethylcarbamazine is the primary drug, and doxycycline is an alternative drug for its management.

Anticoagulation is key for DVT management. Low-molecular-weight heparin, unfractionated heparin, direct oral anticoagulants [direct oral anticoagulants (DOACs), i.e., factor IIa or Xa inhibitors], and vitamin K antagonists (VKAs, i.e., warfarin, acitrom) are prescribed for 3–6 months, longer if risk factors persist. The DOACs are preferred over VKAs for DVT.¹⁸ There is no requirement of frequent monitoring or dietary restrictions for DOACs; however, they are not suitable for severe renal or liver disease. Thrombolysis options for extensive DVT include catheter-directed or systemic thrombolysis.¹⁸

Gradual compression is the basis of treatment for venous insufficiency. Elevation of the legs, calf muscle exercise, including walking, weight management, and compression therapy are standard measures

Generalized edema		Localized edema	
Cardiac disorders	Suggestive features: History of cardiac disease Investigations: Chest X-ray, echocardiography	Deep vein thrombosis	Suggestive features: History of risk factors for DVT Investigations: D-dimers, venous ultrasound, dopplers
Renal disorders	Suggestive features: History of renal disease, DM, HTN Investigations: Serum electrolytes, urea and creatinine, lipids, Urine protein ± renal tract ultrasound	Venous incompetence	Investigations: Venous ultrasound, dopplers
Hepatic disorders	Suggestive features: History of hepatitis, alcohol abuse Investigations: Serum TSH, free T4, and T3 (not required for follow-up visits)	Lymphatic obstruction	Suggestive features: History of surgery Investigations: Lymphoscintigram
Thyroid disorders	Suggestive features: History or symptoms of thyrotoxicosis or hypothyroidism Investigations: Serum TSH, free T4, and T3 (not required for follow-up visits)	Dermatitis	Suggestive features: History of allergy, previous dermatitis
		Cellulitis	Suggestive features: Localised trauma, pain, tenderness No specific investigation is required before treatment

APTT, Activated partial thromboplastin time; DM, diabetes mellitus; DVT, deep vein thrombosis; HTN, hypertension; INR, international normalized ratio; T3, triiodothyronine; T4, tetraiodothyronine or thyroxine; TSH, thyroid-stimulating hormone

for the management of chronic venous insufficiency. Surgery or endovenous therapy is usually for those with persistent discomfort or unresponsive ulcers. The management of vasculitis varies depending on the type of vasculitis. Generally, vasculitis can be treated with induction of remission, maintenance of remission, and regular monitoring.¹⁹

Edema Due to Systemic Causes

Symptomatic patients with edema, such as pulmonary edema, orthopnea, and dyspnea on exertion due to volume overload, need urgent or early appropriate treatment to correct edema. In asymptomatic patients, consider correcting edema gradually. Avoid rapid correction of edema, especially in cirrhotic patients, as rapid diuresis carries the risk of hypokalemia and metabolic alkalosis, causing renal impairment and hepatorenal syndrome.

Depending on the severity of symptoms and causes of edema, the rate of correction of edema is determined. In patients with cirrhosis with edema, 800–1000 mL/day fluid removal is recommended.²⁰ Rate of correction should be monitored and reduced over the period of days as over time the capillary refill from the interstitium decreases as fluid is removed, especially with mechanical measures.^{21,22}

Restriction of salt intake helps to reduce water retention and resultant volume overload and is therefore recommended in acute heart failure, ascites, and edema due to renal diseases.²² Several diuretics used in edema include loop diuretics (sodium-potassium-chloride inhibitors: torsemide, furosemide, bumetanide, ethacrynic acid), distal convoluted tubule diuretics (sodium-chloride inhibitors: chlorthalidone, hydrochlorothiazide, metolazone), and cortical collecting tubule diuretics (aldosterone antagonists: spironolactone, eplerenone; sodium channel blockers: amiloride, triamterene) (Fig. 2).^{23,24}

Different diuretics may impact electrolytes and acid-base balance differently, so consideration of the patient's underlying condition is essential while selecting a diuretic.^{25,26} Dose of diuretics depends on the severity of edema, symptoms due to volume overload, hemodynamic status of the patient, and renal status (Table 1).²⁷

Recommendations for management of edema

- Edema management differs for local and systemic causes.
- Unilateral or asymmetric leg edema due to local causes needs nonpharmacologic measures—limb elevation, compression, massage, cryotherapy, and specific treatment for underlying cause.
- Systemic causes require salt restriction and diuretics.
- Modest salt intake reduction (5–6 gm/day) reduces water retention without harm.
- Diuretics are effective but should be used judiciously when used in systemic causes of edema.
- Diuretics, especially loop diuretics are first-line therapy for edema. Furosemide is the most prescribed loop diuretic.
- Torsemide's pharmacology effects are superior, but observed mortality rate is similar to furosemide.
- Continuous infusion of loop diuretics better than bolus for diuretic effect.
- Short-acting furosemide needs more frequent dose administration; torsemide and spironolactone can be given once daily.
- To achieve faster and greater diuresis or to overcome diuretic resistance increasing dose/frequency, or adding thiazide-like or potassium sparing diuretics for additive effect are useful measures.
- Adjust diuretic to least possible dose to maintain euvolemia, monitor therapy to avoid hypovolemia and electrolyte imbalances.
- Manage edema due to congestive heart failure with modest sodium restriction, loop diuretics, and add metolazone/spironolactone for potent diuresis and protection against hypokalemia and cardiovascular complications.
- In heart failure with reduced ejection fraction (HFrEF) and early chronic kidney disease (CKD), sodium-glucose cotransporter 2 (SGLT2) inhibitors promote osmotic diuresis and natriuresis; monitor diuretics and fluid intake to avoid hypovolemia and electrolyte imbalances.
- Hepatic cirrhosis with ascites should be managed with salt and fluid restriction along with diuretics (spironolactone ± loop diuretics) and albumin infusion in combination with paracentesis.
- Edema in renal disease requires salt restriction and diuretics (preferably loop diuretics), alongside specific treatments; avoid potassium sparing diuretics due to risk of hyperkalemia. Drug interactions to look out for:
 - Combination with an angiotensin-converting enzyme inhibitor (ACE-I), an angiotensin receptor blocker (ARB), or a renin inhibitor—risk of hypotension (usually not a problem).
 - Combination with other diuretics (e.g., loop plus thiazide)—risk of hypovolemia, hypotension, hypokalemia, and renal impairment.
 - Nonsteroidal anti-inflammatory drugs (NSAIDs) may attenuate the effect of diuretic.
- Exercise caution:
 - Significant hypokalemia ($K^+ < 3.5$ mmol/L) may be made worse by diuretic.
 - Significant renal dysfunction [creatinine > 221 mmol/L (> 2.5 mg/dL) or estimated glomerular filtration rate (eGFR) < 30 mL/minute/1.73 m²] may be made worse by diuretic or patient may not respond to diuretic (especially thiazide diuretic).

IMPORTANCE OF PATIENT EDUCATION

Patient education would improve outcomes as understanding of the condition, treatment compliance, and self-management would improve. Additionally, patients will be encouraged toward a preventive mindset and hence, a healthier lifestyle, helping to prevent worsening of

the edema. In order to have a consolidated effort toward creating awareness in the general population about the significance of edema and its screening, which can help detect systemic illness earlier, patients can be guided to seek appropriate medical help. For this, the panelist group suggests a "National Edema Awareness Day" or "Edema Day" on 25th September every year.

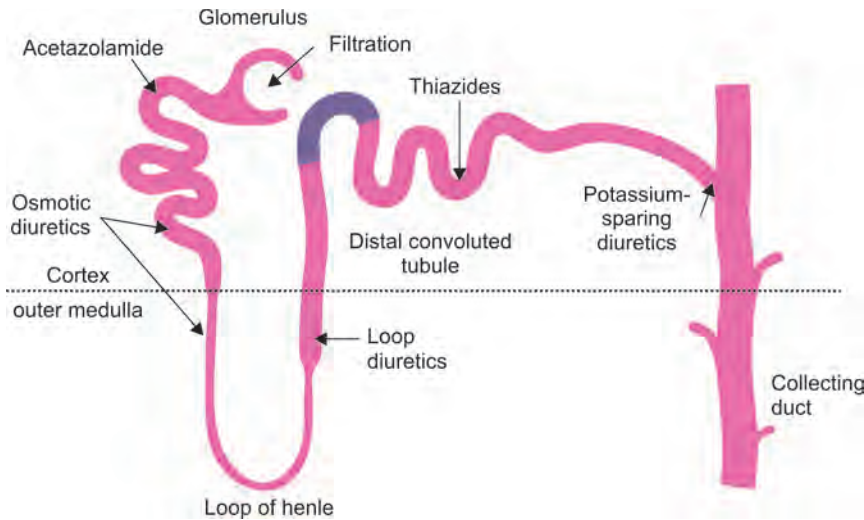


Fig. 2: Diuretics and their site of action

Table 1: Recommended dose of diuretics

Medications	Starting dose	Usual dose
Loop diuretics		
Torsemide	5–10 mg	10–20 mg
Furosemide	20–40 mg	40–240 mg
Bumetanide	0.5–1 mg	1–5 mg
Aldosterone antagonist		
Spironolactone	–	25–50 mg/day, if creatinine <140 µmol/L
Eplerenone	–	25–50 mg/day
Thiazides/thiazide-like diuretics		
Hydrochlorothiazide	25 mg	12.5–100 mg
Chlorothiazide	–	500–1000 mg/day on alternate days
Bendroflumethiazide	2.5 mg	2.5–10 mg
Metolazone	2.5 mg	2.5–10 mg, weekly, daily, or as needed
Nonthiazide sulfonamide		
Indapamide	2.5 mg	2.5–5 mg

CONCLUSION

This consensus on edema provides comprehensive recommendations for diagnosing and managing edema. It stands as a pivotal accomplishment that is poised to revolutionize the approach to diagnosing, monitoring, and treating edema. Through its establishment of a standardized assessment framework, it empowers healthcare professionals to administer more accurate and focused care, thus enhancing patient outcomes and improving overall healthcare quality.

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All authors met the International Committee of Medical Journal Editors (ICMJE) criteria, and

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Autoimmune Encephalitis: A Hidden Enigma Demystified

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ABSTRACT

Autoimmune encephalitis is a condition marked by inflammation in the brain due to an immune system response targeting self-antigens within the central nervous system (CNS). This class of disorders is at least as prevalent as infectious causes of encephalitis and encompasses a wide range of conditions. The field has rapidly expanded thanks to the identification of various pathogenic autoantibodies responsible for varied neurological and neuropsychiatric diseases. These disorders often present with distinct cognitive, seizure, and movement disorder phenotypes, making them clinically identifiable. Swift identification and treatment are pivotal for improving patient outcomes and promptly diagnosing associated tumors. This article zeroes in on autoantibody-mediated encephalitis syndromes involving neuronal cell-surface antigens. It sheds light on practical aspects of diagnosis and treatment, drawing from clinical experiences in managing such cases. Additionally, it underscores the ongoing importance of neuroimmunological advances that will shape the future diagnosis and treatment of these conditions.

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Autoimmune encephalitis stands as a dynamic and rapidly evolving domain in neurology, encompassing a spectrum of disorders where the immune system mistakenly targets self-antigens within the central nervous system (CNS).^{1,2} This poses a significant challenge due to the diverse neurological manifestations exhibited by affected individuals. Key to its identification are autoantibodies targeting neuroglial antigens, disrupting vital synaptic proteins, ion channels, and receptors crucial for normal CNS function. This article not only delineates clinical features aiding in recognition but also sheds light on crucial immunological findings for accurate laboratory testing. The pathogenic nature of these autoantibodies, predominantly targeting extracellular domains, adds complexity to this expanding field. Autoimmune encephalitis, gaining prominence in clinical neurology, presents with varied neurological symptoms, making timely intervention imperative. Early identification and intervention, often met with positive responses to immunotherapies, offer hope in managing once enigmatic disorders. This article provides a comprehensive overview, merging clinical experience with the latest advancements, serving as a practical guide for neurologists and healthcare professionals, enhancing understanding and informed decision-making for improved patient outcomes.

Autoimmune encephalitis manifests as a result of the immune system's misguided assault on components of the CNS, precipitating a cascade of pathophysiological events.³ Initiation of this deleterious process occurs when the immune system

erroneously identifies self-antigens within the CNS as foreign entities, prompting the production of autoantibodies. In a study conducted by Chowdhury et al.,⁴ the causes of *N*-methyl-D-aspartate receptor (NMDAR) encephalitis in India encompassed a variety of infectious agents, such as herpes simplex virus (HSV), Japanese encephalitis virus (JEV), dengue virus, *Salmonella*, *Mycobacterium tuberculosis*, *Treponema pallidum*, *Leptospira*, as well as the presence of ovarian tumors.⁵ These autoantibodies, ranging from those targeting synaptic proteins like the NMDAR and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) to those directed against ion channels and receptors, become pivotal players in the pathophysiology. Their action disrupts normal synaptic transmission, impeding the binding of neurotransmitters and altering receptor function. Simultaneously, the inflammatory response triggered by the immune system compromises the integrity of the blood-brain barrier, facilitating the infiltration of immune cells and antibodies into the brain parenchyma. This breach exacerbates neuronal damage and inflammation, leading to direct injury to neurons and promoting apoptosis. The resulting diverse clinical manifestations, encompassing cognitive impairment, movement disorders, seizures, and psychiatric symptoms, underscore the complexity of the disorder. Antibody-mediated disorders affecting the CNS can be categorized broadly into two groups. Group I antibodies focus on intracellular neuronal antigens, demonstrating a stronger correlation with an associated malignancy. They employ cytotoxic T-cell mechanisms, directing their

actions toward both intracellular neuronal antigens and onconeural antigens as part of the immune response against cancer. Group II antibodies are oriented toward cell-surface neuronal antigens, have a lower likelihood of being linked to underlying malignancies, and rely on more focused humoral immune mechanisms of neurotoxicity, often displaying a favourable response to early immunomodulatory therapy. [Flowchart 1](#) shows various antibodies associated with autoimmune encephalitis.

Autoimmune encephalitis presents a multifaceted clinical panorama characterized by a diverse array of neurological and psychiatric manifestations. Patients commonly display cognitive dysfunction, encompassing memory deficits, confusion, and attention impairments. Movement disorders, ranging from tremors to more intricate motor abnormalities, often coexist with seizures of various types. Psychiatric symptoms, including mood disturbances, psychosis, hallucinations, and altered personality, contribute significantly to the clinical profile. Language dysfunction, such as aphasia, may manifest, and autonomic nervous system involvement can lead to fluctuations in blood pressure, heart rate, and temperature regulation. Sleep disturbances, focal neurological deficits, and peripheral nerve involvement further contribute to the complexity of the presentation. Children have also exhibited atypical presentations, such as autistic regression, catatonia leading to neuroleptic malignant syndrome, and gait disorders. In stark contrast to adults, children typically present with nonpsychiatric initial symptoms, which can include a spectrum of issues like dystonia, seizures, and mutism.⁶ The dynamic nature of symptoms, with fluctuations in intensity over time, necessitates vigilant clinical

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observation. Recognizing the diverse clinical features is paramount for early diagnosis and intervention, as autoimmune encephalitis is often associated with rapid progression. Timely initiation of immunotherapy is crucial, as these patients frequently exhibit positive responses, underscoring the importance of a multidisciplinary approach involving neurologists, psychiatrists, and other healthcare professionals for comprehensive and effective patient care. **Figure 1** shows various classic autoimmune encephalitis syndromes.

In the majority of autoimmune encephalitis cases, magnetic resonance imaging (MRI) scans either appear normal or

reveal nonspecific inflammatory changes.⁷ However, two notable exceptions are limbic encephalitis and anti-gamma-aminobutyric acid type A receptor (GABAAR) encephalitis. In GABAAR encephalitis, which primarily affects children and young adults, fluid-attenuated inversion recovery (FLAIR) images on MRI demonstrate multifocal cortical and subcortical signal abnormalities, primarily in the frontal and temporal lobes, and occasionally in the cerebellum and basal ganglia. Notably, these lesions do not exhibit diffusion restriction or contrast enhancement, bearing a resemblance to lesions seen in acute disseminated encephalomyelitis. Most patients with autoimmune encephalitis

exhibit moderate cerebrospinal fluid (CSF) lymphocytic pleocytosis (typically <100 cells/ m^3). However, it's important to recognize that the absence of pleocytosis does not exclude the diagnosis. Notably, encephalitides associated with leucine-rich glioma inactivated protein 1 (LGI1) or dipeptidyl peptidase-like protein 6 (DPPX) antibodies frequently present with both normal MRI findings and standard CSF study results (including cell count and protein and glucose levels). In most cases of autoimmune encephalitis, including those with normal standard CSF studies, neuronal autoantibodies are detectable in the CSF. However, there are instances, particularly in anti-LGI1 encephalitis, where antibodies are only detectable in either the serum or the CSF, highlighting the need for conducting tests on paired CSF and serum, and clinicians should give due importance to the clinical hypothesis during result interpretation.

The extensive differential diagnosis of autoimmune encephalitis (**Table 1**) encompasses conditions like acute disseminated encephalomyelitis, characterized by MRI abnormalities throughout white and gray matter, often associated with autoantibodies against myelin oligodendrocyte glycoprotein. Neuromyelitis optica spectrum disorders, on

Flowchart 1: Autoimmune encephalitis antibodies

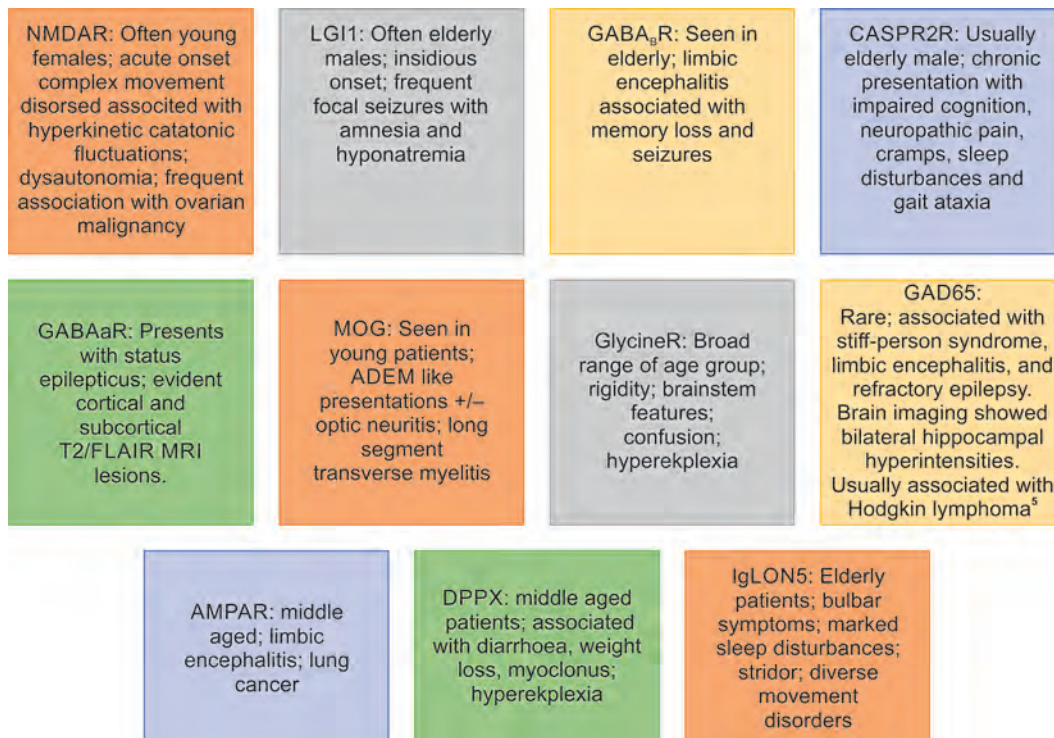
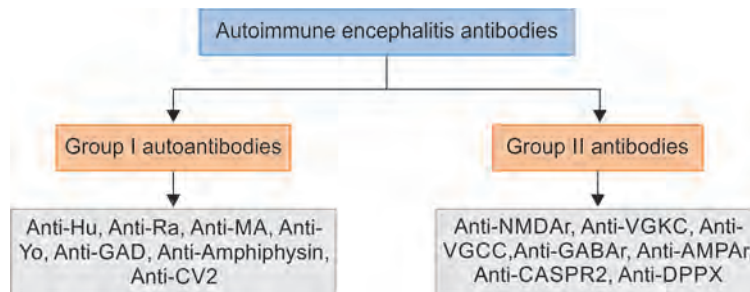


Fig. 1: Classic autoimmune encephalitis syndromes; AMPAR, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2, contact-associated protein 2; DPPX, dipeptidyl peptidase-like protein 6; GABA_A/BR, gamma aminobutyric acid; GAD65, glutamic acid decarboxylase; IgLON5, immunoglobulin-like cell-adhesion molecule 5; LGI1, leucine-rich glioma inactivated protein 1; MOG, myelin-oligodendrocyte glycoprotein, NMDAR, N-methyl-D-aspartate receptor

the other hand, present MRI abnormalities near periventricular and ependymal regions, frequently accompanied by antibodies against aquaporin-4, expressed on astrocyte. Interestingly, these demyelinating syndromes can occasionally co-occur with anti-NMDAR encephalitis, resulting in overlapping clinical presentations.⁸ Furthermore, autoimmune encephalitides may sometimes mimic neurodegenerative processes or exhibit brain damage reflected by restricted diffusion in cerebral cortex regions, emphasizing the need for early recognition as these atypical presentations are potentially treatable with immunotherapy.

The treatment recommendations for autoimmune encephalitis primarily rely on retrospective series and expert opinions,

as there have been limited clinical trials (Flowchart 2). The current approach encompasses immunotherapy and addressing the immunological trigger, especially if it involves tumors.⁹ Prompt tumor treatment is particularly crucial for achieving favorable outcomes. In most cases of autoimmune encephalitis, antibody production and inflammation occur behind the blood–brain barrier, which may explain the limited effectiveness of treatments like plasma exchange and intravenous immune globulin. Nonetheless, in practice, many patients receive initial treatment with glucocorticoids, intravenous immune globulin, or plasma exchange. If there's no clinical response, rituximab and cyclophosphamide are considered. Rituximab, in particular, has proven effective in refractory cases and appears to reduce the risk of clinical relapse, which has led to its increased use as an initial treatment. For all types of autoimmune encephalitides, timely initiation of immunotherapy is associated with better outcomes, as spontaneous clinical improvement is infrequent. The frequency of clinical relapse varies, with cases associated with antibodies against NMDAR, AMPAR, LGI1, CASPR2, or DPPX showing relapse rates ranging from 12 to 35%.⁶ Relapses often occur when immunotherapy is reduced or discontinued.¹⁰ The combination of immunotherapy and tumor treatment typically results in clinical improvement. In addition to addressing the underlying immunological factors, there is

often a need to manage various aspects of patient care, including seizures, movement disorders, behavior, pain, sleep disturbances, autonomic issues, and mood disorders. However, it's worth noting that patients with anti-NMDAR encephalitis may develop complications like hyperthermia, muscle rigidity, mutism, and coma, potentially due to increased susceptibility to neuroleptic agents' adverse effects.¹¹ LGI1-antibody encephalitis typically sees only a 10% success rate in stopping faciobrachial dystonic seizures with antiseizure medications. Patients also risk cutaneous reactions including Stevens–Johnson syndrome with antiseizure medications making this approach less effective and potentially harmful.¹²

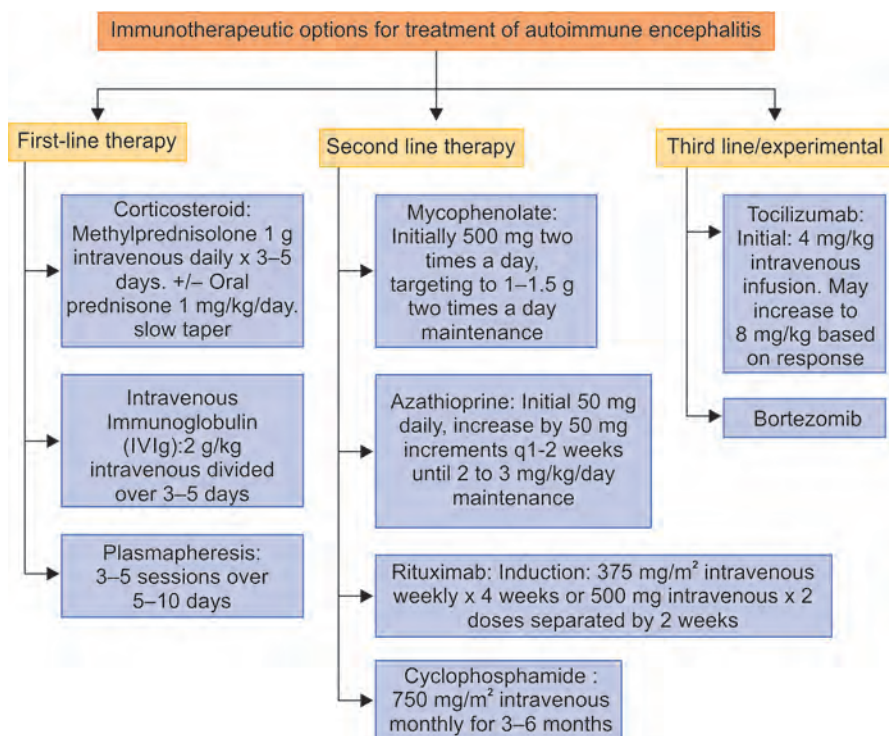
Future directions in autoimmune encephalitis encompass a multifaceted approach. Precision medicine is set to take center stage, tailoring treatments based on specific antibody profiles and clinical presentation. Ongoing research seeks to identify new autoantibodies, potentially revealing previously unrecognized subtypes of the condition. Genetic and environmental factors contributing to disease susceptibility and triggers are under scrutiny. Advanced diagnostic tools and biomarker identification are likely to improve early and accurate diagnosis. Investigating the long-term consequences and outcomes, including potential neurodegenerative effects, is pivotal. Developing standardized clinical guidelines, expanding support networks for patients and caregivers, and raising awareness are key components for comprehensive patient care and management. Investigations are necessary to determine the utility of neuropsychological testing, electroencephalography, advanced neuroimaging, and (¹⁸F)fluorodeoxyglucose–positron emission tomography in diagnosing autoimmune encephalitides, assessing treatment effectiveness, and predicting outcomes.⁷

In conclusion, autoimmune encephalitis is an intricate condition at the intersection of neurology and immunology. Understanding its pathophysiology, recognizing its diverse clinical presentations, and implementing effective diagnostic and treatment strategies are essential in managing this challenging disorder. Advances in research and clinical practice continue to shape our understanding and management of autoimmune encephalitis.

Table 1: Differential diagnosis for autoimmune encephalitis

Differential diagnosis
• Infectious encephalitis (most commonly HSV). • Temporal lobe glioma. • Creutzfeldt–Jakob disease and other rapid dementias. • Metabolic encephalopathies. • In patients with frequent seizures, postictal MRI changes can sometimes resemble the acute phase of autoimmune encephalitis. • Hashimoto's encephalopathy.

Flowchart 2: Immunotherapeutic options for treatment of autoimmune encephalitis



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Responsible Use of Oral Corticosteroids in People with Comorbid Diabetes: An Expert Consensus

Banshi Saboo^{1*}, Shashank Joshi², Amit Gupta³, Anuj Maheshwari⁴, Bharat Saboo⁵, Brij Mohan Makkar⁶, Ganapathi Bantwal⁷, Jothydev Kesavadev⁸, L Sreenivasamurthy⁹, Mangesh Tiwaskar¹⁰, Manoj Chawla¹¹, Minakshisundaram Shunmugavelu¹², Nagendra Kumar Singh¹³, Pratap Jethwani¹⁴, Sanjay Agarwal¹⁵, Sunil Gupta¹⁶, Rajesh Swarnakar¹⁷, Rakesh Sahay¹⁸, Vijay Vishwanathan¹⁹, Charmy Prajapati²⁰, Amit Qamra²¹, Parthasarathy Muralidharan²²

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ABSTRACT

Globally, diabetes mellitus (DM) is a substantial contributor to morbidity and mortality. Comorbidities and intercurrent illnesses in people with diabetes may necessitate the use of steroids. Acute as well as chronic use of steroids contributes substantially to the development of various complications. Despite this, there are no standard guidelines or consensus to provide a unified approach for the rational use of steroids in people with diabetes. Also, there is scant harmonization among clinicians with the use of different steroids in routine practice. To address the inconsistencies in this clinical arena, the consensus working group (CWG) formulated a unified consensus for steroid use in people with diabetes. In people with diabetes, the use of steroids causes hyperglycemia and may precipitate diabetic ketoacidosis (DKA). An increase in weight is directly related to the dose and duration of the steroid therapy. Steroid-related alterations in hyperglycemia, dyslipidemia, and hypertension (HTN) add to the increased risk of cardiovascular (CV) disease. The risk of complications such as infections, osteoporosis, myopathy, acne, cataracts, and glaucoma may increase with the use of steroids. Appropriate and timely monitoring of these complications is necessary for early detection and treatment of such complications. Given the systemic effects of various antihyperglycemic drugs, there is a possibility of aggravating or diminishing the specific complications. Preference to a safer steroid is required matching the steroid dose equivalence and individualizing patient management. In conclusion, short-, intermediate-, or long-term use of steroids in people with diabetes demands their rational use and holistic approach to identify, monitor, and treat the complications induced or aggravated by the steroids.

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INTRODUCTION

Among the noncommunicable diseases (NCD), diabetes mellitus (DM) is a major NCD affecting the global population. The International Diabetes Federation (IDF) estimates India as the second highest prevalent country for DM. The disease unawareness is substantial with one out of two adults living with DM being unaware of the disease.¹ A recent ICMR-INDIAB-17 study identified 11.4 and 15.3% prevalence of diabetes and prediabetes, respectively. Prevalence also significantly varies in different regions in India. Projections suggest that currently, 101.3 and 136 million are suffering from diabetes to prediabetes, respectively.² Hypertension (HTN) is the most prevalent comorbid condition in people with diabetes. ICMR-INDIAB study projected over 315 million people with HTN in India.² People with diabetes have an increased likelihood of certain comorbid conditions or may develop intercurrent illness that requires treatment with short-, intermediate-, or long-term use of corticosteroids.³⁻⁹ Such use of steroids in people with diabetes can increase the risk of various complications.^{10,11} As no specific guidelines or consensus are

addressing the issue of appropriate use of steroids in preexisting diabetes, the consensus working group (CWG) provides the Indian expert consensus for the rational use of oral steroids in people with diabetes.

MATERIALS AND METHODS

In this consensus development, the CWG used the nominal group technique. This technique allows for the direct interaction of the experts.¹² In the first CWG meeting, consensus topics were discussed to arrive at a specific conclusion on a given consensus. Various topics included challenges with the use of steroids in people with diabetes, monitoring and management of different complications, considerations about the use of antihyperglycemic drugs, drug-drug interactions, and the concept of steroid equivalence. Based on the discussions in the first CWG meeting, evidence related to the chosen consensus topics was discussed in detail and a manuscript with draft consensus statements was prepared. In a subsequent working group meeting, further discussions on evidence led to the finalization of consensus statements. After approval of the

final manuscript draft from all the experts, it was submitted for publication.

DIABETES AND CORTICOSTEROIDS: A DOUBLE WHAMMY

In people with diabetes, the use of steroids is associated with an increased risk of various

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complications. In understanding the rates of complications, Caughey et al.¹⁰ assessed 18,226 people with diabetes, of which 67.2% had received steroid treatment within the past year and 5.9% had chronic obstructive pulmonary disease (COPD). In this study, there was a 94% increased risk of hospitalization for diabetes-related complications and the risk persisted irrespective of the route of steroid administration, that is, inhaled, oral, or both. Another study reported an increased risk of diabetes progression and osteoporosis onset with the use of steroids among the COPD population.¹³ The risk of new infections and infections-related hospitalizations are also significantly increased by the use of steroids in people with diabetes than those without diabetes.¹⁴ These data highlight the need to consider the rationale use of steroids in people with diabetes. Table 1 highlights the various complications that can occur with the use of steroids in people with diabetes.

Endocrine and Metabolic Complications

Hyperglycemia and Diabetic Ketoacidosis

The use of steroids is associated with an increased risk of hyperglycemia.^{15–19} Hyperglycemia can occur as early as 5–8 hours after oral steroids.²⁰ Figure 1 provides a schematic representation of mechanisms by which steroids cause increased glucose levels and ketonemia.^{18,21–27} In the short-term, hyperglycemia is usually the result

of hepatic gluconeogenesis, increased glucagon secretion, reduced uptake of glucose in peripheral tissues, reduced insulin sensitivity, and reduced adiponectin levels in adipose tissues. Increased appetite and leptin resistance are mediated through central mechanisms. With longer use of steroids, there may be reduced insulin secretion, progressive β -cell failure, and reduced muscle mass further accentuating hyperglycemia. Further, hyperglycemia, insulin deficiency, osmotic diuresis, and increased catabolism may precipitate diabetic ketoacidosis (DKA) in vulnerable patients. Multiple reports suggest a possible likelihood of DKA after the initiation of steroids in people with diabetes.^{28–30} Early identification of steroid-induced hyperglycemia is essential to avoid progression to DKA.

- **Expert consensus:** In people with diabetes, the use of steroids causes hyperglycemia and may precipitate DKA in vulnerable populations.

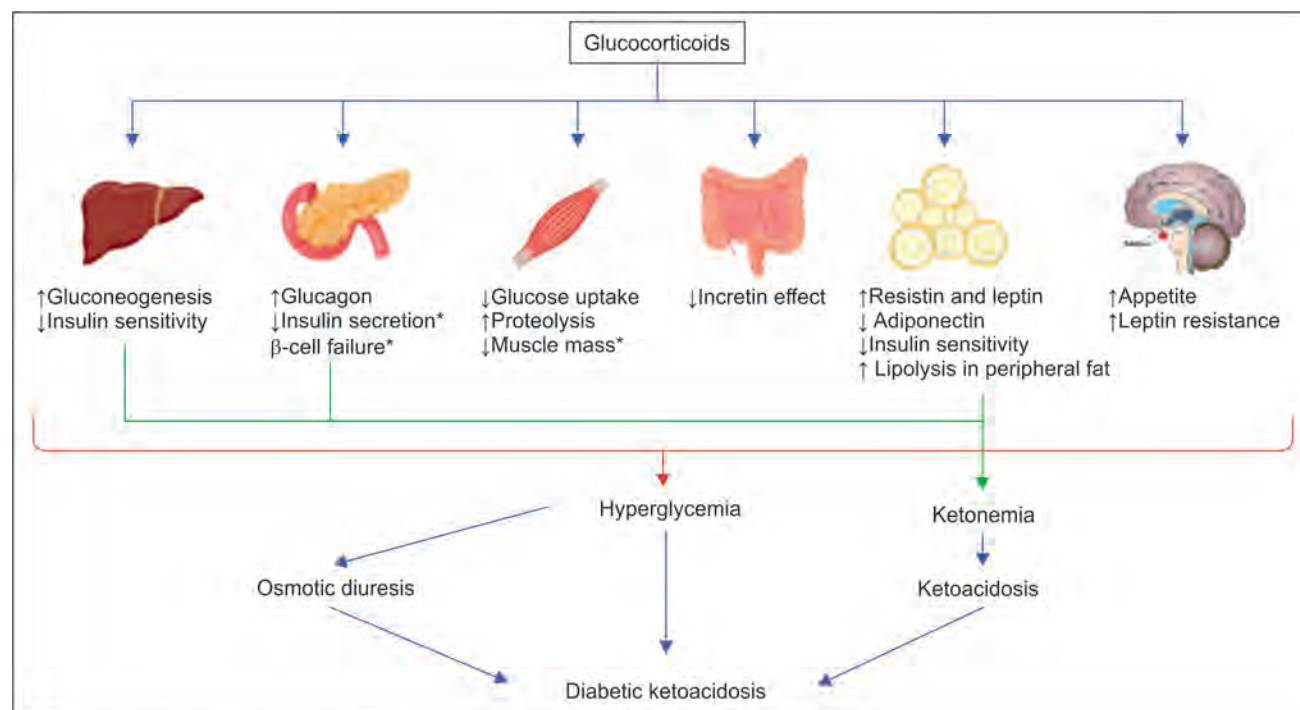
Weight Gain

Weight reduction of even 5% is known to improve glycemic control and reduce the need for antihyperglycemic medications. Such effects are mediated *via* improved insulin sensitivity and better β -cell function.³¹ Chronic glucocorticoid therapy (>3 months) is associated with weight gain. Higher doses and previous exposure to glucocorticoids increase the risk of weight gain.³² A year of steroid

therapy can lead to a weight gain of >10 kg in nearly one-fifth of patients.³³ Such weight gain may further contribute to hyperglycemia and metabolic derangement in people with diabetes.

Table 1: “Double whammy” of DM and corticosteroid use

Endocrine and metabolic complications
• Hyperglycemia
• DKA
• Weight gain
• Hypothalamic–pituitary–adrenal axis suppression
CV complications
• HTN
• Dyslipidemia
• CVD
• HF
• Atrial fibrillation
Immunological complications
• Infections (bacterial, viral, fungal)
• Wound healing
• Acne
Musculoskeletal complications
• Myopathy
• Osteoporosis and bone fractures
• Avascular necrosis
Ophthalmological complications
• Cataract
• Glaucoma



*With prolonged use of glucocorticoids

Fig. 1: Mechanisms underlying glucocorticoid-induced hyperglycemia; *with prolonged use of glucocorticoids

- **Expert consensus:** In people with diabetes, weight gain is expected during steroid therapy and is directly related to the steroid dose and duration of the steroid therapy.

Hypothalamic–Pituitary–Adrenal Axis Suppression

Systemic use of steroids is known to impact the hypothalamic–pituitary–adrenal (HPA) functioning causing immediate and prolonged suppression in asymptomatic individuals.³⁴ In people with diabetes, there is diurnal variation and altered regulation of the HPA axis. Increased levels of basal adrenocorticotrophic hormone (ACTH) and cortisol are seen. These increased levels of endogenous steroids hamper the glycemic levels and contribute to increased cardiovascular (CV) risk.^{35,36} Clinically, suppression of the HPA axis may manifest as adrenal insufficiency (AI) or adrenal crisis and usually presents with nonspecific symptoms and signs (Table 2). Adrenal suppression can occur earlier than expected, especially with high doses of steroids. Sudden discontinuation of steroids also results in AI and, therefore, tapering of steroids is a common practice globally.³⁷ Thus, in people with diabetes, there may be a need for monitoring of AI.

- **Expert consensus:** In people with diabetes, AI can occur with discontinuation of steroids. AI is not related to the dose or duration of steroids.

Iatrogenic Cushing's disease, though uncommon, can occur and may go unnoticed causing disruptions in cardiometabolic features.^{38,39} Risk factors include younger age, high basal body mass index (BMI), and higher calorie intake.⁴⁰ The incidence of cushingoid features is directly proportional to the steroid dose. Even at a small dose of <5 mg/day of prednisolone equivalent (PEQ), there is a 4.3% risk of iatrogenic Cushing's disease, and the risk increases to 15.8%, and 24.6% with a PEQ dose of 5–7.5 mg/day and >7.5 mg/day, respectively.⁴¹

- **Expert consensus:** In people with diabetes, iatrogenic Cushing's syndrome is a possibility that is directly proportional to steroid dose.

Table 2: Symptoms and signs indicative of possible AI

Excessive tiredness or fatigue
Insomnia
Palpitations
Brain fogging
Frequent dizziness
Hypotension

Cardiovascular Complications

Hypertension, Dyslipidemia, and Cardiovascular Disease

Hypertension in individuals with diabetes significantly increases the risk of CV events and mortality.⁴² Steroids can induce HTN by affecting the water and electrolyte balance. However, other possible mechanisms involving vascular smooth muscles and nonvascular mechanisms also play a role in the causation of HTN.⁴³ A cumulative PEQ dose of ≥7.5 mg/day is associated with a 17% increased risk of HTN.⁴⁴ In people with diabetes, such steroid-induced HTN may further increase the CV risk.^{43,45}

In Indians, diabetic dyslipidemia is characterized by high postprandial triglycerides (TGs), low high-density lipoprotein cholesterol (HDL-C), normal or increased low-density lipoprotein cholesterol (LDL-C), and substantial presence of small dense LDL-C particles.⁴⁶ Corticosteroids are reported to have dose-dependent effects on lipoprotein.⁴⁷ They trigger lipolysis, lipoprotein lipase activity, adipokine activity, inhibit fatty acid oxidation, and increase insulin resistance.^{46,48} Therefore, dyslipidemia in people with diabetes may be precipitated by the concurrent use of steroids.

Diabetes is considered a coronary heart disease risk equivalent.^{49,50} Dysglycemia, dyslipidemia, and HTN with steroid use contribute to increased CV risk. Chronic steroid use impacts the vascular endothelium and contributes to the accelerated atherosclerotic process and thereby CV disease (CVD).^{51–53} This has been proven in various clinical studies. Pujades-Rodriguez et al.⁵² identified that with the prescribed steroid dose in 87,794 persons with immune-mediated inflammatory

disorders and no history of CVD at baseline, there was a significant dose-dependent increase in the risk of CVDs at a 5-year median follow-up, regardless of the disease activity level. CVD risk at a PEQ dose of <5 mg/day and up to 25 mg/day was studied. The 5-year cumulative risk for CVD increased from 7.1% in nonusers to 28% for PEQ dose of ≥25 mg/day. Figure 2 shows the risk of various CVDs with different doses of steroids.⁵² It indicates even with the lowest dose of <5 mg/day PEQ, the risk of CV events is increased.

- **Expert consensus:** In people with diabetes, steroids may cause or exacerbate HTN and dyslipidemia. The risk of CVDs is increased even at a PEQ dose of <5 mg/day.

Heart Failure

In people with diabetes, there is diastolic dysfunction in the early stages that ultimately progresses to systolic dysfunction over a period if not intervened.⁵⁴ Heart failure (HF) with preserved ejection fractions (HFpEF) represents nearly 50% of HF cases.⁵⁵ Oral glucocorticoid use is independently associated with an elevated risk of HF. Even after adjustment for drugs such as antihyperlipidemic, antihypertensive, and oral antihyperglycemic agents, oral corticosteroid use is independently associated with an increased risk of CV events such as HF.⁵² Thus, in people with diabetes and HF, steroids may precipitate HF. The mineralocorticoid activity of oral steroids also needs to be considered when using them, especially in patients with HTN and HF.

- **Expert consensus:** In people with diabetes, steroids may precipitate HF and thus consider the mineralocorticoid activity of steroids in such populations.

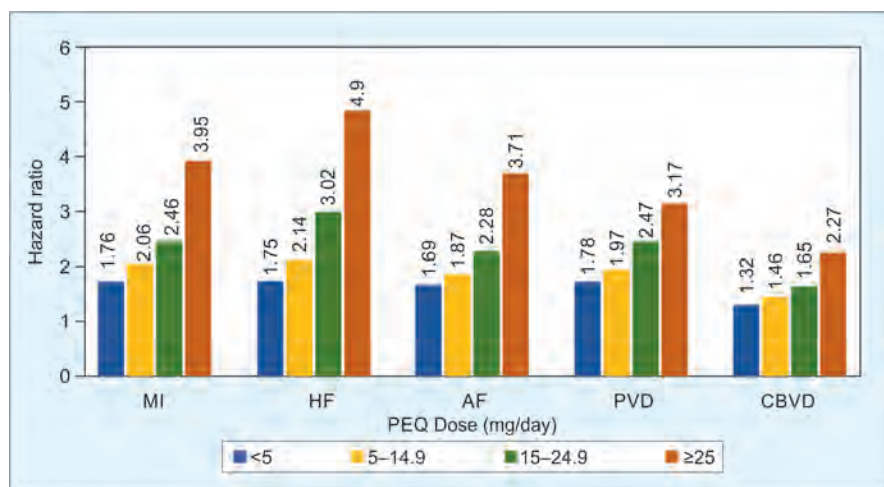


Fig. 2: Risk (hazard ratios) of different CVDs with different doses of steroids⁵²; AF, atrial fibrillation; CBVD, cerebrovascular disease; HF, heart failure; MI, myocardial infarction; PEQ, prednisolone-equivalent; PVD, peripheral vascular disease

Immunological Complications

Infections

Diabetes compromises the functioning of neutrophils, the antioxidant system, and humoral immunity, and decreases the secretion of inflammatory cytokines.⁵⁶ The anti-inflammatory and immunosuppressive effects of steroids make them useful in various inflammatory and autoimmune disorders.⁵⁷ The Atherosclerosis Risk in Communities (ARIC) study on people with diabetes reported a significantly increased risk of hospitalizations and mortality related to infections.⁵⁶

The suppression of the immune system and the worsening of preexisting diabetes by steroids further increases the risk of infection in people with diabetes. Conversely, infections in people with diabetes might result in other diabetic complications such as hypoglycemia and ketoacidosis.^{58,59} The risk of infections increases proportionally with the dosage and duration of steroids. Elderly age and concurrent use of other immunosuppressive medications increase infection risk further. Due to the inhibition of cytokine release and the resulting decrease in inflammatory and febrile responses, patients using glucocorticoids may not exhibit typical signs and symptoms of infection (e.g., fever), making it difficult to diagnose infections early.⁶⁰ One important consideration is the risk of genital mycotic infections (GMIs) with the use of sodium-glucose cotransporter-2 inhibitors (SGLT2i). A study from the United Kingdom analyzed the data of nearly 21,000 patients and found no increased risk of GMIs with oral steroid use. However, the study may not be powered to detect a small increase in the risk of GMIs.⁵⁹ Thus, future research is necessary to understand whether steroids increase the risk of GMIs in people with diabetes receiving SGLT2i.

- **Expert consensus:** In people with diabetes, steroids may increase the risk of bacterial, viral, and fungal infections. Classical features of infections may not be evident in some of the patient populations. Further research is necessary to understand the risk of infections in such populations.

The risk of drug interactions is an important consideration when using appropriate antimicrobials (Table 3).^{61,62} The use of CYP3A inhibitors concomitantly with steroids likely increases the risk of systemic side effects. For example, antifungals such as ketoconazole, antibiotics like clarithromycin, and antivirals like ritonavir can increase the systemic exposure of steroids and cause toxicity. On the other hand, rifampin can reduce steroid exposure and reduce its efficacy. Therefore,

monitoring of patients for possible toxicity signs of steroid overdosage is necessary and dose alteration may be needed in some patients taking such concurrent medications.

- **Expert consensus:** In people with diabetes, steroids may have drug interactions with some antimicrobials and other medications. A watch for systemic toxicity of steroids is necessary with the concomitant use of certain medications.

Wound Healing

Uncontrolled DM impairs wound healing. Concurrent long-term use of steroids in people with diabetes hampers wound healing. In one study, the postoperative use of steroids for over 30 days was associated with a 4-fold higher mortality, a 2–3-fold increase in wound dehiscence, and a 5% increase in infection rates.⁶¹

- **Expert consensus:** In people with diabetes, steroids might delay wound healing. Caution is necessary in people with diabetes with preexisting foot ulcers.

Acne

Acne flares can be seen with the use of steroids in people with diabetes. Risk factors for steroid acne include the following:

- Higher steroid dosage.
- Application of steroid with occluded patch.
- Young age (<30 years).
- Previous history of acne.

There may be a faster progression of acne and the formation of hyperkeratosis, microcomedone production, papulopustular lesions, and follicle ruptures.⁶³

- **Expert consensus:** In people with diabetes, steroids may increase the occurrence of acne, especially with higher dosage and in the presence of risk factors.

Musculoskeletal Complications

Myopathy

Skeletal muscles are an important part of the “ominous octet” essential to the regulation

of blood glucose. Diabetes-related myopathy is characterized by a failure to maintain adequate functioning of muscles. Diabetes affects the muscle progenitor cell population and impairs mitochondrial functioning which is critical in maintaining skeletal muscle health.⁶⁴ Compared to nondiabetics, there is a 1.5 times greater risk of sarcopenia in people with diabetes.^{65,66} In the Indian population, sarcopenia is seen in nearly 17% of people with diabetes.⁶⁷ The use of steroids in people with diabetes may further cause muscle damage because of its direct catabolic effects. Muscle damage associated with steroid use can occur after weeks to months and may appear early with higher dosages.⁶⁰

- **Expert consensus:** In people with diabetes, steroids may increase the risk of myopathy and it may occur early in the course with a higher dosage of steroids.

Osteoporosis and Bone Fractures

Evidence suggests that one in three women and one in five men aged over 50 years will sustain an osteoporotic fracture.⁶⁸ Both DM and osteoporosis can coexist, especially in the elderly, and are impacted by aging and lifestyle changes. There is a direct relationship between type 2 diabetes mellitus (T2DM) and bone strength.⁶⁹ In people with diabetes, advanced glycation end-product accumulation, changes in collagen cross-linking, and suppression of bone turnover are the main factors affecting bone strength.⁷⁰ T2DM alone is a significant risk factor for major osteoporotic fractures (MOFs) such as low trauma hip fractures, and fractures at the proximal humerus, clinical spine, and distal radius. The risk is regardless of bone mineral density (BMD) and BMI. T2DM raises the risk of a fracture by at least 20–30%. Such an increase in risk is comparable to rheumatoid arthritis or a familial hip fracture.⁶⁹

Glucocorticoid-induced osteoporosis (GCOP) is usually an iatrogenic osteoporosis and is a frequently observed cause of osteoporosis. Nearly, 30–50% of patients on chronic glucocorticoid therapy may get

Table 3: Drug interactions of steroids

Drug groups	Interaction
Antivirals (e.g., ritonavir, indinavir), ciclosporin	Inhibit metabolism
Antifungals (e.g., ketoconazole, itraconazole)	↑ Systemic steroid exposure
Macrolides (e.g., erythromycin, clarithromycin)	
Rifampicin, rifabutin, carbamazepine, phenobarbitone, phenytoin, primidone, ephedrine, and aminoglutethimide	Increased metabolism
Anticoagulants (e.g., warfarin), aspirin, other nonsteroidal anti-inflammatory drugs	↓ Steroid systemic exposure and effect
Diuretics (e.g., furosemide, hydrochlorothiazide)	↑ Gastrointestinal bleeding
Methotrexate	↑ Hypokalemia
	Hematological toxicity

fractures. Long-term oral steroid therapy increases fracture risk. Fractures may occur at a lower threshold of BMD.⁷¹ PEQ dose of >5 mg daily leads to a reduction in the BMD with a rapid increase in fracture risk within 3–6 months of starting steroid therapy. The risk of fractures is independent of underlying disease, age, and gender.⁷² Thus, combined with diabetes, the risk of bone loss and fractures may get substantially elevated with concomitant steroid therapy.

- **Expert consensus:** In people with diabetes, steroids increase the risk of osteoporosis even at a PEQ dose of 5 mg or more. Duration of steroids is associated with such risk of osteoporosis and related bone fractures.

Avascular Necrosis

In people with diabetes, the risk of avascular necrosis may be increased slightly. A meta-analysis of six observational studies reported a nonsignificant increase in the risk of avascular necrosis at sites other than the jaw.⁷³ The use of steroids is one of the most common causes of iatrogenic avascular necrosis of various bones and joints. The prevalence of steroid-induced avascular necrosis ranges between 3 and 38%. Though femoral and humeral heads are the most common sites, avascular necrosis can occur in other bones such as knee joints, foot bones, ankles, and hands. A positive correlation with a steroid dose of ≥ 40 mg/day of PEQ dose is reported.⁷⁴ Exposure to bolus doses increases the risk of avascular necrosis substantially.^{74,75} A study in Taiwan identified a 16% greater risk of avascular necrosis of the femoral head in people with diabetes compared to those without diabetes. Also, a 34% increased risk of avascular necrosis of the femoral head with oral steroid use was reported.⁷⁶

- **Expert consensus:** In people with diabetes, steroids may increase the occurrence of avascular necrosis of the femur and the risk is probably higher with a higher dose of steroids.

Ophthalmological Complications

Cataract

The risk of cataracts in people with diabetes is five times higher than in nondiabetics. It commonly produces cortical and/or posterior subcapsular cataracts.⁷⁷ Prolonged use of steroids increases the risk of posterior subcapsular cataracts and nuclear cataracts.⁷⁸ A study reported that intravitreal use of triamcinolone for diabetic macular edema over 3 years led to a significantly higher proportion of cataract extractions compared to sham-treated eyes (56 vs 8%, $p < 0.0001$).⁷⁹ In another study assessing a population with

diabetic retinopathy, the concomitant use of systemic steroids led to an increased risk of sight-threatening cataracts.⁸⁰ Thus, in people with diabetes, long-term use of systemic steroids accelerates cataract formation.

- **Expert consensus:** In people with diabetes, steroids increase the risk of cataracts and the risk increases with the duration of their use.

Glaucoma

The risk of glaucoma is significantly higher in people with diabetes. A meta-analysis of seven prospective studies identified a risk ratio of 1.36 (95% CI 1.24–1.50) for primary open-angle glaucoma (POAG).⁸¹ It is well established that the use of steroids is associated with increased intraocular pressure (IOP) leading to glaucoma.⁸²

- **Expert consensus:** In people with diabetes, steroids may increase the risk of glaucoma.

MONITORING FOR COMPLICATIONS DURING STEROID THERAPY

As discussed in previous sections, the “double-whammy” of diabetes and corticosteroid use leads to complications that affect the overall health of an individual. Monitoring for these complications can be useful to detect them early and treat them adequately. Table 4 provides the schedule of monitoring of different functions in people with diabetes receiving steroids.⁶⁰

Glycemia Monitoring

Postprandial hyperglycemia is the first observable dysglycemia response with the use of short- or intermediate-acting steroids such as prednisolone. The effect on glucose levels can be evident within a few hours to days after initiating steroids.⁸³ Therefore, it is advised to screen blood glucose levels for frequent intervals in the first few days of starting treatment. The Canadian guidelines advocate monitoring of glycemic parameters for at least 48 hours after initiation of steroids.⁸⁴ The frequency of monitoring in the long run is not fixed. Higher baseline glycated hemoglobin (HbA1c) is associated with a greater increase in glucose after steroid initiation.⁸⁵ Thus, monitoring should be individualized according to baseline glycemic status, number of medications, age, DKA risk, etc. There are intraday variations in blood glucose levels among patients with steroid-induced hyperglycemia. People with diabetes may have glucose levels above the target range for at least 6 hours daily with over 1 hour of severe hyperglycemia.⁸⁶ Longer duration

above the normal glycemic target shows that the glycemic variability may be greater in people with diabetes receiving steroids. Thus, there may be a need for continuous glucose monitoring (CGM) in some cases. CGM is an established modality for both type 1 and type 2 diabetes especially for those who are receiving insulin. CGM can provide better treatment guidance and personalized diabetes care.⁸⁷ In the Indian context, CGM is useful in patients with diabetes and should be offered to those who can afford it. For patients on insulin, the use of CGM with time-in-range (TIR) metric may be done for at least 2 weeks to adjust the antihyperglycemic drugs. Patients with a frequent hypoglycemia history get more benefits from CGM.⁸⁸ CGM can help understand the glycemic fluctuations after steroid initiation and guide the therapy for steroid-induced hyperglycemia. However, physicians need to be cautious while assessing the TIR metric in such situations. For optimization of decision-making, CGM-TIR can be combined with self-monitoring of blood glucose.

- **Expert consensus:** In people with diabetes, specific monitoring approaches are essential for early detection and treatment of various complications.

MANAGEMENT CONSIDERATIONS

The complications and difficulties arising out of steroid use in comorbid diabetes can be complex and difficult to manage. Despite their occurrences, we need to continue the antihyperglycemic treatments to provide optimal glucose control. This can be done by assessing the benefit–risk balance with antihyperglycemic medications. Table 5 prompts the possible risks and benefits of currently available antihyperglycemic drugs.^{89–102} This can help make individualized treatment changes in the routine management of people with diabetes using steroids.

Hyperglycemia

In India, the Research Society for Study of Diabetes in India (RSSDI) 2022 guidelines provide effective management strategies for treating steroid-induced hyperglycemia.¹⁰³ It is advised to review the current treatments and modify them to achieve mean blood glucose control in the range of 106–180 mg/dL. However, the goals need to be set by considering the individual characteristics, comorbidities, compliance, and risk of hypoglycemia. Table 6 provides various glycemic goals for patients developing steroid-induced hyperglycemia in specific scenarios.

Steroid-induced hyperglycemia should be persuaded with care. Depending on the severity

Table 4: Monitoring of different complications in people with diabetes initiating long-term steroid

<i>Endocrine and metabolic monitoring</i>	<i>Monitoring actions</i>
Baseline assessments	Anthropometry: Height, weight, BMI Glycemic: FBG, PPBG, and HbA1c Ophthalmic: Vision, intraocular pressure Other: Blood pressure, complete blood count
Glycemia monitoring	Individualized based on: Baseline glycemic status Number of medications Age DKA risk More frequent in the 1st week of steroid therapy CGM If available, may be considered in patients receiving or requiring insulin CGM can be taken for at least 2 weeks with special consideration of TIR CGM with SMBG provides a better understanding of glycemic changes
Adrenal insufficiency	Only in suspected cases Monitor morning (8 AM) serum cortisol levels (e.g., every 12 weeks). Levels <3 µg/dL (80 nmol/L) suggest AI If AI is strongly suspected with normal cortisol levels, perform low dose ACTH stimulation test After 1 µg of cosyntropin, peak cortisol <18 µg/dL (<500 nmol/L) at 0, 30, 60 minutes: diagnosis of AI
CV monitoring	
Lipids profile	After 1 month and then every 6–12 months More frequent in patients with existing dyslipidemia
CVD	Individualized assessment
Musculoskeletal monitoring	
Myopathy	Screen for symptoms and signs related to muscle damage in every clinical visit Educate patients about muscle pains or aches Perform tests of muscle strength (such as hand grip strength, etc.) at regular intervals to assess myopathy
Bone health	Children BMD at 3 months after starting steroid If normal, reassess every year More frequent in patients with cushingoid features, vertebral growth deceleration, and fractures after mild trauma Adults BMD at 1 year after starting steroids If normal, reassess every 2–3 years Frequent assessment in obese, frail, and physically inactive patients
Height/weight velocity	Assess the height of children annually and plot the growth curve (e.g., every 6 months) Use IAP growth charts for height/weight velocity monitoring
Avascular necrosis	Screen for bone or joint pain radiating to nearby areas that are likely avascular necrosis MRI, if strong clinical suspicion
Ophthalmic monitoring	
Cataract	Assess at baseline before starting steroids Reassess every 3–6 months Frequent assessment in elderly (>60 years)
Glaucoma	Assess IOP at baseline Reassess annually Frequent IOP measurement Family history of glaucoma High myopia cases Comorbid connective tissue disorders

BMD, bone mineral density; CGM, continuous glucose monitoring; IAP, Indian Academy of Pediatrics; IOP, intraocular pressure

Table 5: Antihyperglycemic agents benefits and risks in view of steroid use in comorbid diabetes^{89–102}

Complications	Metformin	SUs	TZDs	DPP4i	SGLT2i	GLP-1 RAs	AGIs
Hyperglycemia	B	B	B	B	B	B	B
DKA	–	–	–	–	R	–	–
Weight gain	B/NR	R*	R	NR	B	B	NR
HTN	NR	U	U	NR	B	B	NR
Dyslipidemia	NR	U	B	NR	U	U	U
HF	U	U	R	R/NR [†]	B	U	U
Bone fractures	U	U	R	NR	R/NR [#]	U	U

*Glimepiride and gliclazide modified release do not increase weight; Isaxagliptin and alogliptin worsen heart failure and sitagliptin and linagliptin do not increase HF events; [#]canagliflozin increased fracture risk whereas dapagliflozin and empagliflozin do not increase fracture risk; B, beneficial; NR, not risky; R, risky; U, unclear

Table 6: Research Society for Study of Diabetes in India 2022 glycemic goals for subjects with diabetes developing steroid-related hyperglycemia¹⁰³

Population	Glycemic goals (mean glucose level)
Hospitalized patients	140–180 mg/dL
Frailty	120–200 mg/dL (round the clock)
Care home residents	126–216 mg/dL

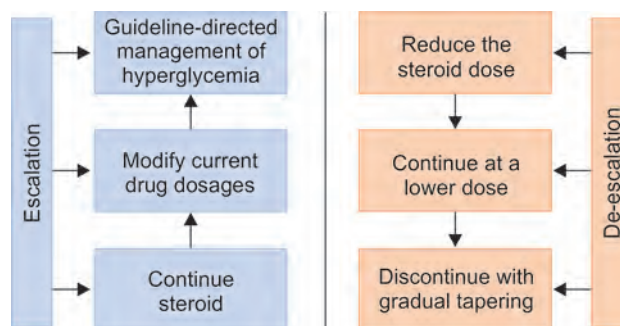
of hyperglycemia and the pharmacodynamic action of steroids, existing antihyperglycemic drug modifications and/or the addition of newer agents can be considered. We recommend “escalation” and “de-escalation” approaches (Fig. 3). Figure 4 provides a broad schematic treatment approach for type 1 and type 2 diabetes. Table 7 lists the possible antihyperglycemic medications according to the type and timing of steroid administration.¹⁰³ One must consider the insulin of choice based on insulin(s) pharmacokinetics that match with pharmacodynamic impact of specific steroids on glycemic excursions.⁶⁰ A series of four cases reported good efficacy of exenatide in improving the glycemic levels in such patients.¹⁰⁴ Figure 5 provides a glycemic profile after the use of different duration steroids and likely useful insulin according to such profile. As recommended by the RSSDI guidelines, a correction factor is necessary when the use of insulin is necessary. A correction factor is equal to 1800 divided by the total daily dose if insulin analog is used or 1500 divided by the total daily dose if regular insulin is used.¹⁰³ Detailed dosing recommendations on insulin use are out of the scope of this paper. Clinicians should follow the local recommendations for determining insulin doses and appropriate titration of insulins.

In the escalation approach, modify the doses of existing antihyperglycemic drugs as per the severity of steroid-induced hyperglycemia. For the use of additional antihyperglycemic drugs, consider guidelines-directed management of hyperglycemia. In the de-escalation approach,

Table 7: Preferred antihyperglycemic by the type of steroid

Steroid	Preferred antihyperglycemic drugs	Insulin dose [#]
Short-acting (e.g., hydrocortisone)	SU* ± short-acting insulin [†]	Initiate at 0.01 IU/kg Intensify based on pre-prandial glucose: 200–300 mg/dL: 0.04 IU/kg >300 mg/dL: 0.08 IU/kg
Intermediate-acting (e.g., prednisolone)	SU* ± NPH insulin [†]	Initiate at 0.4 IU/kg
Long-acting (e.g., dexamethasone)	SU* ± NPH + short-acting insulin, OR long-acting insulin (e.g., insulin glargine) [†]	NPH/detemir twice daily: Initiate at 0.3 IU/kg Glargine/degludec once daily: Initiate at 0.2 IU/kg

*Gliclazide may be preferred over other sulfonylureas if it is not included in the current management algorithm of the index patient; [†]when used to manage steroid-induced hyperglycemia; [‡]as necessary (for e.g., use NPH insulin twice daily if steroid is used two times a day)

**Fig. 3:** Escalation and de-escalation approach for the use of steroids in people with comorbid diabetes

reduce the steroid dose and continue at a lower dose to understand the glycemic response. If persistently raised glucose levels are seen, consider discontinuation of steroids with gradual tapering.

Diabetic Ketoacidosis

Diabetic ketoacidosis should be managed in the intensive care unit as per the standard DKA treatment protocol involving fluids, insulin, and electrolyte treatment. For patients who develop DKA, it is advisable to reduce the dosages or stop steroids if possible.

Weight Gain

Adequate nutrition and exercise, till the steroids are continued, can help prevent weight gain.

The current evidence from randomized trials is very limited. Studies in children with lupus, and hematological malignancies have shown that a low-calorie diet and home-based exercises helped to promote weight loss over 6 weeks to 1 year.^{105–107} However, there is a need to generate further evidence as to which dietary and exercise interventions would best fit to contain weight gain with the use of steroids.¹⁰⁷ As people with diabetes need to follow aggressive lifestyle interventions, weight gain with steroid use may be expected to be lower. However, it needs to be studied further in prospective trials. Based on the current evidence, one can prefer the medications that promote weight loss in diabetes. SGLT2i and glucagon-like peptide 1 receptor agonists (GLP-1RA) help promote

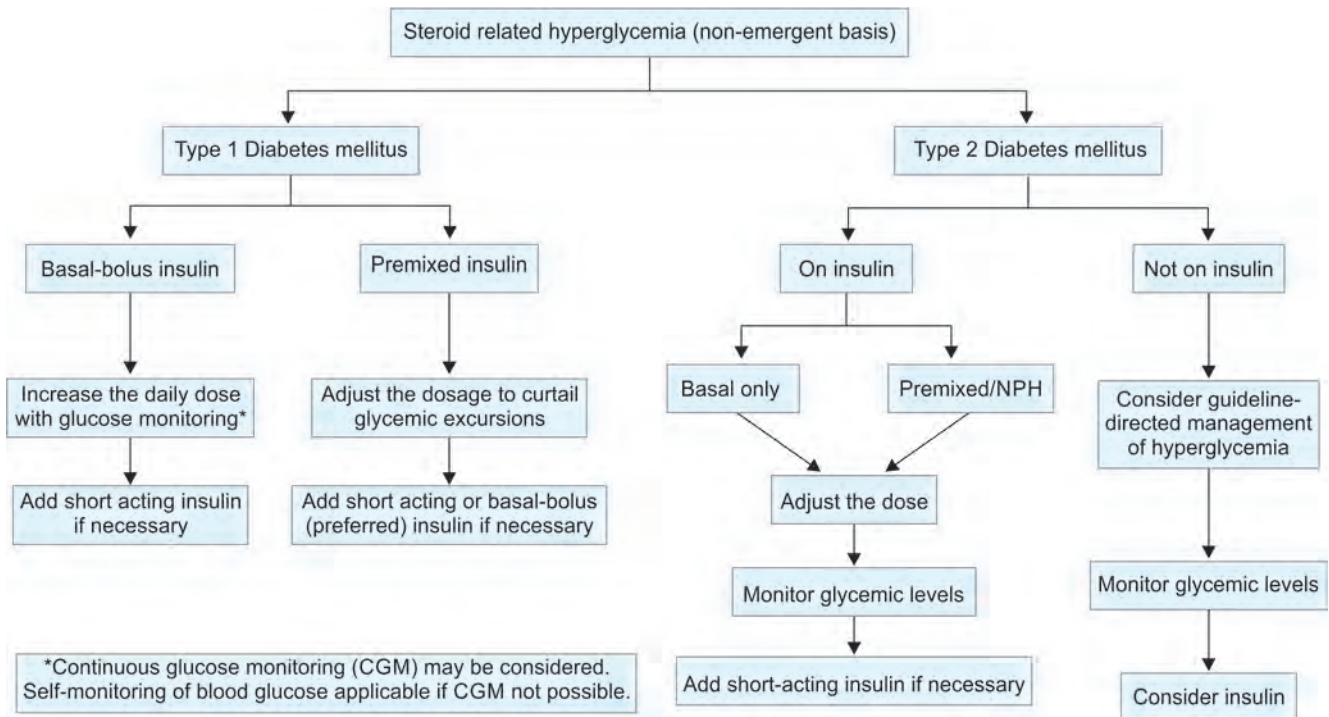


Fig. 4: Treatment approach to steroid-induced hyperglycemia in people with comorbid diabetes proposed by CWG

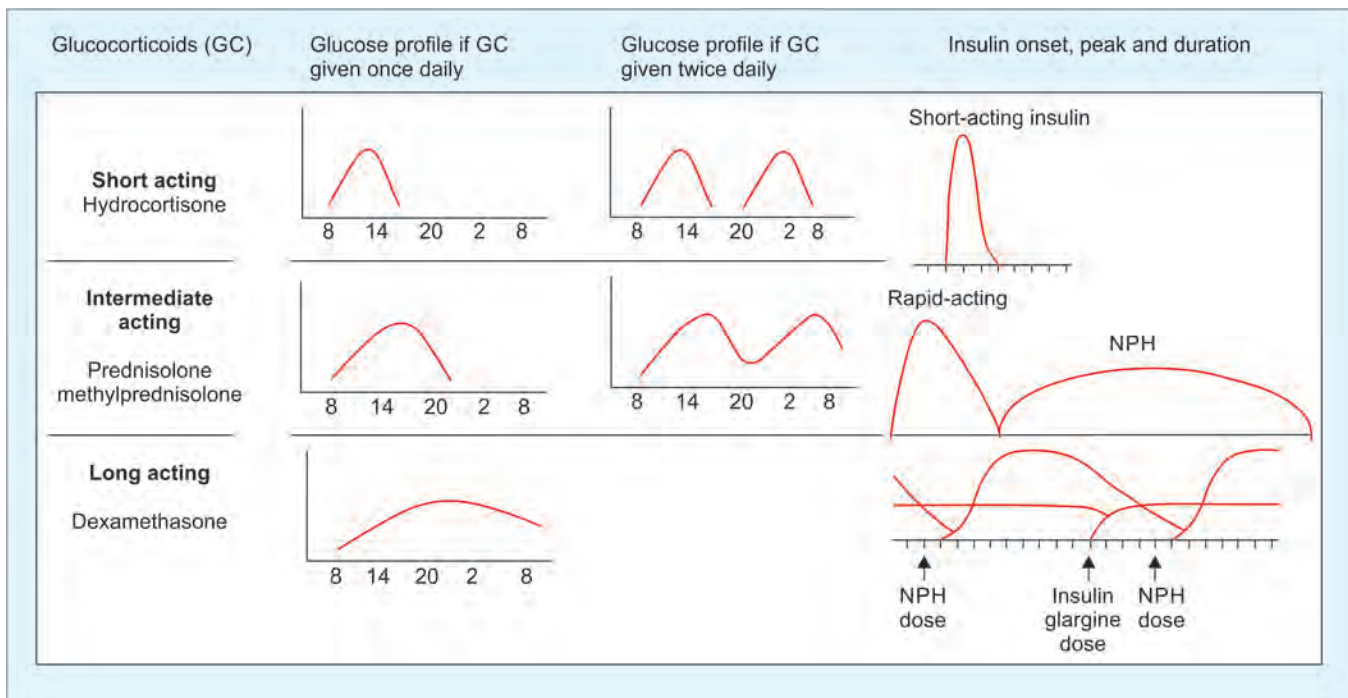


Fig. 5: Representative profile of hyperglycemic effect from steroids to matching profile of different insulins

weight loss in people with diabetes.¹⁰⁸ These agents can be preferred over other medications for patients using steroids who are at a greater risk of weight gain. However, it is notable to mention here that SGLT2i use carries a risk of DKA in insulinopenic patients.

Heart Failure

Among the antihyperglycemic drugs, SGLT2i and GLP-1RA have proven benefits

in CVD protection.^{109,110} The dipeptidyl peptidase-4 inhibitors (DPP4i) (e.g., sitagliptin, linagliptin) have shown CV safety. Saxagliptin and alogliptin have shown worsened HF outcomes.¹¹¹ Therefore, in cases where CVD risk is estimated to be higher, preference for individual classes of drugs should be considered. When using these medications, one needs to understand possible side effects. SGLT2i as a group may precipitate DKA,

especially in insulinopenic patients.¹¹² Reports indicate the precipitation of DKA in a patient with diabetes treated with dexamethasone.¹¹³ For HF, SGLT2i are first-line drugs whereas saxagliptin, alogliptin, and pioglitazone need to be avoided in HF patients.^{114,115}

Infections and Wound Healing

Stricter glycemic control, appropriate antibiotic cover, and adequate local wound

care are necessary to improve wound healing.

Acne

Acne may disappear after 2–6 weeks of stopping steroids.¹¹⁶ For the treatment of acne, a referral to a dermatologist should be sought.

Myopathy

Tests for muscle strength and quantitative tests to observe muscle loss can help diagnose myopathy. Besides glycemic control and reduction in steroid dose, aerobic and resistance exercises are recommended.⁶⁶ The protein intake is strongly related to skeletal muscle mass in older T2D patients. Essential amino acid supplementation helps improve muscle loss and increase muscle strength.^{117–119}

Osteoporosis

In patients who are at risk of bone loss, therapeutic considerations are essential. Vigorous walking combined with weight-bearing activity and moderate-intensity aerobic exercise are advised. Supplement steroid therapy with a Mediterranean-style diet, omega-3 fatty acids calcium, and vitamin D with monitoring of bone health to prevent osteoporosis and subsequent fracture risk. Bisphosphonates, teriparatide, and denosumab may be considered with substantial bone loss.⁷¹

Another important aspect is antihyperglycemic therapy. Thiazolidinedione independently increases the risk of osteoporosis and fractures.^{120,121} However, metformin, sitagliptin, and other DPP4i are neutral with effect on bone.^{122–124} Among SGLT2i, a meta-analysis finds no significant increase in the risk of fractures in comparison to placebo.¹²⁵ However, canagliflozin increases the risk of fractures. Incretin-based therapies are safer concerning the effect on bone.¹²⁴

Avascular Necrosis

Complaints of hip pain being referred to buttock, thigh, or knee, and shoulder pain

radiating around the axilla can be early signs of avascular necrosis in the hip or humerus. Avoiding high bolus doses can be one preventive strategy. Stopping the steroid, if possible, should be done.

Glaucoma

Thus, monitoring of IOP is necessary in all patients with DM taking systemic steroids. With discontinuation of steroids, IOP may regress to normal levels within 4 weeks. However, in nearly 3% of cases, the response may be irreversible.¹²⁶ A timely referral to an ophthalmologist should be considered.

- **Expert consensus:** The complexity brought on by steroids in people with diabetes is enormous and clinical decisions in patient management should be individualized.

STEROID EQUIVALENCE CONCEPT

Steroids are one of the most widely prescribed drugs globally and indications for their use are multifold. They differ in their relative anti-inflammatory and mineralocorticoid activities. The drug potencies of different steroids are indicated by their equivalent doses. The doses of different steroids are expressed as “prednisone equivalent” which means the dose of other steroids is as equally potent as the prednisolone dose.¹²⁷ Table 8 provides the dose equivalent potencies of different corticosteroids.^{89,90,128,129} Dose-to-dose conversion should consider the equivalent dose of different steroids. In defining the conventional dosing with different corticosteroids, one should consider following the dose approach.

- Low dose: ≤ 7.5 mg/day PEQ.
- Medium dose: > 7.5 to ≤ 30 mg/day PEQ.
- High dose: > 30 to ≤ 100 mg/day PEQ.
- Very high dose: > 100 mg/day PEQ.
- **Expert consensus:** The “steroid equivalence” should be considered in routine clinical

practice appropriately to avoid underdosing or overdosing when shifting from one steroid to another steroid.

Among the intermediately acting steroids, deflazacort (DFZ) is one effective and safe steroid that is used widely for various indications (Table 9). DFZ is an oxazoline derivative of prednisolone. After intake, DFZ is converted to an active metabolite DFZ-2I-hydroxide. The oral bioavailability of DFZ is nearly 68%. It is metabolized in the liver and is excreted via urinary ($\sim 2/3$ rd) and fecal ($\sim 1/3$ rd) routes.¹² DFZ has been studied in various indications in comparison to prednisolone and methylprednisolone (MP). Below is brief evidence from select clinical studies that bring the comparative efficacy and safety of DFZ and establish the concept of steroid equivalence.

Steroid Equivalence: Clinical Evidence

Clinical studies have identified the steroid equivalence and established the efficacy and safety of different steroids (Table 10).^{133–138} In a South Indian study involving 70 adult cases of active systemic lupus erythematosus (SLE) defined by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score of ≥ 3 , 35 each were treated with 1.2 mg/kg/day of DFZ or 1 mg/kg/day of prednisone (PDN). Dose tapering was done every 3 weeks over 3–6 months. The efficacy of DFZ was similar to PDN at 3 and 6 months based on changes in SLEDAI score, renal SLEDAI, anti-double stranded deoxyribonucleic acid (anti-dsDNA) titers, and C3 and C4 levels. However, at 6 months, safety parameters revealed that DFZ was safer than PDN in terms of absolute percent increment in Cushing's severity index (100 vs 200%), body weight (3.3 vs 8.4%), and hirsutism score (11 vs 33%). Overall, the total number of serious adverse effects was also significantly lower with DFZ (4.8 vs 9.4%). Effect on the fasting blood glucose (FBG)

Table 8: Dose to dose steroid equivalence of different corticosteroids

Steroids	Equivalent glucocorticoid dose	Anti-inflammatory potency relative to hydrocortisone	Mineralocorticoid activity relative to hydrocortisone
Short acting (biological $t_{1/2} < 12$ hours)			
Hydrocortisone	20 mg	1	1
Intermediate acting (biological $t_{1/2}$ 12–36 hours)			
Prednisolone	5 mg	4	0.8
Methylprednisolone	4 mg	5	0.5
Deflazacort	6 mg	3–4	0
Long acting (biological $t_{1/2} > 36$ hours)			
Dexamethasone	0.75 mg	30	0

For example, a 20 mg dose of hydrocortisone is glucocorticoid equivalent to 5 mg of prednisolone. Also, 5 mg prednisolone is equivalent to 4 mg of oral MP and 6 mg of DFZ. This means that an individual receiving 20 mg of PDN needs to be shifted to 24 mg of DFZ for similar efficacy

Table 9: Approved indications of DFZ from the United States, United Kingdom, and India

Regulatory authority (approval year)	Approved indications
United States (2017) ¹³⁰	Duchenne muscular dystrophy (DMD) in patients aged ≥ 5 years
United Kingdom (1994) ¹³¹	- Anaphylaxis, asthma, severe hypersensitivity reactions - Rheumatoid arthritis, juvenile chronic arthritis, polymyalgia rheumatica - SLE, dermatomyositis, mixed connective tissue disease (other than systemic sclerosis), polyarteritis nodosa, sarcoidosis - Pemphigus, bullous pemphigoid, pyoderma gangrenosum - Minimal change nephrotic syndrome, acute interstitial nephritis - Rheumatic carditis - Ulcerative colitis, Crohn's disease - Uveitis, optic neuritis - Autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura - Acute and lymphatic leukemia, malignant lymphoma, multiple myeloma - Immune suppression in transplantation
India (2004) ¹³²	Asthma, rheumatoid arthritis

Table 10: Efficacy and safety of DFZ to other steroids in steroid equivalent dose

Authors (year)	Study design	Population	Groups	Efficacy results	Safety results
Ganapati et al. (2018) ¹³³	Prospective, observational	SLE: Adults ≥ 18 years, SLEDAI ≥ 3	DFZ ($n = 35$) vs PDN ($n = 35$)	Assessment at 3 and 6 months No differences in: SLEDAI score Renal SLEDAI Serum dsDNA Serum C3 and C4 levels No differences in remission rates at 3 (51.6 vs 58.6%) and 6 (77.4 vs 86.2%) months	At 6 months Weight increase: 3.3 vs 8.4% ($p = 0.001$) Hirsutism score change: 11 vs 33% ($p = 0.002$) Cushing severity index change: 100 vs 200% ($p = 0.03$) Absolute change in: FPG: -5 vs $+9$ mg/dL TC: -12 vs $+17$ mg/dL LDL-C: -7 vs $+10.5$ mg/dL BMD LS: Overall AEs: 4.8 vs 9.4% ($p < 0.05$) Infection requiring hospitalization: 2 vs 0
Singhal et al. (2015) ¹³⁴	Randomized, prospective	Idiopathic nephrotic syndrome children (2–12 years)	DFZ ($n = 12$) vs PDN ($n = 13$)	Remission rates: 12 (100.0%) vs 11 (84.6%), $p = 0.480$ Time to induce remission: 10.25 ± 2.41 vs 12.55 ± 1.44 days, $p = 0.012$ Relapse: 1 (9.1%) vs 3 (27.3%), $p = 0.586$	Height change: 2.13 ± 0.50 vs 1.44 ± 0.45 cm, ($p = 0.0030$) Weight gain: 1.36 ± 0.96 vs 1.38 ± 0.56 kg ($p = 0.950$)
Lippuner et al. (1998) ¹³⁵	Randomized, double-blind	Renal transplantation	DFZ ($n = 8$) vs PDN ($n = 11$)	78-week f/u Rejection: 2 vs 3 No difference in: Serum creatinine Ionized calcium ALP Urinary deoxypyridinoline	At 78 weeks BMD Lumbar: Reduced significantly in PDN not in DFZ group ($p < 0.05$ intergroup) Upper femur: Significant reduction in both groups Whole body: Decreased significantly in PDN but not in DFZ group Body weight: 1.8 ± 1 ($p = 0.180$) vs 3.8 ± 2 ($p < 0.05$) kg Lean body mass: Decreased significantly in both groups Fat mass: 3.5 ± 1.4 vs 7.1 ± 1.8 Significant increase in TC ($p < 0.03$), LDL-C ($p < 0.01$), and LpB2 ($p < 0.03$) with PDN in comparison to DFZ TG: Increased in PDN and decreased in DFZ group No significant differences in HbA1c change

Contd...

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Authors (year)	Study design	Population	Groups	Efficacy results	Safety results
Kim et al. (1997) ¹³⁶	Randomized, prospective	Renal transplantation with either pre-Tx DM or post-Tx DM	Conversion from PDN to DFZ (conversion group, $n = 42$) vs continuation of PDN (control group, $n = 40$)	Mean follow-up: 13.2 months No significant difference in two groups for serum creatinine, required cyclosporin A dose No significant change graft function or acute rejection after conversion	Significant reduction HbA1c from pre-Tx to post-Tx: -1.7% ($p < 0.05$) vs 0.3% FBG from pre-Tx to post-Tx: 167 ± 68 to 119 ± 34 ($p = 0.009$) vs 153 ± 51 to 156 ± 63 , $p = 0.004$ (EOS comparison) Insulin Daily dose reduction $<50\%$: 12.8 vs 7.5% Daily dose reduction $\geq 50\%$: 15.4 vs 2.5% Insulin free, on OADs: 5.1 vs 2.5% Free of insulin or OADs: 10.3 vs 0 Absolute change in: Body weight: -1.74 vs -0.58 kg TC: -23.1 vs -2.9 mg/dL ($p = 0.04$) Severe infections requiring hospitalization: 12.8 vs 17.5%
Bruno et al. (1987) ¹³⁷	Randomized, double-blind	Insulin treated diabetics requiring steroid treatment	DFZ first f/b PDN ($n = 5$), PDN first f/b DFZ ($n = 5$)	–	After 4 weeks HbA1c (%) change: DFZ: 8.53 ± 1.3 to 8.81 ± 1.19 PDN: 8.53 ± 1.30 to 10.71 ± 1.17 ($p < 0.05$) Body weight (kg) change: DFZ: 75.3 ± 2.2 to 76.8 ± 1.3 PDN: 75.3 ± 2.2 to 74.3 ± 2.2 ($p < 0.01$) Insulin (U/day) requirement: DFZ: 28.5 ± 11.4 to 29.3 ± 11.6 PDN: 28.5 ± 11.4 to 46.3 ± 2.0 ($p < 0.001$)
Ferraris et al. (2007) ¹³⁸	Randomized, prospective	Renal transplantation, prepubertal patients	At mean of 2.1 years, switched to DFZ ($n = 15$) vs continued MP ($n = 16$)	3-year follow-up Rejection: 0 vs 1	Height velocity Significant increase with DFZ in 1st year Significant decrease with MP for 2 years Significant reduction in IGF-1 with MP but not DFZ Lean body mass increased in both groups, increase over time greater with DFZ Number of overweights: Increased significantly in MP (9 vs 1) TC: Significant increase in MP and decrease in DFZ HDL-C: Significant increase in DFZ but unchanged in MP LDL-C: Significant decrease in DFZ and significant increase in MP BMD: Significant decrease in lumbar spine and whole body BMD over 3 years in MP group, whereas decrease was seen in DFZ only at 3rd year Glucose/insulin ratio >7 : Significantly associated with DFZ at 2 and 3 years

OAD, oral anti-diabetic agent; EOS, end of study; ALP, alkaline phosphatase; AE, adverse event

(absolute change: -5 mg/dL in DFZ and 9 mg/dL in PDN groups), postprandial blood glucose (PPBG) (absolute change: 1 mg/dL in DFZ and 7 mg/dL in PDN groups), total cholesterol (TC) (absolute change: -12 mg/dL

in DFZ and 17 mg/dL in PDN groups), and LDL (absolute change: -7 mg/dL in DFZ group and 10.5 mg/dL in PDN groups) also indicated that DFZ is safer than PDN in terms of glycemic and lipid parameters.¹³³

Another Indian study in children (2–12 years) with idiopathic nephrotic syndrome who were treated with DFZ ($n = 12$) (2.4 mg/kg/day daily for 6 weeks followed by 1.8 mg/kg/alternate day for

6 weeks) or PDN ($n = 13$) (2.0 mg/kg/day daily for 6 weeks followed by 1.5 mg/kg/alternate day for 6 weeks). Time to induce remission, remission rate, and relapse rate were all similar in both groups with no significant differences. Change in weight and proportion of children who developed cushingoid features did not differ significantly in the two groups. However, the height gain was significantly lower in PDN than DFZ group (1.44 ± 0.45 vs 2.13 ± 0.50 cm) indicating possible growth retardation.¹³⁴

In a double-blind, randomized controlled trial from Switzerland, patients who underwent kidney transplants were randomized in a dose equivalent manner to PDN ($n = 11$) or DFZ 6 mg ($n = 8$) and were followed up over 78 weeks.

Rejection episodes occurred in three and two cases in PDN and DFZ groups, respectively. Whole body BMD declined significantly in the PDN group but not in the DFZ group. Lumbar BMD declined significantly in PDN than DFZ group (9.1 ± 1.8 vs $3.0 \pm 2.4\%$) with no difference for the loss of BMD in the hip. This data indicates that DFZ can help slow the decline rate of spinal and hip BMD.¹³⁵ Another study in kidney transplant patients assessed the impact of the shift from PDN to DFZ ($n = 42$) and continuation of PDN ($n = 40$) in the posttransplant period. Over a mean follow-up of 13 months, there were no episodes of rejection or graft dysfunction. In the conversion (DFZ) group, there was

a significant reduction in FBG levels (167 ± 68 to 119 ± 34) compared to the PDN group where levels remained elevated (153 ± 51 to 156 ± 63). A similar trend was evident in HbA1c which reduced significantly in the DFZ group (-1.7%) but not in the PDN group (-0.3%). The requirement for antihyperglycemic medication including insulin was reduced in the posttransplant period. About 10.3% of patients in the DFZ group were free of antihyperglycemic medications. The reduction in glycemia was also accompanied by a significant reduction in TC (-23.1 in DFZ vs -2.9 in the PDN group). Thus, conversion from PDN to DFZ in the posttransplant period is associated with improved glycemia and

Table 11: Key summary of expert consensus statements

Hyperglycemia and DKA:

In people with diabetes, the use of steroids causes hyperglycemia and may precipitate DKA in vulnerable populations

Weight gain:

In people with diabetes, weight gain is expected during steroid therapy and is directly related to the steroid dose and duration of the steroid therapy

Adrenal effects:

In people with diabetes, AI can occur with discontinuation of steroids. AI is not related to the dose or duration of steroids

In people with diabetes, iatrogenic Cushing's syndrome is a possibility that is directly proportional to steroid dose

Dyslipidemia, HTN, and CV risk:

In people with diabetes, steroids may cause or exacerbate HTN and dyslipidemia. The risk of CVDs is increased even at a PEQ dose of <5 mg/day

HF:

In people with diabetes, steroids may precipitate HF and thus consider the mineralocorticoid activity of steroids in such populations

Infections:

In people with diabetes, steroids may increase the risk of bacterial, viral, and fungal infections. Classical features of infections may not be evident in some of the patient populations. Further research is necessary to understand the risk of infections in such populations

Drug interactions:

In people with diabetes, steroids may have drug interactions with some antimicrobials and other medications. A watch for systemic toxicity of steroids is necessary with the concomitant use of certain medications

Wound healing:

In people with diabetes, steroids might delay wound healing. Caution is necessary in people with diabetes with preexisting foot ulcers

Acne:

In people with diabetes, steroids may increase the occurrence of acne, especially with higher dosages and in the presence of risk factors

Myopathy:

In people with diabetes, steroids may increase the risk of myopathy and it may occur early in the course with a higher dosage of steroids

Osteoporosis and bone fractures:

In people with diabetes, steroids increase the risk of osteoporosis even at a PEQ dose of 5 mg or more. Duration of steroids is associated with such risk of osteoporosis and related bone fractures

Avascular necrosis:

In people with diabetes, steroids may increase the occurrence of avascular necrosis of the femur and the risk is probably higher with a higher dose of steroids

Cataract and glaucoma:

In people with diabetes, steroids increase the risk of cataracts and the risk increases with the duration of their use

In people with diabetes, steroids may increase the risk of glaucoma

Complications monitoring:

In people with diabetes, specific monitoring approaches are essential for early detection and treatment of various complications

Complications management:

The complexity brought on by steroids in people with diabetes is enormous and clinical decisions in patient management should be individualized

Steroid equivalence:

The "steroid equivalence" should be considered in routine clinical practice appropriately to avoid underdosing or overdosing when shifting from one steroid to another steroid

Deflazacort is an effective and safe steroid with lesser risks of complications. Given its better safety, it can be considered one of the initial choices for people with diabetes requiring steroids

cholesterol levels.¹³⁶ Another randomized study in transplant recipients reported that after a follow-up of 2 years, there was a significant increase in lean body mass in the DFZ group than MP group. In lipid parameters, a significant increase in TC and LDL-C occurred in the MP group whereas they decreased significantly in the DFZ group.¹³⁸ In insulin-treated people with diabetes, the use of DFZ in PDN equivalent doses has significantly lower rise of HbA1c at 4 weeks compared to PDN. Insulin requirement was significantly lower in DFZ than PDN group (29.3 vs 47.3 U/day). Thus, for subjects with diabetes treated with insulin, DFZ is a wise choice when glycemic control is necessary.¹³⁷ These effects of DFZ in comparison to other steroids are due to its lower lipid solubility because of which the transport of active metabolite 21-desacetyl-DFZ across blood blood-brain barrier is limited leading to lesser HPA axis suppression.¹²⁹ Therefore, the steroid equivalence concept is very relevant clinically and can help choose appropriate doses of alternative steroids in clinical situations where it is necessary to shift to a safer steroid like DFZ.

- **Expert consensus:** Deflazacort is an effective and safe steroid with lesser risks of complications. Given its better safety, it can be considered one of the initial choices for people with diabetes requiring steroids.

CONCLUSION

Diabetes is a complex metabolic disorder with multisystem involvement. The comorbidities or intercurrent illnesses that require short-, intermediate-, or long-term use of steroids pose significant challenges in the clinical management of people with diabetes. The complications induced or aggravated by such steroid use may often be overlooked and become evident only when serious enough to attract the attention of the patient and physician. It is important on the part of treating physicians to be aware of likely possibilities with the use of steroids in people with diabetes. Besides the management of glycemia, a holistic approach considering all possible complications discussed in this paper is necessary to maintain the benefit-risk balance in favor of patients (Table 11). The concept of steroid equivalence needs to be rooted in the clinical practice to take appropriate steroids in a dose-equivalent manner to avoid underdosing or overdosing.

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Reevaluating Diagnosis of Sarcoidosis: Biopsy with Necrosis in Mycobacterial Endemic Areas



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ABSTRACT

Background: Sarcoidosis is a multisystem inflammatory disease with a variable presentation. The most characteristic feature of sarcoidosis is nonnecrotizing granulomas. However, when sarcoidosis presents with rare organ involvement, and biopsy shows necrosis, the diagnosis becomes challenging.

Case presentation: Here, we present three cases of sarcoidosis with unusual organ involvement and biopsy findings of necrosis, leading to a delay in diagnosis and treatment. Case 1 was presented with lymphoreticular involvement within the intraparotid lymph node and genitourinary area. Biopsy from the epididymis showed necrosis, initially leading to treatment for tuberculosis (TB). Case 2 describes lymphoreticular involvement and cardiac symptoms. His cervical and bone marrow biopsies showed necrosis. Case 3's presentation was disseminated lymphadenopathy with hepatosplenomegaly, initially suspected as malignancy or TB.

Conclusion: While biopsy plays a significant role in diagnosing sarcoidosis, the presence of necrosis alone should not lead to its exclusion.

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INTRODUCTION

Sarcoidosis is a multisystem inflammatory disease with variable presentation. The most common organ involved is the lung, and the presentation varies according to the type of organ involved.^{1,2} The most characteristic feature of sarcoidosis is nonnecrotizing granuloma. The diagnosis depends on compatible clinical characteristics, nonnecrotizing granulomas on biopsy samples of at least one organ involvement and excluding other causes.³

Occasionally, sarcoidosis can present with rare organ involvement, making it difficult to diagnose. Moreover, if it involves necrotizing granulomas, it is, again, tricky to diagnose.⁴ In mycobacterial endemic regions, differentiating it from tuberculosis (TB) is practically impossible. Table 1 outlines key

points to differentiate between sarcoidosis and tuberculosis. Here, we are presenting three cases of sarcoidosis with rare organ involvement and necrotic granulomas, which delayed the diagnosis and, hence, treatment.

CASE 1

A 35-year-old gentleman presented with cough and mucoid expectoration, polyarthralgia of large joints for 2 years, and a holocranial dull, aching type of headache for the last 10 days. He did not have hemoptysis, breathlessness, fever, chest pain, loss of appetite, or weight loss. Around 2 years ago, when he experienced these symptoms, he was suspected to have either disseminated TB or sarcoidosis. He was started on anti-TB treatment (ATT). Initially, he showed some

improvement. After 3 months (in July 2018), during reevaluation, the cough was persisting. After 8 months on ATT, he developed a palpable swelling of the epididymis, for which a biopsy was performed, showing necrotizing granulomatous inflammation. Hence, ATT was continued. After 11 months, ATT was stopped. At this point in time, he was found to have two cervical lymph nodes on the left side, each measuring 2 × 2 cm, nontender, and nonmatted, as well as right diffuse scrotal swelling. On evaluation, his hemoglobin was 13 gm/dL, erythrocyte sedimentation rate (ESR) was 48 mm, and C-reactive protein (CRP) was 8 mg/L. His renal function was within the normal limit, but liver function showed raised alkaline phosphatase (330 U/L). He had hypercalcemia (12.66 mg%) with an elevated angiotensin-converting enzyme (ACE) level (150 U/L; normal 20–70 U/L). The tuberculin skin test was negative. Computed tomography (CT) of the thorax and abdomen were obtained, which showed mediastinal and abdominal necrotic lymphadenopathy and splenomegaly. The epididymis was thickened. On scrotal ultrasound, a right epididymal cyst was detected. Magnetic resonance imaging of the brain with contrast showed an enlarged intraparotid lymph node. Xpert TB polymerase chain reaction (PCR) from sputum, lymph nodes, and epididymis biopsy were negative. Considering all investigations, clinical features, and inadequate response to ATT treatment, a diagnosis of sarcoidosis with multisystem involvement (pulmonary, lymphadenopathy, splenomegaly, hepatomegaly, genitourinary tract, and hypercalcemia) was made. His electrocardiogram (ECG) and Holter were

Table 1: Differentiating features of sarcoidosis and tuberculosis

Favor sarcoidosis	Favor tuberculosis
Histopathology	
Noncaseating granulomas	Caseating granulomas
Schaumann bodies and asteroid bodies	Mycobacterial stain
Liver: granuloma in mostly portal areas	Granuloma seen in both portal and lobular
Lung: subpleural and around bronchovascular location and along the lymphatic route	It can be seen anywhere
Extrapulmonary involvement of eye and skin	Hemoptysis
Radiology	
Galaxy sign: micronodules in the periphery coalescing into consolidated mass	Cavitation
Perilymphatic distribution of nodules	Tree in bud

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normal. Hypercalcemia was treated with aggressive hydration and calcitonin nasal spray. Due to disseminated involvement, he was treated with 1 mg/kg of prednisolone. After the initiation of steroids, his headache improved. On follow-up, his cough, cervical lymphadenopathy, and scrotal swelling resolved. ACE level decreased to 25 U/L. CT thorax and abdomen showed resolution of splenomegaly and lung findings with a significant reduction in lymphadenopathy (Fig. 1). After stopping steroids at 3 months, his lung nodules increased with a raised ACE level of 52 U/L. The patient was started on steroids and methotrexate due to the relapse of the disease upon stopping steroids. After stopping steroids and using methotrexate, the patient was in remission at the end of a 4-year follow-up.

CASE 2

A 70-year-old gentleman came to us with a loss of appetite for 6 months, a dry cough, and weight loss. There was no history of fever or recent contact with TB.

A total of 14 years ago, he had a history of uveitis, which was treated with oral drugs (details of which were not available). For these above symptoms, he was started on ATT, after which his cough, weight, and appetite initially improved. He completed 6 months of ATT. On evaluation, his serum calcium was 12 mg%. His ESR was 32 mm, CRP 7.2 mg/L, and ACE level was 112 U/L. His positron emission tomography (PET) scan suggested metabolically active right hilar lymph nodes with patchy uptake in the liver and spleen. A cervical lymph node biopsy showed granulomatous inflammation with a negative acid-fast stain. Bone marrow biopsy showed granulomatous inflammation with foci of necrosis. Xpert TB PCR from sputum, lymph nodes, and bone marrow biopsy

was negative. He was started on 1 mg/kg of steroids. After starting steroids, his cough improved, and his calcium levels decreased from 12 to 8 mg% in 1 month. To assess cardiac involvement, he underwent an ECG and Holter monitoring. His Holter monitoring suggested intermittent high-grade A-V block, leading to permanent pacemaker implantation.

CASE 3

A 35-year-old lady presented with a history of high-grade intermittent fever without chills and rigor. She had abdominal pain, which was a dull, aching, diffuse type with no other associated symptoms. She also experienced a weight loss of 12 kg in 4 months. On examination, she was febrile, and other general, musculoskeletal, and systemic examinations were normal. Her blood counts, liver function, renal function, inflammatory markers, and blood cultures were negative. Alkaline phosphatase levels were 1069, and ACE levels were 128. An ultrasound scan showed multiple abdominal lymphadenopathy with hepatosplenomegaly, and the fine needle aspiration cytology (FNAC) report suggested malignancy. For confirmation, she was referred to our center. The PET scan showed increased uptake in the mediastinum,

abdomen, and pelvis. The liver and spleen were enlarged with multiple discrete confluent hypodense lesions. An ultrasound-guided biopsy was performed on liver lesions, which suggested granulomatous inflammation with necrosis and fibrosis, raising the possibility of sarcoidosis or TB (Fig. 2). Malignancy was ruled out based on the biopsy results. Her alkaline phosphatase remained high at 1069 U/L (normal range: 40–125 U/L), while her serum calcium was normal. She was started on ATT, which she continued for 3 months. However, her fever did not improve on ATT, so she was referred to our department. Since malignancy had already been ruled out, and she had been on an ATT trial for TB, she was started on 0.5 mg/kg prednisolone (30 mg per day) and methotrexate. Her fever responded to the steroid treatment. Her ACE level decreased from 128 to 73, and her alkaline phosphatase decreased from 1069 to 279 U/L. ATT was stopped, and she was diagnosed with sarcoidosis.

DISCUSSION

The presentation of these three patients was highly suggestive of sarcoidosis; however, there was a delay in diagnosis and treatment due to the involvement of rare

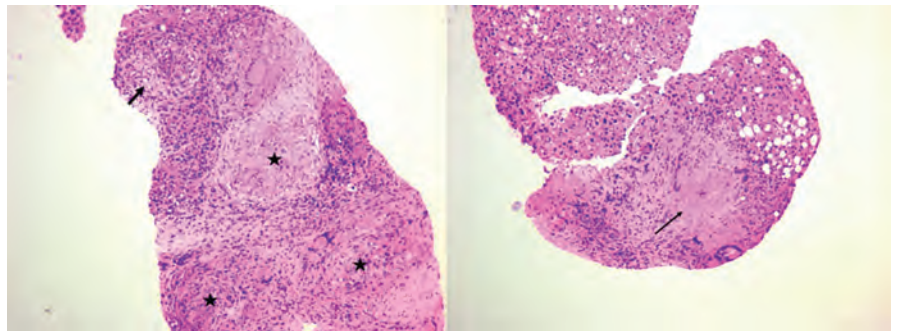


Fig. 2: Liver core biopsy with portal-based (star) and lobular-based (arrow) epithelioid granulomas with the central area of necrosis (arrow) (hematoxylin and eosin staining; 100× magnification)

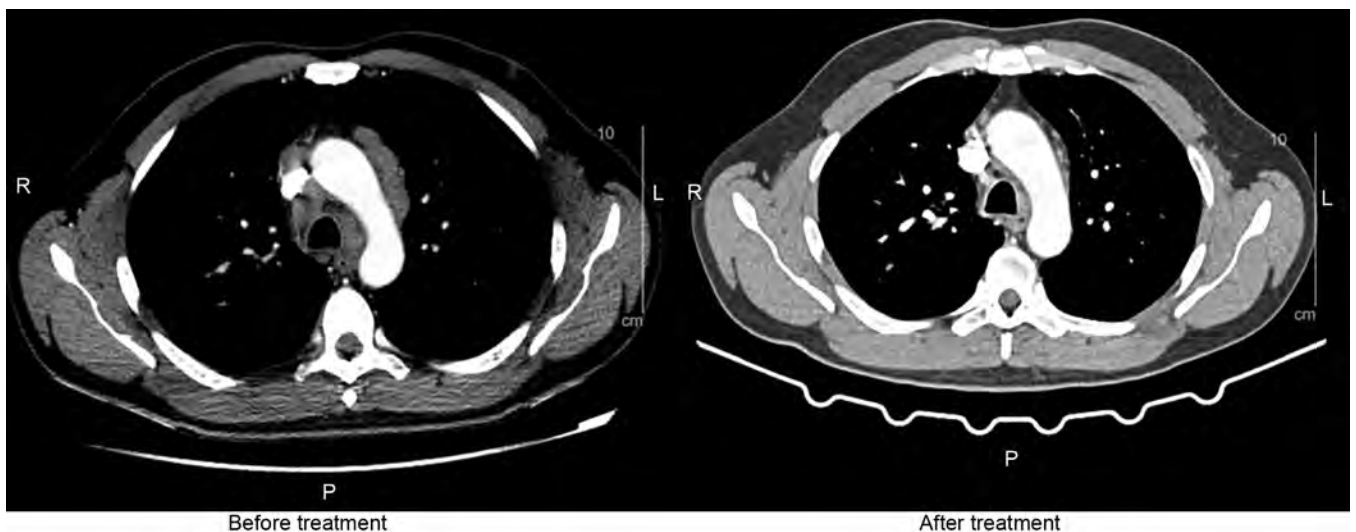


Fig. 1: Computed tomography (CT) of the chest showing resolution of lymphadenopathy on treatment

organs. The first case exhibited epididymal involvement, the second case had bone marrow involvement, and the third case presented with hepatosplenomegaly along with extensive lymphadenopathy. In the third case, it was crucial to consider malignancy as well as infection during the diagnostic process. The presence of necrosis in all three cases further complicated the diagnostic challenge.

In the diagnosis of sarcoidosis, in addition to the clinical presentation, the presence of compact, epithelioid, nonnecrotizing granulomas with lymphocytic infiltration is a diagnostic feature.⁵ In sarcoidosis, nonnecrotizing and noncaseating granulomas are characteristic. However, necrotizing granulomas have been reported in 6–35% of cases of sarcoidosis. In sarcoidosis, necrosis is associated with intact reticulin.⁵ In sarcoidosis, hepatic granulomas are characterized by scattered nonnecrotizing granulomas in portal spaces.⁶ Calcitriol and hypercalcemia due to calcitriol-related increased gastrointestinal absorption, as well as high immunoglobulin G levels, can serve as surrogate markers for diagnosis. However, these markers have limited diagnostic accuracy. Several factors can contribute to the diagnosis with certain limitations: (1) sarcoidosis can exhibit a partial response to ATT due to its anti-inflammatory properties; (2) elevated serum calcium levels can be observed in 25% of patients with TB⁶; (3) serum ACE levels can be elevated in various diseases, including TB, and are raised in only 60% of sarcoidosis patients. Elevated ACE levels can serve as a prognostic indicator, reflecting granuloma burden.⁷ Typical biopsy findings in sarcoidosis are well-formed and

discrete nonnecrotizing granulomas in a lymphangitic distribution. Nonnecrotizing granulomas are often indicative of sarcoidosis and can aid in diagnosis. It is important to rule out other causes of nonnecrotizing granulomas, such as infectious granulomatous diseases, chronic beryllium disease, and foreign body granulomas (e.g., talc).⁶ The presence of dense granulomas can mask malignancy, requiring specific staining (pan-cytokeratin stain). Diagnosis becomes particularly challenging when the granuloma in sarcoidosis is associated with necrosis (up to 35%).⁷

This less common variant of sarcoidosis characterized by prominent necrosis and vasculitis is known as necrotizing sarcoid granulomatosis (NSG). First described by Liebow in 1973,⁸ NSG exhibits pathological features that can be difficult to differentiate from TB, resulting in underreporting and delayed diagnosis.⁹ In cases where there is no microbiological isolation or a lack of response to TB treatment for disseminated disease and/or rare sites of involvement, NSG should be considered a potential differential diagnosis.⁹ NSG responds well to steroid treatment. Extrapulmonary sites are most affected, and serum ACE levels are typically within the normal range for NSG.¹⁰ Due to its unique pathological features and presentation, this entity is frequently underdiagnosed, particularly in areas with a high prevalence of TB. In our three cases, necrosis was not extensive, so we have not labeled it as NSG.

In conclusion, while biopsy plays a significant role in diagnosing sarcoidosis, the presence of necrosis alone should not lead to

its exclusion. A thorough consideration of the clinical presentation and lack of response to ATT is essential to contemplate the potential diagnosis of sarcoidosis.

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Podophyllin Toxicity: Case Report of a Rare Poisoning

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ABSTRACT

Podophyllin poisoning is a rare but serious emergency, often fatal, that involves multiple systems, predominantly the nervous system. Usually, it results from the resin extract derived from certain plants, and podophyllotoxin is the most toxic chemical present in it. The toxicity mechanisms involve suppression of cellular nucleoside transport and microtubule disruption. Due to the delayed onset of symptoms, there can be a delay in diagnosing and treating the condition. In addition, the initial and dominant central nervous system (CNS) symptoms can be mistaken for CNS infection or brainstem stroke. Therefore, early diagnosis (based on a high degree of suspicion, and circumstantial evidence) and prompt treatment (primarily decontamination and supportive care) are crucial to prevent unfavorable outcomes. We present a rare case of a 23-year-old male who accidentally ingested podophyllin and initially experienced severe neurological symptoms, subsequently developing into multisystem involvement and culminating in death within 4 days of its ingestion.

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INTRODUCTION

Podophyllin poisoning is a rare but critical condition with systemic involvement. It initially and primarily affects the nervous system, but ultimately, multiple organs such as the gastrointestinal, cardiovascular, and hematological systems are also significantly involved.¹⁻³ It may have a fatal outcome¹ (as in our case), and in patients that survive, it can lead to the sequelae of peripheral neuropathy in a great number of cases.^{2,4-6}

The toxic substance in podophyllin is the resin extract derived from the rhizomes and roots of certain plants² (with umbrella-shaped leaves); some examples of these plants include North American *Podophyllum peltatum* (mayapple or mandrake), Indian species *Paeonia emodi*, Taiwanese *Podophyllum pleianthum*, in which all parts of the plant except ripe fruit are toxic. Toxicity can occur through oral administration,^{1,2} injection, topical application⁴ (especially on broken skin), or as part of herbal medication.⁵ The resin has 16 chemicals with podophyllotoxin (a lipid-soluble compound that readily crosses cell membrane) being the chief toxic culprit.^{1,2} The mechanism of toxicity involves suppression of cellular nucleoside transport, as well as the disruption of microtubule structure and function, similar to colchicine.^{7,8} Its predominant effect on the nervous system results from microtubule dysfunction, affecting axoplasmic flow, and reducing cellular respiration through cytochrome oxidase and succinoxidase activity.^{1,8,9} Historically, podophyllin was used to treat health conditions like syphilis, scrofula, warts,

and cancer, but its cathartic property and potential toxicity were noted earlier in 1890 when the first fatality was registered.¹⁰ The fatal dose of podophyllin resin in humans is 0.3–0.6 gm, (equivalent to half a teaspoonful of commercially available 20–25% podophyllin resin in benzoin tincture).^{1,2,9} We report a case of a 23-year-old male who experienced severe systemic toxicity and ultimately succumbed to the illness after accidentally ingesting podophyllin.

CASE DESCRIPTION

A 23-year-old male presented to the emergency department in a delirious state, approximately 7 hours after accidentally ingesting around 10 mL of commercially available 20% podophyllin resin paint. There was no previous history of any psychiatric illness, head trauma, alcohol abuse, fever, or other toxin exposure. He experienced severe vomiting and excessive salivation within an hour of ingestion; followed by agitation, restlessness, aggressive behavior, and ataxia. Upon arrival at the hospital, he was delirious, with a Glasgow Coma Scale (GCS) of E3V3M5, temperature of 102°F, a heart rate of 140/minute (sinus tachycardia), systolic blood pressure of 70 mm Hg, respiratory rate of 50 deep breaths per minute, and saturation of 90%. His pupils were bilaterally miotic (pinhead size, symmetrical), and his oculocephalic reflex showed delayed cortical correction, with a latency of a few seconds. Quadriplegia with absent deep tendon reflexes and mute plantar reflexes were observed. We contacted

the National Poisons Information Centre, All India Institute of Medical Sciences, New Delhi, India for guidance in management. He received oxygen through a venturi mask, intravenous (IV) antibiotics, hydrotherapy for fever, inotropes, gastric lavage, and activated charcoal. Blood investigations showed leukocytosis (24,000 cells/ μ L), elevated liver enzymes (aspartate aminotransferase at 158 IU/L), hypokalemia (sodium at 140 meq/L and potassium at 2.8 meq/L), and deranged PT-INR (1.86). An arterial blood gas analysis revealed high anion gap metabolic acidosis (AG at 20 meq/L) due to lactic acidosis (lactate at 5 mmol/L) with respiratory compensation (pH at 7.3, HCO_3^- at 10 mmol/L, PaCO_2 at 17 mm Hg, PaO_2 at 71 mm Hg, FiO_2 at 60% on O_2 at 15L/minute via venturi mask. Chest X-ray was normal. Initial noncontrast computed tomography (NCCT) head (Fig. 1) and cerebrospinal fluid reports were normal. He received IV fluids with potassium supplementation. However, his condition worsened, requiring intubation and mechanical ventilation. The next day, the patient had a medial deviation of the left eye with a GCS of E1VTM1 and the patient was persistently hypotensive needing inotropic support. A total leukocyte count of 2,400 cells/ μ L (leukopenia) and platelet count of 24,000 cells/ μ L were seen. Peripheral smear showed vacuolated blood cells. Severe metabolic acidosis was present (pH at 7.1, HCO_3^- at 12 mmol/L, PaCO_2 at 17 mm Hg, PaO_2 at 79 mm Hg). He was also given a sodium bicarbonate infusion. A repeat NCCT scan of the head which was possible on 3rd day revealed hemorrhage in the right frontal and temporal lobes (Fig. 2). Platelet transfusion was also done, but his condition

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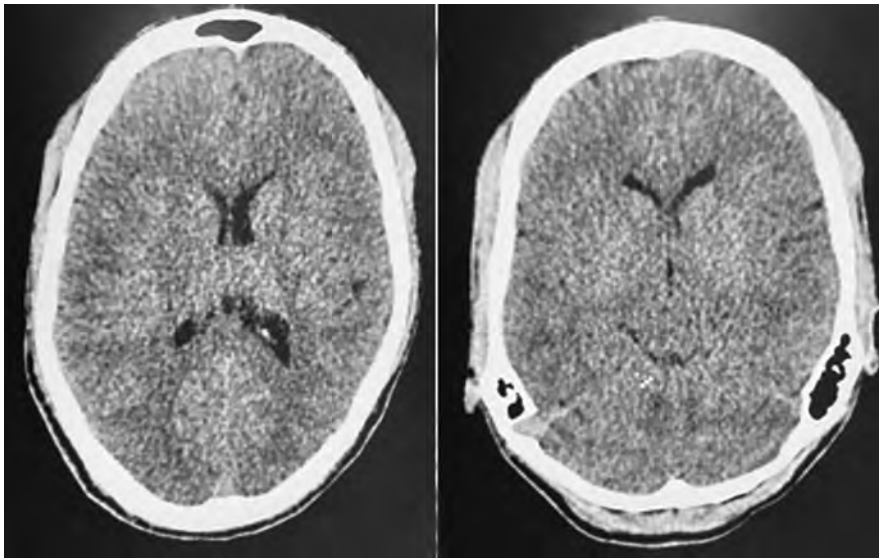


Fig. 1: Initial NCCT head (normal)

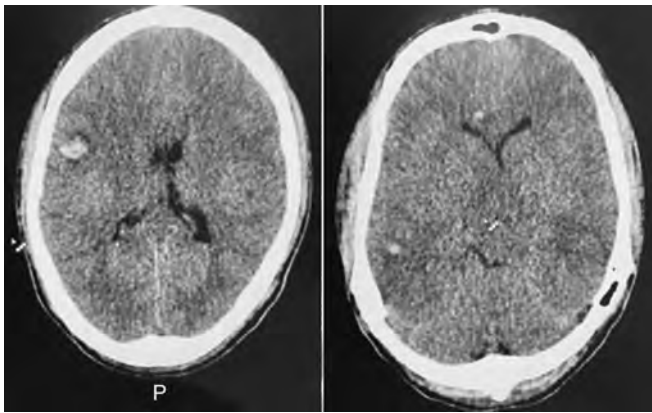


Fig. 2: Repeat NCCT head showing intraparenchymal bleed in the right frontal and temporal lobes

remained critical and he went into cardiac arrest in the early morning of the 4th day and unfortunately succumbed to the illness despite all resuscitative measures.

DISCUSSION

Podophyllin is primarily used topically to treat common warts and genital warts. Its active ingredient, podophyllotoxin,^{1,9} is believed to be responsible for its therapeutic effects. Podophyllin's constituents have diverse cellular actions, including suppression of cellular nucleoside transport, reduction of cytochrome oxidase and succinoxidase activity, and interference with microtubule structure and function.⁷⁻⁹ Podophyllotoxin has colchicine-like effects and acts by attaching to tubulin subunits and disrupting microtubule structure as well as function.^{8,9}

In our case, podophyllin toxicity manifested with multiple system involvement, chiefly nervous system, hematological, cardiovascular, and hepatic manifestations. Nervous system involvement with podophyllin toxicity is usually both central and peripheral.^{2,9} This

was also evident in our case in the form of loss of consciousness, cranial nerve involvement, and quadriplegia with loss of deep tendon reflexes. Central nervous system (CNS) toxicity may show recovery within 10 days of exposure, whereas peripheral neuropathy may take several months to recover.⁹ Hematologic manifestations may include leukocytosis initially (noted in our patient as well), followed by leukopenia, thrombocytopenia, and even pancytopenia.^{1,9} Thrombocytopenia in this patient was accompanied by normal mean platelet volume—12.1 fL, normal platelet distribution width, and a high platelet-large cell ratio—50%, with the platelet histogram not touching the baseline (Fig. 3); all features suggesting peripheral platelet destruction combined with bone marrow suppression. Platelet destruction is scantily reported in the literature.² Peripheral smear showed vacuolated cells, which is also rarely reported.¹¹ Podophyllin exposure during pregnancy may also have teratogenic effects.⁴

In our case, a male patient, without any underlying health conditions, presented with

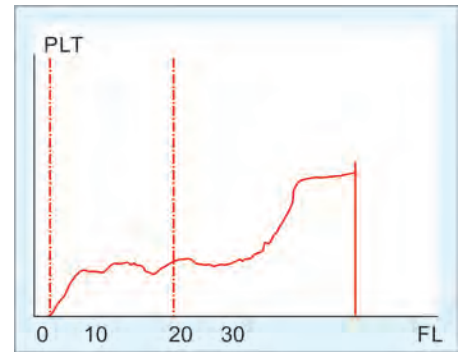


Fig. 3: Platelet histogram of our patient

fever and pinhead-sized pupils. Although he presented with febrile encephalopathy, the prompt consideration of the drug toxicity and the valuable history provided by the patient's guardian played a crucial role in reaching a diagnosis. Moreover, the initial normal computed tomography head scan proved to be highly valuable in ruling out brain hemorrhage and other causes as the primary cause of encephalopathy.

Treatment is primarily decontamination (orogastric lavage with activated charcoal), symptomatic and supportive measures as no specific antidote is available.¹² Topically applied resin should be removed and the area should be cleaned. Extracorporeal elimination techniques (resin and charcoal hemoperfusion) have been used but are of uncertain efficacy.^{2,13} Ingestion of a high amount (roughly 2 gm, exceeding the lethal threshold) of podophyllin resin and a significant delay in seeking medical attention might have accounted for the fatal outcome in our case. However, literature also records variable outcomes, irrespective of the dose ingested. For example, a 60-year-old lady passed away after ingesting a small dose of 325 mg¹⁰ whereas a 25-year-old lady survived even after taking a huge amount (2.8 gm), but with neurological sequelae.³

Our main aim in reporting this case is to create general awareness for healthcare professionals and thereby to patients and caregivers about this highly toxic drug. Local application should be limited to a place, avoiding raw areas. It is pertinent to instruct patients to keep it in a safe place. Centers for Disease Control and Prevention has issued specific instructions to refrain from using this drug and to explore alternative treatment methods for anogenital warts.¹⁴ In particular settings, it should be considered as a differential diagnosis of febrile encephalopathy or brainstem bleeding.

ETHICAL APPROVAL

Informed consent for the publication of this case report was obtained from the wife of the patient.

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Primary Duodenal Aspergillosis in Poorly Controlled Diabetes: A Rare Entity

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ABSTRACT

Aspergillosis mostly involves the lung and sinuses in severely immunocompromised patients like those with hematological malignancies, postorgan transplants, acquired immunodeficiency syndrome (AIDS), and secondary to chemotherapeutic agents. Duodenal aspergillosis is very rare and mostly occurs as a part of disseminated disease or in classical immunosuppressive conditions. We report a middle-aged female with uncontrolled diabetes who presented to us with epigastric pain and was finally diagnosed as a case of primary duodenal aspergillosis. Diabetes mellitus should also be kept as one of the predisposing conditions for it, and a high index of suspicion should be kept for it to reduce morbidity and mortality.

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INTRODUCTION

Aspergillus spores are ubiquitous environmental molds that mostly colonize the airways, nose, and facial sinuses and cause sinopulmonary infection. Invasive aspergillosis (IA) involves the lung in 90–98% of cases.¹ Extrapulmonary aspergillosis is very rare and occurs in severely immunocompromised states as a part of disseminated infection and can involve the brain, skin, eyes, and the gastrointestinal system. We report a case of primary duodenal aspergillosis (PDA) without classical immunosuppressive conditions, which is very rare and rarely reported.

CASE DESCRIPTION

A 56-year-old female presented with pain in the abdomen for 1 month, which was epigastric in location, intermittent with no radiation, more in the fasting state, and reduced after meals. She was on oral proton pump inhibitors for 15 days without any relief. There was no history suggestive of usage of any painkillers. It was not associated with nausea, vomiting, change in bowel habits, gastrointestinal bleed, loss of weight, fever, chest pain, cough, sputum, or shortness of breath. There was no similar history in the past or in the family. She was a known diabetic for 10 years on oral hypoglycemic agents. Her menstrual and obstetric history was normal. On examination, her body mass index was 27.2 kg/m². Her general and systemic examination was unremarkable. Her routine blood investigation, including complete blood counts, renal function test, and liver function test, were normal except for raised blood sugars. Her fasting blood sugar was 224 mg/dL, postprandial blood sugar

was 520 mg/dL, and glycated hemoglobin (HbA1c) was 9.4%. She was nonreactive for human immunodeficiency virus (HIV) and hepatitis B. Her ultrasonography of the abdomen and X-ray chest was also normal. Then her upper gastrointestinal endoscopy was done, which showed a large oval to circular ulcer with blackish discoloration at its base in the first part of duodenum (Fig. 1). Multiple biopsies were taken from its edge to know its etiology and were sent for histopathological examination. Hematoxylin and eosin-stained sections from duodenal ulcer revealed acute inflammatory exudate with areas of necrosis and shadows of fungal elements (Fig. 2). Grocott's methenamine silver stain demonstrated the presence of fungal spores and filaments with acute angle branching deep into the lamina propria suggestive of aspergillosis (Fig. 3). Giemsa staining for *Helicobacter pylori* was negative. Then her upper gastrointestinal endoscopy was repeated, and a fresh biopsy sample was sent for culture, which confirmed the

presence of *Aspergillus niger*. So, she was started on oral voriconazole 400 mg twice a day on the first day followed by 200 mg twice a day for 6 weeks along with strict diabetic control. Her pain vanished after 2 weeks of therapy, and a repeat upper gastrointestinal

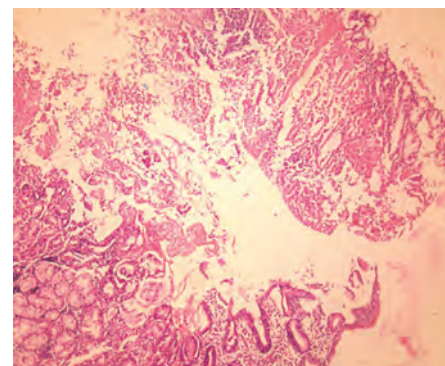


Fig. 2: Hematoxylin and eosin staining showing duodenal ulcer with acute inflammatory exudate and areas of necrosis

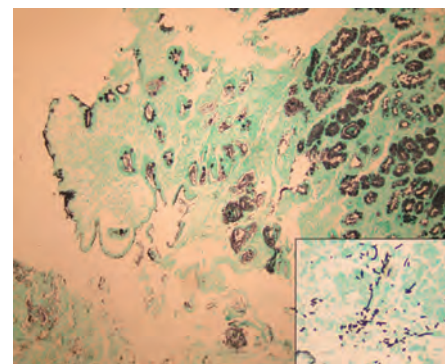


Fig. 3: Silver methenamine staining demonstrated the presence of fungal spores and filaments with acute angle branching suggestive of aspergillosis

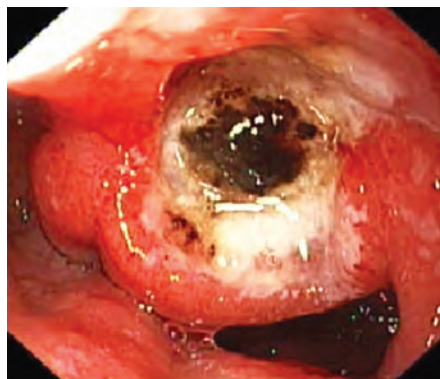


Fig. 1: Upper gastrointestinal endoscopy image showing a large duodenal ulcer with blackish discoloration

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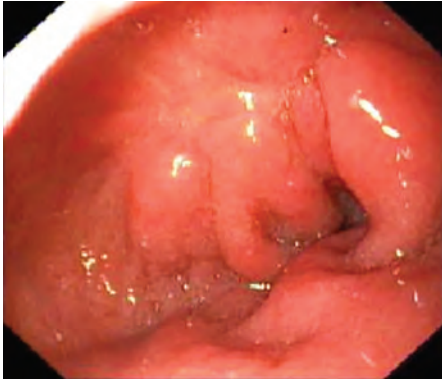


Fig. 4: Upper gastrointestinal endoscopy after 6 weeks of antifungal therapy showing complete healing of the ulcer

endoscopy after 6 weeks showed complete healing of the ulcer (Fig. 4).

DISCUSSION

Aspergillus is a saprophytic mold that is ubiquitous in the environment. *Aspergillus* spores are usually acquired by inhalation of environmental molds that cause infection in the lungs and sinuses, but these spores can also be ingested, which can cause primary gastrointestinal aspergillosis.² The most common species responsible for the majority of infections are *Aspergillus fumigatus*, followed by *Aspergillus flavus*, *Aspergillus terreus*, and *A. niger*. It involves the lung in the majority of cases (90–98%). Gastrointestinal aspergillosis is very rare and mostly occurs secondary to pulmonary aspergillosis as a part of disseminated disease. Chakrabarti et al. reviewed IA in developing countries and did not find any case of primary gastrointestinal aspergillosis.³ IA mostly occurred in severely immunocompromised states like acquired immunodeficiency syndrome (AIDS), hematological malignancies,

secondary to chemotherapeutic agents, and after hematopoietic and solid organ transplantation.¹ Besides these classical immunosuppressive states, IA has also been reported with new predisposing conditions such as liver failure, chronic obstructive pulmonary disease, diabetes, and tuberculosis.³

Aspergillus is an invasive fungus that causes tissue necrosis due to vascular invasion. Once colonized, it can penetrate the mucosa in susceptible host. Its angiotropic properties enable it to penetrate the vascular wall, proliferate in vascular lumen, causing thrombosis and infarcts leading to necrosis and perforation.⁴

Duodenal aspergillosis is extremely rare and mostly occurs as a part of disseminated disease and in severely immunocompromised state. Kazan et al., in a large multicenter retrospective review of gut aspergillosis in hematological disease patients, showed duodenal aspergillosis in only four cases over a period of 13 years.⁵ PDA is very rare, with only a few case reports in the literature. However, very rarely, it can occur in conditions like poorly controlled diabetes mellitus and cirrhosis of the liver as in our case.⁶ *A. niger* is a very rare cause of aspergillosis, and to the best of our knowledge, it has not been reported in PDA. The blackish discoloration of duodenal ulcer was probably due to black conidia of it. To the best of our knowledge, there is no such case reported till date in the literature from tropical countries.

Clinical and radiological features of duodenal aspergillosis are nonspecific, and the diagnosis is mostly done by histopathology and culture. IA is diagnosed by histopathological evidence of septate hyphae with acute dichotomous branching with tissue destruction.² It can then be further confirmed by growing *aspergillus* in culture. Serological

markers of *aspergillus* like galactomannan are nonspecific for gastrointestinal aspergillosis.⁷ Due to its nonspecific presentation, its diagnosis is often delayed, which leads to complications such as intestinal obstruction and perforation, and its final diagnosis is made in surgical specimens or at autopsy.

Voriconazole is the drug of choice for gastrointestinal aspergillosis. Its dose in adult patients weighing >40 kg is 400 mg twice daily on day 1 followed by 200 mg twice daily for 6–12 weeks.⁸

To conclude, we report a case of PDA due to *A. niger* in a middle-aged female with uncontrolled diabetes and without any classical immunosuppressive conditions. To the best of our knowledge, such a case has not been reported from any tropical countries till date. A high index of suspicion should be kept for PDA in diabetic patients with duodenal ulcers as delay in diagnosis can lead to increased morbidity and mortality.

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Dermatological Conundrum: Puzzling Pigmentation in Vitamin B₁₂ Deficiency and Addison's Disease



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ABSTRACT

We report a case series of two patients who had similar skin pigmentation but were caused by vitamin B₁₂ deficiency and Addison's disease. We further discuss the pathophysiology of skin hyperpigmentation in both of these disorders and the response to treatment. Our case report highlights the importance of the identification of simple bedside clinical signs to diagnose reversible causes of skin pigmentation.

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INTRODUCTION

Differential diagnosis of skin pigmentation remains a clinical dilemma. Irrespective of similar brown-black pigmentation of fingers, toes, and knuckles seen in two different cases with different clinical and biological diseases include hematology and endocrinology, respectively. Vitamin B₁₂ deficiency was identified as a health concern nearly 100 years ago. Vitamin B₁₂ deficiency is a common condition that can present with nonspecific clinical features and neurological and hematological abnormalities. Megaloblastic anemia, a nutritional deficiency either due to B₁₂ or folic acid (vitamin B₆) deficiency, is common in India. The main dietary sources of vitamin B₁₂ are meat, eggs, and dairy products. The liver acts as a depot for vitamin B₁₂; reduction of dietary vitamin B₁₂ deficiency takes 5–10 years to manifest clinically. Common clinical effects include weakness, fatigue, paresthesias, pigmentation of the tongue, knuckles of fingers and toes, and loss of scalp hair. Hypermatured granulocytes are often noted in the peripheral blood film. At times, poor concentration of vitamin B₁₂ binding protein, antidepressants, anticonvulsants, and benzodiazepines may give pseudo serum B₁₂ level. Maximum vitamins are lost during food preparation such as washing and cooking. Vitamin B₁₂ is synthesized by the intestinal microflora. On vegetarian diet, the vitamin B₁₂ content is present in trace amounts. Gastric parietal and distal ileum cells secrete intrinsic factors, which help in B₁₂ absorption. Similarly, extensive skin pigmentation all over the body, in addition to thick pigmentation seen on knuckles, nails of feet, and hands, is observed. Addison's disease, due to deficiency of adrenocortical hormones, results in raised levels of melanin

synthesis, hypotension, loss of weight, and hyperkalemia.

A similar pigmentation pattern over knuckles makes it easy to differentiate between megaloblastic anemia and Addison's disease. Here, we present two cases, including megaloblastic anemia and Addison's disease, and their response to B₁₂ supplementation and oral steroids, respectively.

CASE 1

A 21-year-old woman was reported to the outpatient department with complaints of generalized weakness, easy fatigability, and an episode of blackout while standing from a sitting position. She was unable to recall or remember the names of her friends. She experienced a pins and needles burning sensation in her feet, hands, and mouth. She complained of a loss of taste sensation for beverages and food, as well as a bitter taste. She denied any history suggestive of malabsorption, chronic blood loss, or any other prolonged illness. She also complained of hair loss, which she noticed while combing her scalp, which was full of loose brown hair, and she was unable to braid her hair. Her diet was plant-based. On examination, her pulse rate was 90/minute and collapsing in character, blood pressure was 130/70 mm of Hg. A brown and dark black pigmentation over her fingers' knuckles and palms was noticed but nails are devoid of pigments (Figs 1A and B). Pigmented spots and a bald tongue were also observed (Fig. 1C). On investigation, her hemoglobin concentration was 13.7 gm/dL (normal 12–15) and a mean corpuscular volume of 108.6 ft (normal 83–98). Her leukocyte count was 10,720 (normal 4,000–10,000), and the peripheral

blood smear showed oval macrocytic and hypersegmented neutrophils (Fig. 1D). Her serum B₁₂ concentration was 166 pg/mL (normal 189–883) and her folic acid level was 13.3 ng/mL. Her thyroid profile was normal. She was treated with vitamin B₁₂ supplements. At the end of 4 months, her symptoms improved. However, her pigmentation was still persistent at the end of 6 months.

CASE 2

A 26-year-old male was brought by his wife with a history of extensive black pigmentation all over his body, including his fingers, palms, feet, gums, neck, and nails of his fingers and toes (Figs 2A to D). He also reported generalized weakness, confusion, and had lost 8 kg of weight during the last 4 months. He was obtunded and unable to sit upright while talking; instead, he immediately lay down. His blood pressure was not recordable, and his pulse was 90/minute, with low volume and feeble. His extremities were cold. Random blood sugar was 40 mg/dL. Cortisol at fasting in the morning was 6.30 ug/dL (normal 5–25), and serum adrenocorticotrophic hormone was 920.20 pg/mL (normal 7.2–63). Aldosterone was 33.21 pg/mL (normal 70–300). Hemoglobin was 16 gm/dL, serum creatinine was 6.46 mg/dL (normal 0.5–15), serum potassium was 6.43, serum sodium was 132.1, and blood urea nitrogen was 126.80 mg/dL (normal 14–40). The thyroid stimulating hormone was 10.80 uIU/mL. The electrocardiogram showed tented T waves (Fig. 3). He was resuscitated with 10 units of crystalline insulin in 25% dextrose (100 cc), 1000 mL of normal saline, 300 mg of hydrocortisone, 50 mL

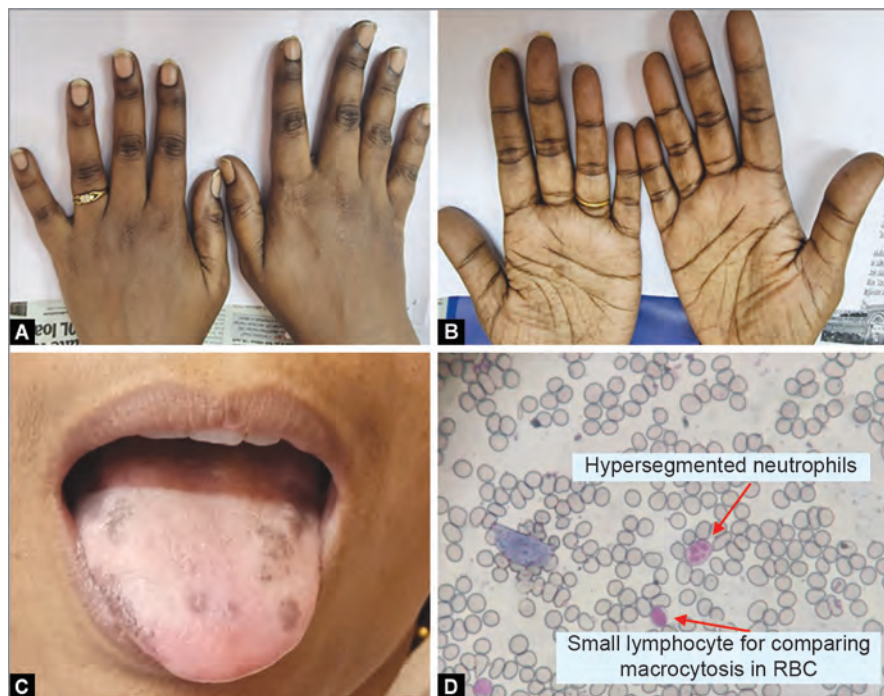
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of sodium bicarbonate, and 100 mL of calcium gluconate by intravenous route. He improved hemodynamically and was transferred to a tertiary care hospital. He denied consumption of any medicine preceding this illness. His wife provided a

history that he had suffered from severe dengue fever 8 months back and was admitted to the intensive care unit, where he received blood transfusions. Since then, his skin turned black and brown pigmented. Detailed reports were not available, except

for a platelet count of 140,000 and a WBC count of 1,900. He was further investigated at a tertiary care center. A computerized abdominal scan showed that the left adrenal gland appeared mildly bulky, with calcifications seen. There was mild reduced enhancement compared to the right adrenal gland. Both lobes of the thyroid showed mildly raised vascularity in color Doppler. Magnetic resonance imaging of the brain was normal. Procalcitonin was 0.21 ng/dL (normal <0.05), aldosterone serum by clinical laboratory improvement amendment (CLIA) in the supine position was 33.21 pg/mL (normal 30–160), and parathyroid hormone was 60.40 pg/mL (normal 15–65). He was treated with flucortisone 100 mg once a day, potassium bind sachets, and hydrocortisone 100 mg three times a day. Upon discharge, he was advised to take prednisolone 10 mg. On the 18th of August, he was contacted by phone, and he sent photos that showed remarkable improvement and the absence of pigmentation over his fingers, palms, toes, and face, except for minimal pigmentation seen over the left great toenail (Figs 2E to H).



Figs 1A to D: (A) Hand—brown-black pigmentation of the knuckle of fingers; (B) Palms—brown-black pigmentations of palm; (C) Tongue—brown-black pigmentation spots over the tongue; (D) Blood smear—peripheral blood smear showing macrocytic and hyperpigmented premature neutrophils

DISCUSSION

Here, we present two different cases with similar skin pigmentations. Shorb¹ demonstrated that the lactobacillus lactic growth is inhibited by an amino acid basal medium in the presence of synthetic B₂



Figs 2A to H: (A) Dorsum of hands and nails—hyperpigmented; (B) Palms—hyperpigmented; (C) Feet nails—pigmented; (D) Face and gums—hyperpigmented; (E) Posttreatment—hands reduction of pigmentation; (F) Posttreatment palms—reduction of pigmentation; (G) Posttreatment—feet reduction in pigmentation; (H) Posttreatment—total disappearance facial pigmentation

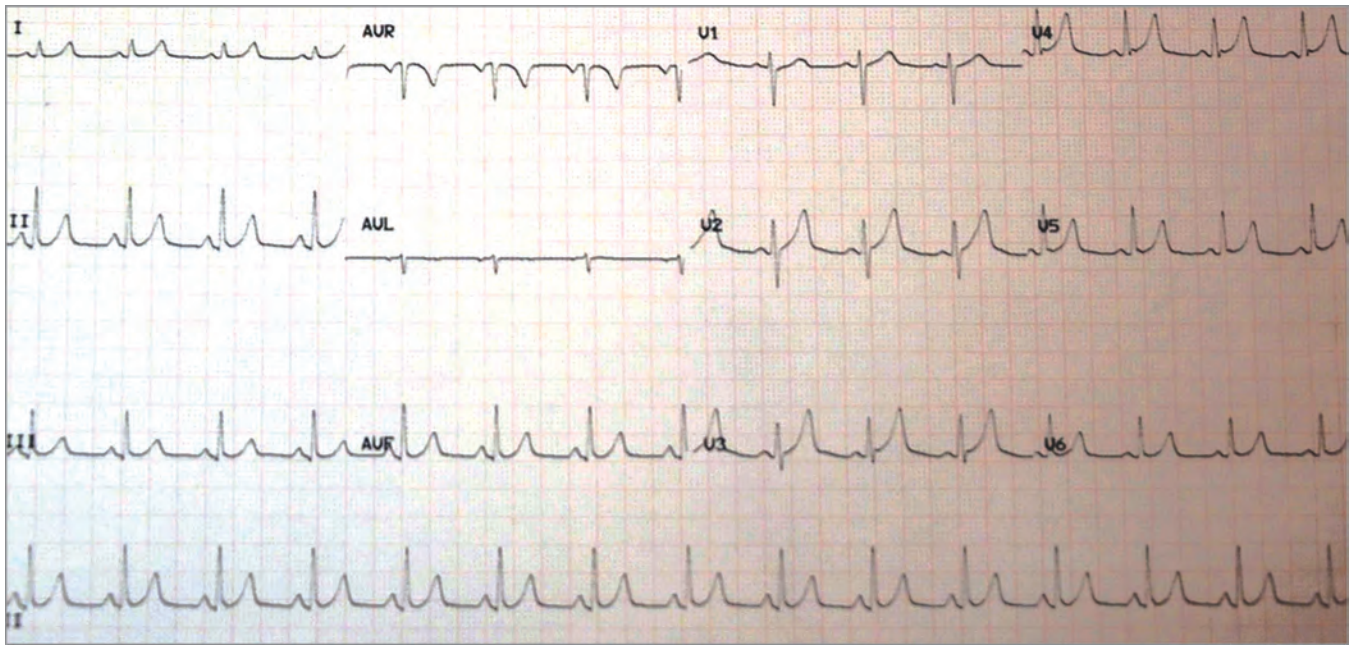


Fig. 3: Tented T waves serum potassium 6.43 Meq

and tomato juice by the addition of extra liver extract.¹ Skin hyperpigmentation accompanied by macrocytic anemia responded to liver extract and B₁₂ complex.² The presence of macrocytic anemia with a raised mean corpuscular volume of 108.6 in these cases confirmed the diagnosis of B₁₂ deficiency anemia. Macrocytic anemia is often accompanied by gastrointestinal disturbances and memory dysfunction. In these cases, the absence of family history and the response to supplement treatment confirmed acquired nutritional deficiency.³ The presence of prematurely released macrocytic and hypersegmented neutrophils is characteristic of both folic acid and B₁₂ deficiency anemia, resulting in pronounced anemia.^{4,5} Vitamin B₁₂ prevents hyperhomocysteinemia, a risk factor for atherosclerosis, stroke, and infarction, by synthesizing methionine from homocysteine.⁶ Hyperpigmentation of the skin, palm, interphalangeal joints, terminal phalanges of the soles of the feet, and oral mucosal membrane is not uncommon in B₁₂ deficiency in Indian adults and infants. Amino acid tyrosine plays an important role in melanin preparation.⁷ Reduction in hyperpigmentation is accompanied by decreased levels of tyrosine, resulting in reduced synthesis of melanin. This mechanism of underlying hyperpigmentation is attributed to a reduction in glutathione levels, which are responsible for the activation of tyrosinase and the transfer of melanin to melanocytes.

A defect in melanin transfer between melanocytes and keratinocytes leads to hyperpigmentation. Brown hair color is affected by cobalamin deficiency, and loss of hair color and hair loss can be improved with B₁₂ supplement treatment.^{8,9} In these cases, the fingernails and toenails were free from pigmentation. During the development of the megaloblastic process, erythrocytic precursors are larger in size than normal matured cells due to vitamin B₁₂ and folate deficiency, resulting in defective RNA and DNA synthesis.¹⁰ Furthermore, hyperhomocysteinemia and a rise in methylmalonic acid are results of defective biochemical processes. Pigmentation of the skin and nail beds is a sign of malnutrition often observed in patients with malabsorption syndrome and strict vegetarian diets. Repeated antibiotic consumption can kill the intestinal bacteria responsible for B₁₂ synthesis, and routine spraying of pesticides and washing of vegetables can remove deposited B₁₂ from bacterial colonies. There is a significant reduction in the content of postcooked food, including meat, compared to precooked food and meat.

In the second case, the significantly raised level of adrenocorticotrophic hormone confirmed the hypothalamic–pituitary origin of Addison's disease in addition to adrenal gland dysfunction due to dengue infection. There is a history and clinical manifestation during dengue infection suggestive of Waterhouse–Friderichsen

syndrome, which is further confirmed by improvement with intravenous saline and hydrocortisone.¹¹ Hypoaldosteronism is attributed to the serious status of an Addisonian crisis.¹²

Hyperpigmentation is a characteristic feature of chronic primary adrenal insufficiency, resulting from cortisol deficiency and increased production of proopiomelanocortin, a prohormone cleaved into biologically active hormones, including corticotropin and melanocyte-stimulating hormone (MSH). Elevated MSH levels lead to increased melanin synthesis, causing hyperpigmentation. Melanin is synthesized in epidermal melanocytes just below the basal cells of the epithelium. Longitudinal banded pigmentation of nails through the stimulation of functional nevi is also a possibility.¹³ Hyperpigmentation typically fades within several days and largely disappears after a few months of adequate glucocorticoid therapy. Recovery occurs due to keratinization and sloughing of the pigmented basal layer of the epidermis. Fading of hair and nails takes longer because the pigmented part of the hair shaft or nail grows out slowly. Scars never fade because melanin is trapped in fibrous connective tissue.¹⁴

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Embolized Stent after Branch Pulmonary Artery Stenting

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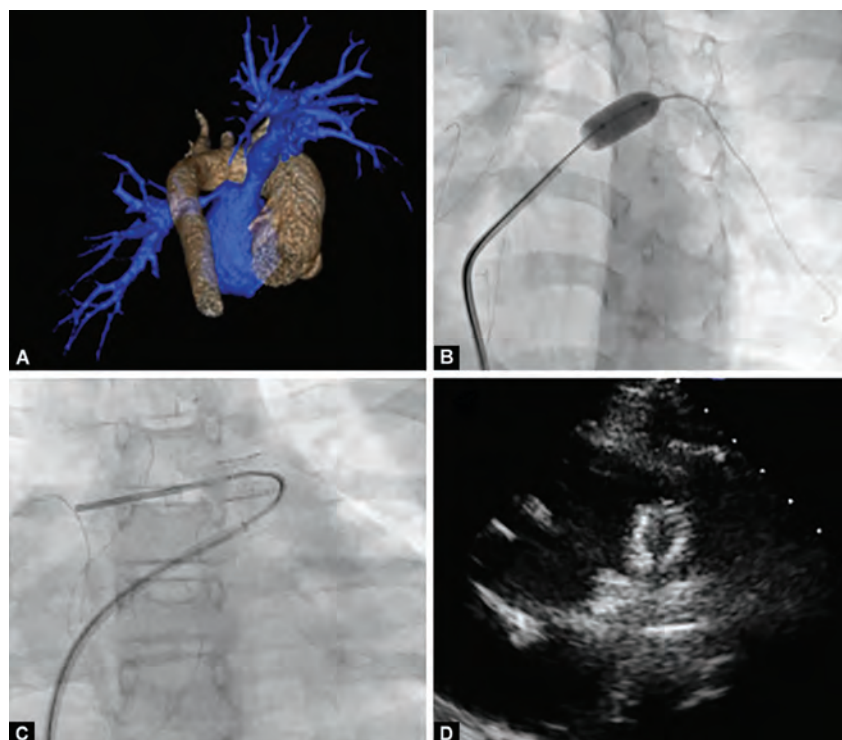


Stenosis of the pulmonary artery, isolated or associated with other cardiac defects, occurs in 2–3% of all patients with congenital heart diseases. Stenting provides better short and midterm results than balloon angioplasty. Various procedural complications might

occur.¹ We are reporting a case where the stent got embolized in the main pulmonary artery (MPA).

A 9-year-old boy weighing 39 kg, follow-up case of repaired tetralogy of Fallot at the age of 1 year, developed progressive

symptomatic severe left branch pulmonary artery stenosis. He was taken for branch stenting. Preoperative computed tomography (CT) angiography revealed challenging anatomy due to acute angle origin of left branch apart from significant ostial stenosis (Fig. 1A). Through right trans femoral venous access with the help of 7 French long sheath, a 10 × 20 mm cook formula stent was successfully deployed without any residual waist and ostial flaring was performed (Fig. 1B). However, the stent got embolized into MPA (Figs 1C and D). It was a terrible nightmare with a fully expanded stent freely moving in MPA. It was not possible to advance it in either branch due to ostial stenosis in both. Surgical and critical care teams joined immediately. The boy was sedated and intubated. It was decided that endovascular retrieval would be attempted first and upon failure, surgical removal would be performed. The 7 French sheath was exchanged with a 12 French long sheath over super stiff wire which was already coursing the stent through and through the lumen. Now, an Amplatz 25-mm Goose Neck™ snare (ev3,



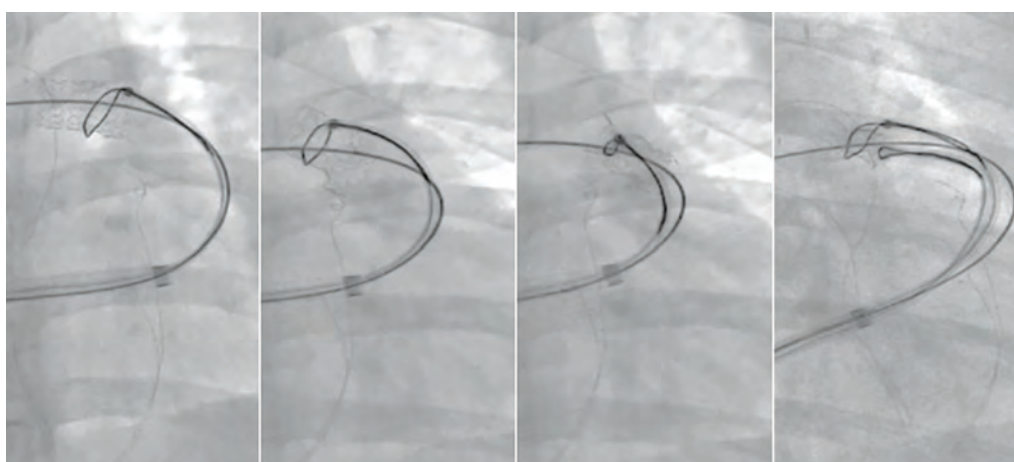
Figs 1A to D: (A) Ostial stenosis with acute angle origin of left branch pulmonary artery in volume rendered CT angiography from posterior view; (B) A 10 × 20 mm stent was deployed with full expansion; (C) It got embolized as visible in angiography and; (D) In transthoracic echocardiography

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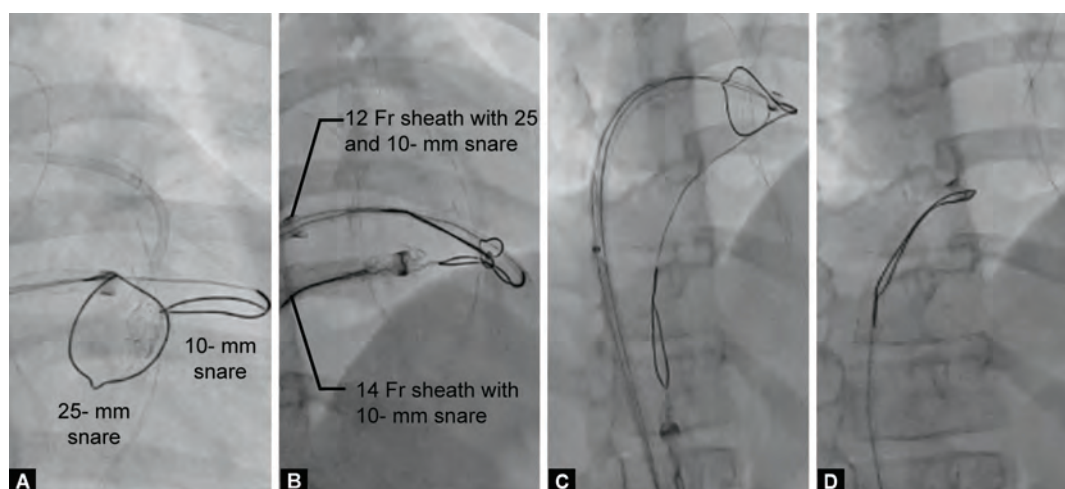
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Figs 2A to D: (A to C) The stent was crimped at multiple places with a 25 mm gooseneck snare. It got stuck to some fractured strut distally; (D) Proximal end was caught with another 10 mm snare



Figs 3A to D: (A) The stent fell into the RV cavity in an attempt to advance the 12 French sheath. Now this stent with attached (and stuck) 10 mm snare and free but intermingled 25 mm snare could not be pulled into the sheath; (B) The free end of the stent was grasped with 10 mm snare advanced through another 14 French sheath; (C) This assembly of 14 French sheath with snare and grasped stent was pulled en masse while the previous 10 mm snare attached to opposite end followed; (D) The remaining 12 French sheath and 25 mm snare could be withdrawn easily



Fig. 4: Image of the retrieved deformed stent

Plymouth, MN) was advanced and the stent was crimped at multiple places (Figs 2A to C). It became stuck in some fractured distal stent strut and could not be disengaged. Another 10 mm gooseneck snare was advanced and

it caught the proximal end (Fig. 2D). During all these steps, the sheath gradually pushed back into the right ventricle (RV) which could not be advanced in MPA. Rather in attempts to advance the sheath, the stent fell back into the RV cavity. Now despite all the possible maneuvers, the stent could not be pulled into the sheath. Somehow, the snares got intermingled in such a way that none could be withdrawn (Fig. 3A). All the hopes of successful retrieval then vanished with deformed and crimped stent lying in the RV cavity and 12 French sheath along with two snares coursing from groin to RV. Finally, a last attempt was planned. At that time the 25 mm snare was freely moving while the 10 mm snare was stuck to the proximal end of the stent. Through another 14 French long sheaths, advanced through opposite trans femoral venous access, with the help of a 10 mm gooseneck snares

the opposite free end of the stent was caught (Fig. 3B), and it was sucked into this sheath. The whole assembly (14 French sheath, snare cum stent) was pulled out and the previous 10 mm snare followed (Fig. 3C). The 12 French sheath and remaining 25 mm snare could be withdrawn easily (Figs 3D and 4). There was no trauma to the heart valves or vessels. The boy was hemodynamically stable and was extubated. He was discharged the next day. The case illustrates the challenging situation where a fully expanded big-size stent got embolized and could be retrieved successfully via the endovascular approach.

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Michael Smith and Site-directed Mutagenesis

Jayant Pai-Dhungat



Michael Smith and deoxyribonucleic acid (DNA) molecule with oligonucleotides.
Palau, 2000



Stylized DNA molecules from M/S issued by China during Stamp Exhibition, 2017



Har Gobind Khorana, Nobel Prize in Medicine
1968 Dominica, 1995

Michael Smith (1932–2000), a British-born Canadian biochemist, received his PhD from the University of Manchester, England, in 1956. Soon, he moved to Vancouver to undertake postdoctoral research with Har Gobind Khorana (a Nobel Prize winner himself) at the British Columbia Research Council in Vancouver, Canada.

Subsequently, Smith worked at the Fisheries Research Board of Canada Laboratory in Vancouver, and after holding a number of positions in Canada and the United States, he returned to the faculty of the University of British Columbia in 1956. Smith ultimately became the director of the university's biotechnology laboratory in 1987.

Michael Smith first conceived the idea of site-directed mutagenesis in the early 1970s and devoted several years to working out the

details of the technique. He found a way to create specific mutations at specific sites in genes and, therefore, the proteins that they encoded.

Before the advent of Smith's method, techniques used by biochemical researchers to create genetic mutations were done by X-ray irradiation, chemicals, etc. This was a haphazard and imprecise approach, which made it a difficult and time-consuming task. Smith remedied this situation by developing oligonucleotide-based, site-directed mutagenesis.

Throughout his career, he looked for the potential medical and commercial applications of his work. He became a Canadian citizen and founded a biotechnology company, ZymoGenetics Inc.

Smith received the 1993 Chemistry Nobel Prize "for his fundamental contributions to the establishment of oligonucleotide-based, site-directed mutagenesis and its development for protein studies," which he shared with Kary B. Mullis [for his work on polymerase chain reaction (PCR)].

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Solitary Areolar Milium

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Dear Editor,

A pearly white round lesion was noticed at birth on the areola of the right nipple of a term healthy female newborn. On further examination, the lesion was a solitary, 3 × 3 mm, firm, hemispherical, pearly white papule with a smooth surface and regular margins present on the areolar ridge (Fig. 1). There were no signs of lesional or perilesional inflammation, erythema or induration. The rest of the cutaneous examination, including the left nipple-areolar complex, was unremarkable. No other system was involved. On the basis of history and examination, a diagnosis of solitary isolated milium of the areola was reached.¹ The parents were informed about the clinical diagnosis, and a skin biopsy was avoided in view of the benign and self-limiting nature of the condition. The infant was followed up at the age of 6 months when the skin lesion was found to be resolved after spontaneous shedding of the milium, as reported by parents.

Milia are epidermal inclusion cysts containing keratin. Numerous pin-sized milia are common facial lesions in term neonates.² A larger isolated variant is reported to occur



Fig. 1: Solitary, 3 × 3 mm, firm, hemispherical, and pearly white papule with smooth surface and regular margins present on the areolar ridge

over the nipple, scrotum, or eyelids.^{3–5} Areolar milium is also categorized as an inclusion cyst similar to the Bohns nodule (gums) or Epstein pearls (hard palate) containing varying amounts of keratin. Congenital areolar milium, as observed in our patient, is under-reported in the literature. An acquired areolar milium may also arise after trauma (squeezing for witch's milk) or a bullous skin disorder.⁶ Management is usually supportive, and excision should be avoided as it may lead to scarring.⁶ The differential diagnosis of congenital milium also includes calcinosis, trichoepithelioma, or a fibroadnexal polyp. It can often be confused with cutaneous pustular lesions or molluscum contagiosum. Awareness among clinicians

regarding this benign condition is important to avoid unnecessary interventions and the risk of complications like infection and scarring.

INFORMED CONSENT

Written informed consent for the publication of their clinical details and clinical images was obtained from the parents.

AUTHOR CONTRIBUTION

CK took the image of the infant. He wrote the initial manuscript. SK gave critical inputs to the manuscript.

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