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

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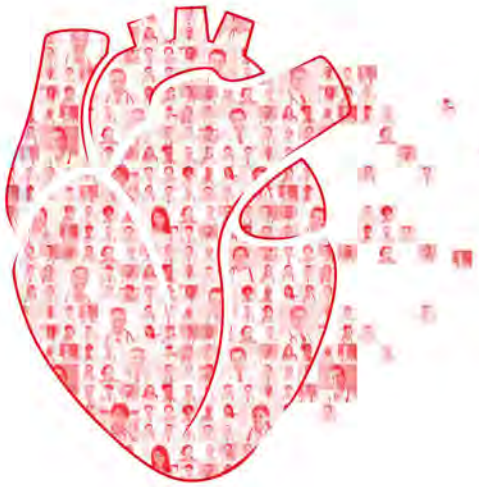

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There has been no long term use of Telmisartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated. **Dual Blockade of the Renin-Angiotensin-Aldosterone System**: 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, Mutogenesis, 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. 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EDITORIAL

Understanding Body Composition Analysis in Obesity Management

Khushboo Agarwal[1], Felix Manoharan[2], Nitin Kapoor[3*]

Introduction

The incidence of lifestyle diseases, namely obesity, diabetes mellitus, hypertension, metabolic syndrome, etc., is increasing across the world. There are different phenotypes of obesity, and body composition analysis has now become an essential part of clinical practice. It is needed to provide a better understanding of the functional capacity of the body, the muscle composition, and the amount of fat in various parts of the body.

Obesity causes alterations in body composition, which impact metabolism, insulin sensitivity, and the development of diabetes and other metabolic diseases.[1] There is a need to measure muscle mass and strength accurately to identify individuals at risk of developing these diseases so that adequate preventive interventions can be taken. Additionally, these measurements can also be used to assess the effect of each intervention.

Radiological imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI), which can also measure fat deposition and infiltration in various organs, are the gold standard for body composition assessment.[2] The body composition methods can be divided as the following[3]:

- Direct methods: These methods involve analysis at the cellular level and include neutron activation, total body counting, and isotope dilution.
- Criterion methods: These methods use a property of the body, such as the density of bone, fat, muscle, etc., to describe their amount and distribution in the body and include CT, MRI, and dual energy X-ray absorptiometry (DEXA).
- Indirect methods: These include anthropometry and bioimpedance analysis (BIA). They depend on the measurement and distribution of various tissues among the normal population and hence are prone to larger predictive errors.[4]

All the methods of body composition assume a fixed concentration of water and electrolytes or density of body tissues and the interrelationship and distribution of various components of the body, such as muscle, fat, and bone, in healthy individuals.[5] The assumptions may not hold true in chronic disease, cachexia, or morbid obesity. It is important to assess these results within the scope of their limitations.

Models of Body Composition

Assessment of body fat has historically been difficult. There are four models of body composition.[6]

Two-compartment (2C) Model

In the two-compartment (2C) model, the body is divided into fat mass (FM) and fat-free mass (FFM). The FFM is easier to estimate, and the FM is the difference between total body weight and FFM. The method involves measuring total body density, and FFM density is assumed to be constant.[7] The methods include air displacement plethysmography (ADP), hydrodensitometry, and hydrometry. The model assumes a constant density across ages: a density of 0.732 L/kg for body water[8] and 68.1 mEq/kg for body potassium.[9] The method was based on the analysis of young male cadavers,[10] and the assumptions of fat mass calculation were not accurate for extremes of age, different ethnicities, and females.

Three-compartment (3C) Model

The three-compartment (3C) model divides FFM into total body water (TBW) and solids (proteins, minerals, fat-free dry mass). It involves measurement of TBW and body density, assuming a constant mineral-to-protein ratio of 0.359.[7] It is better than the 2C model as it accounts for variation in hydration status. Body density measurement will not be accurate in people with low bone mineral or protein mass; therefore, estimation of FM can also be inaccurate. An example of the 3C model is DEXA.

Four-compartment (4C) Model

It divides the body into fat, mineral, TBW and protein and does not assume any definite proportion between these constituents. In this model, the density of protein is assumed to be 1.34 kg/L and that of minerals to be 3.075 kg/L.[11] It requires neutron activation analysis for protein measurement and DXA for bone mineral measurement. Since it is not widely available, protein mass is taken to be proportional to the BMC of the person.

There is an alternate four-compartment (4C) model, which divides the body's FFM into body cell mass (BCM), extracellular water (ECW), and extracellular solids (ECS). The BCM measurement is based on total body potassium.[12] The ECW is measured using bromide or sulfate compounds.[13] The ECS compartment includes measurement of BMC, usually by DXA. The FFM is defined as BMC + ECW + ECS, and total body fat mass as body weight minus FFM.

The main drawback is that each primary measurement has a possible error, which can accumulate. The use is also limited due to time, cost, and equipment needed for the multiple compartment measurements and is mainly used to validate other methods of body composition.

Multicompartment Models

It involves direct analysis of elements like water, nitrogen, calcium, potassium, sodium, and chloride in the body.[14] While more accurate, high expense and radiation exposure make its use limited to experimental settings. It is particularly accurate for the first two years of life.[15] A comprehensive description of all the body composition models is described in Figure 1.

Methods of Body Composition

Indirect Methods

Anthropometry

They describe the size and shape of the individual and were the initial methods of body composition assessment.[3] These noninvasive

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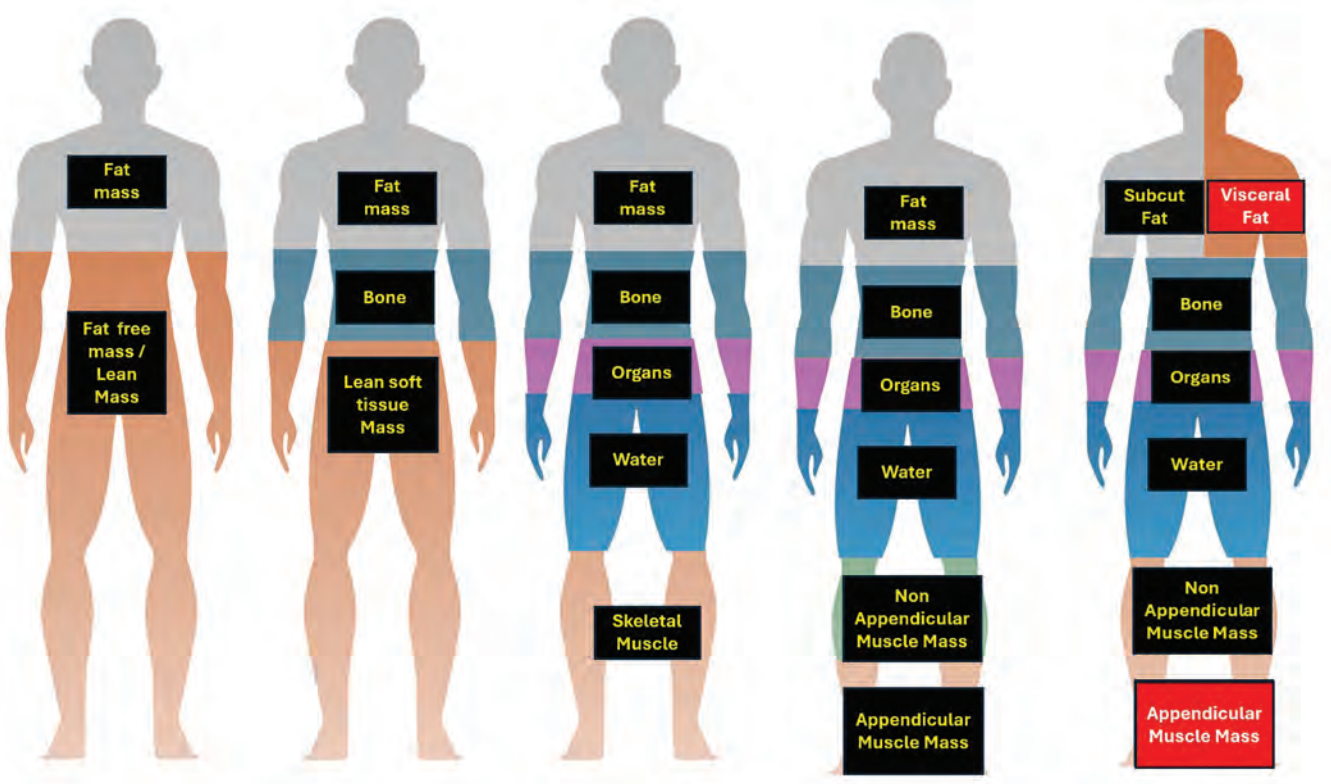


Fig. 1: Understanding different components of body composition

methods are useful to assess nutritional status, identify at-risk individuals, and assess the efficacy of nutrition or exercise interventions. They are simple to measure, nonexpensive, and easier for follow-up studies but cannot differentiate between muscle or fat loss.[16]

Weight, Stature, and Body Mass Index

The most frequent measure of obesity is body weight, but it can be inaccurate as the changes can correspond to alterations in body water, fat, and/or muscle mass. One of the ways this is overcome is by the use of body mass index (BMI). BMI is weight divided by stature squared (kg/m^2). The main advantage of BMI is the presence of a reference database and multiple studies validating its relationship with levels of body fatness, morbidity, and mortality in adults.[17] It is ideal for wide population-based studies. For a given BMI, the percentage of body fat does not remain the same, as it changes with sex, ethnicity, and age.[18] It is not a sensitive indicator of body fat and metabolic risk,[19] especially in Asians. The Endocrine Society of India Obesity guidelines mention that a BMI of 23–24.9 kg/m^2 is considered overweight, while a BMI >25 kg/m^2 is considered obese.[20]

Waist Circumference

It is a measure of abdominal obesity. It is measured in a standing position at the center of the line drawn from the lowest rib cage and the iliac crest at the end of expiration.[17] The cutoff used in Asian Indians is >80 cm for females and >90 cm for males.[20] Higher waist circumference increases the risk of developing type 2 diabetes mellitus, metabolic syndrome, and mortality.[21]

Waist–Hip Ratio

Waist–Hip Ratio (WHR) tells us about the distribution of body fat. The cutoff defined for Indians is >0.8 for females and >0.9 for males.[20] In a study with over 500 subjects from North India, WHR and WC were the best predictors of metabolic syndrome.[22] In another population-based study, WC and WHR were the best predictors of diabetes.[23]

Skinfold Thickness

Skinfold thickness (SFT) assesses subcutaneous fat, usually done with calipers measuring to the nearest 0.2 mm. It is measured at the biceps, triceps, subscapular, and supra-iliac areas, which are then used to calculate body density.[24] The main limitation is that most calipers have an upper limit of 45–55 mm, therefore of little use in people with morbid obesity. There is a national reference database for triceps and subscapular SFT. SFT is especially useful in children, as they have mostly subcutaneous fat, even at higher BMI.[25]

METS-VF is another simple tool used to assess visceral adipose tissue in individuals with the help of anthropometry and simple biochemistry that has been validated in the Indian population.[26]

Bioelectrical Impedance Analysis

Bioelectrical impedance analysis (BIA) depends on the electric conductive properties of the body,[27] involving measurement of impedance (Z) or interference to a low-electrical current (800 µA) at a fixed frequency (50 kHz). It can be a single or multifrequency device. It is based on the electricity conduction properties of water, electrolytes, and fat. The errors in measurement result from differences in the length of the limb, nutritional status, hydration, blood chemistry, ovulation, and placement of electrodes.[28] To correct for these, bioimpedance spectroscopy (BIS) or multifrequency BIA can be used, which differentiate BCM and TBW,[29] which correlate with estimates from 4C models. In individuals with obesity, the trunk has a greater proportion of body mass and body water, increasing the ratio of extracellular to intracellular water and decreasing the hydration of FFM,[30] because of which FFM is overestimated in obese individuals.[29] However, by optimal standardization, they provide a quick estimate of FFM. Because of large predictive errors, small improvements with treatment can be missed.[31] The BIA instrument is portable and relatively low-cost, and therefore can also be used in large population-based studies. Age- and gender-

based equations for optimal calculation in the Indian population are needed.

Direct Methods

Isotope Dilution Method (Hydrometry)

Hydrometry is the measurement of TBW based on the already known concentration of the tracer (isotope).[13] Since it is mainly present in FFM, TBW can be used to estimate FFM. The isotopes used are D_2O and ^{18}O. The isotope is measured in saliva, urine, or blood before and 3–4 hours after administration of the dose by isotope ratio mass spectrometry or infrared spectrophotometry. It is accurate within 1–2% to measure TBW.[32] The errors result from mistakes in the time taken to reach equilibrium, incorrect dilution, or errors in the measurement of the isotopic enrichment.

Whole-body Potassium Counter

The 4C model divides the body into fat, BCM, ECF, and extracellular solids (ECS). The BCM contains approximately 98 percent of the body's potassium.[33] It is accurately measured with WBKC. It can also give an indirect estimate of body protein and skeletal muscle mass.[34] It is useful in conditions with changing hydration status, pregnancy, malnutrition, and infancy. The body potassium is estimated from the proportion of ^{40}K in the body. The total body nitrogen (TBN), protein (TBP), and BCM can be calculated with the equations and assumptions of potassium to nitrogen ratio of 2.15 mmol K/gm N,[35] TBP = 6.25 × TBN (gm),[36] and BCM (kg) = 0.0092 × TBK (mmol).[37]

Criterion Methods

Hydrodensitometry (Underwater Weighing)

It is the estimation of total body density by measuring the displaced water when the body is fully submerged, along with measuring the residual lung volume. An individual with higher FFM will weigh more in water, as bone and muscle are denser than water, whereas an individual with higher FM will be lighter in water, as fat floats in water. The body fat can be estimated using the 2C model after measuring the body density. For correct measurement, it should account for air in the lungs and intestines. When compared to the 4C model, the UWW method has an error rate of –2.8 to 1.8%.[38] The method is time-consuming and uncomfortable for the individual.

Air Displacement Plethysmography

Air displacement plethysmography (ADP) measures the body volume (BV) by measuring the volume of air in an empty chamber and the volume of air in the chamber after the person sits in it, the difference being BV. The volume of the air is calculated from the changes in air pressure.[39] The whole process takes 5–8 minutes. The instrument is easy to use but is expensive and not widely available. The accuracy of this method is similar to UWW.[39] In a study from South India, BOD POD underestimated FM by 1.1%.[14]

Dual-energy X-ray Absorptiometry

DEXA uses the principle of measurement of attenuation of X-rays with photon energies by the underlying tissue. It is fast, requires little technical assistance, and has low radiation exposure. It is the gold standard for measurement of bone mineral density.[40] It is also used for estimation of total and regional body fat and lean mass. It assesses body composition when compared to the 4C model with a mean error of 1.6 kg.[14] One drawback is that DEXA assumes that the amount of fat over bone is similar to bone-free tissue. Another limitation is that it assumes constant hydration of lean soft tissue. There is limited data from DEXA in children <2 years of age.[41]

One DEXA scan exposes a patient to about 4–5 µSv of radiation, which is even lower than the natural background dose (6.7 µSv).[42] Proper positioning is important for accurate measurement of FM and FFM. Meals increase the lean mass in the trunk and whole body.[43] Whereas exercise can cause an apparent increase in FFM of limbs due to the movement of fluids from the trunk to the limb.[44] It is also important to position the patient correctly using the reference lines on the table. The patient should be positioned in the center of the scan without a pillow, the upper limbs lying on the side of the body without touching, and the lower limbs slightly internally rotated.[45] There should be uniformity while placing regional lines: the upper horizontal line under the jaw, while the pelvis horizontal placement is just above the iliac crests. The vertical lines separate limbs from the trunk on both sides, and one vertical line separates the legs (Fig. 2).[46]

Figure 3 shows a typical body composition report with various adipose and lean indices, which can be used to interpret various case scenarios.

- Sarcopenia:
  The European Working Group on Sarcopenia in Older People 2 (EWGSOP 2) has defined sarcopenia as two out of low muscle mass, low muscle strength, and low function. The South Asian Working Group on Sarcopenia[47] has defined the cutoff for Asian Indians: <7 kg/m² for males and <5.4 kg/m² for females. Figure 4 shows a case of sarcopenic obesity.
- Adipose indices:
  Fat mass index: It is defined as total fat mass divided by height.[2] The current thresholds for FMI are derived from NHANES data.[48] These are shown in Table 1. Studies have shown that higher FMI corresponds to

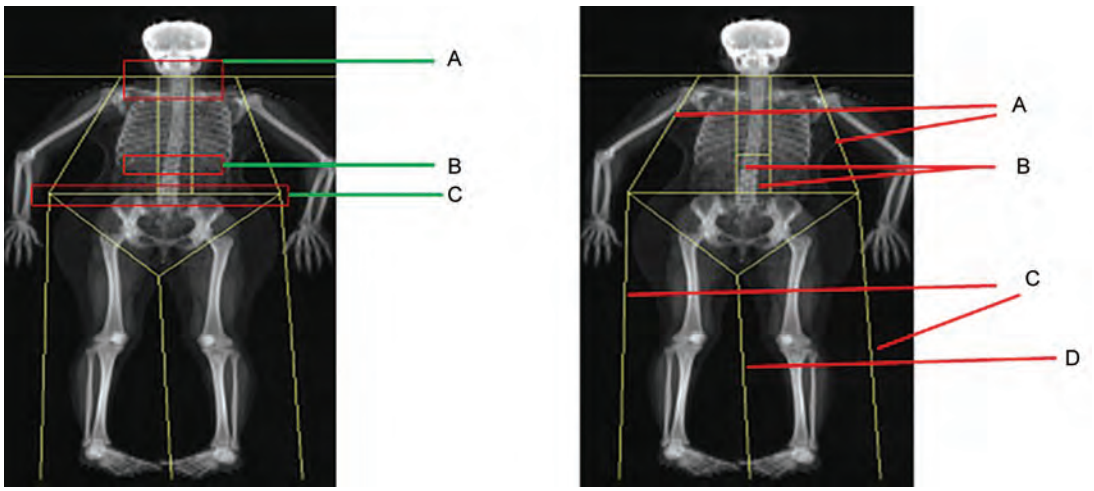
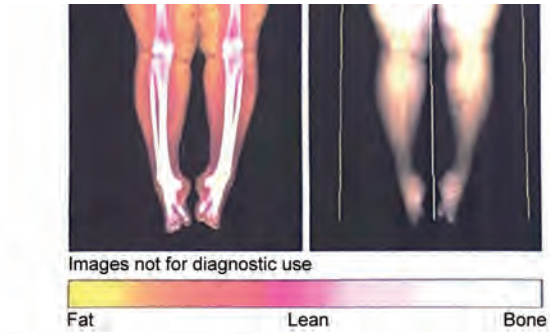


Fig. 2: Positioning of lines



World Health Organization Body Mass Index Classification
BMI = 50.1 WHO Classification

Underweight | Normal | Overweight | Obesity I | Obesity II | Obesity III

10 15 20 25 30 35 40 45

BMI has some limitations and an actual diagnosis of overweight or obesity should be made by a health professional. Obesity is associated with heart disease, certain types of cancer, type 2 diabetes, and other health risks. The higher a person's BMI is above 25, the greater their weight-related risks.

Body Composition Results

Region	Fat Mass (g)	Lean + BMC (g)	Total Mass (g)	% Fat	%Fat Percentile YN	%Fat Percentile AM
L Arm	4412	2793	7205	61.2	99	99
R Arm	4706	2716	7421	63.4	99	99
Trunk	33412	23558	56970	58.6	99	99
L Leg	11996	9543	21538	55.7	99	98
R Leg	11243	8927	20170	55.7	99	98
Subtotal	65769	47536	113306	58.0	99	99
Head	3156	5290	8446	37.4		
Total	68925	52827	121752	56.6	99	99
Android (A)	5333	3976	9309	57.3		
Gynoid (G)	9379v	8369	17748	52.8		

Scan Date: 14 February 2022
Scan Type: a Whole Body
Analysis: 14 February 2022 13:05 Version 13.6.0.5
Auto Whole Body Fan Beam
Operator:
Model: Horizon A (S/N 301451M)
Comment:

Adipose Indices

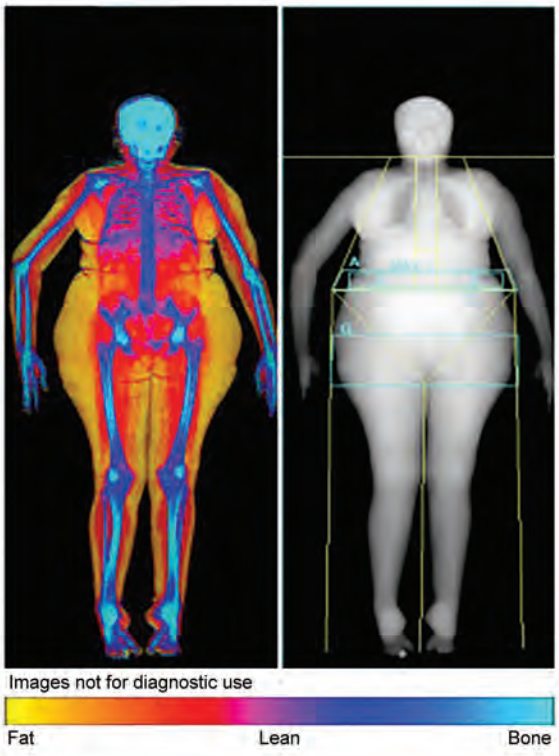
Measure	Result	Percentile YN	Percentile AM
Total Body % Fat	56.6	99	99
Fat/Mass Height² (k/m²)	28.3	99	99
Android/Gynoid Ratio	1.08		
% Fat Trunk/% Fat Legs	1.05	94	87
Trunk/Limb Fat Mass Ratio	1.03	85	69
Est. VAT Mass (g)	1084		
Est. VAT Volume (cm³)	1172		
Est. VAT Area (cm²)	225		

Lean Indices

Measure	Result	Percentile YN	Percentile AM
Lean/Height² (kg/m²)	21.0	97	96
Appen. Lean/Height² (kg/m²)	9.50	98	97

Est. VAT = Estimated Visceral Adipose Tissue
YN = Young Normal
AM = Age Matched

Fig. 3: Typical body composition report by DXA



Underweight | Normal | Overweight | Obesity I | Obesity II | Obesity III

10 15 20 25 30 35 40 45

BMI has some limitations and an actual diagnosis of overweight or obesity should be made by a health professional. Obesity is associated with heart disease, certain types of cancer, type 2 diabetes, and other health risks. The higher a person's BMI is above 25, the greater their weight-related risks.

Adipose Indices

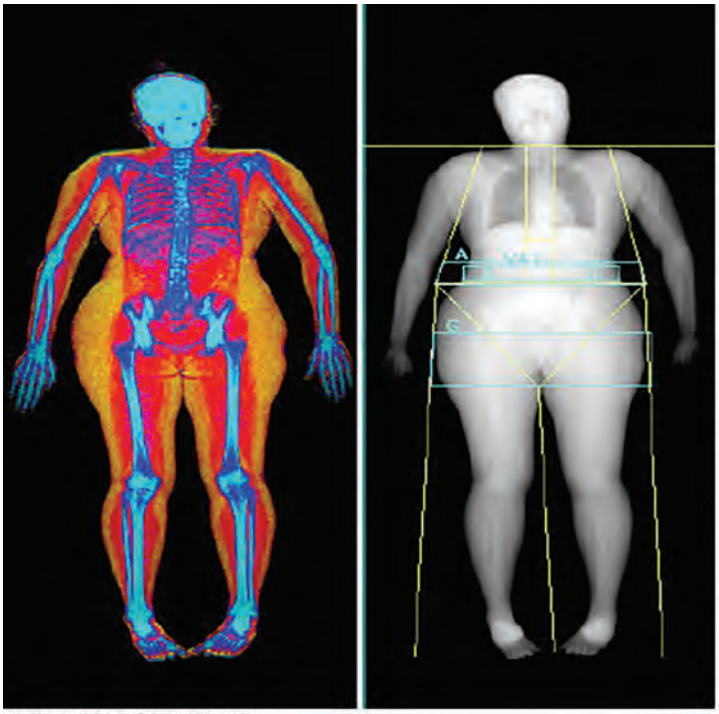
Measure	Result	Percentile YN	Percentile AM
Total Body % Fat	52.7	98	98
Fat Mass/Height² (kg/m²)	16.3	90	82
Android/Gynoid Ratio	0.95		
% Fat Trunk/% Fat Legs	0.81	56	31
Trunk/Limb Fat Mass Ratio	0.87	63	33
Est. VAT Mass (g)	764		
Est. VAT Volume (cm³)	825		
Est. VAT Area (cm²)	158		

Lean indices

Measure	Result	Percentile YN	Percentile AM
Lean/Height² (kg/m²)	13.8	24	20
Appen. Lean/Height² (kg/m²)	5.39	12	14

Est. VAT = Estimated Visceral Adipose Tissue
YN = Young Normal
AM = Age Matched

Fig. 4: Sarcopenic obesity



World Health Organization Body Mass Index Classification
BMI = 22.6 WHO Classification Normal

Underweight | Normal | Overweight | Obesity I | Obesity II | Obesity III

10 15 20 25 30 35 40 45

BMI has some limitations and an actual diagnosis of overweight or obesity should be made by a health professional. Obesity is associated with heart disease, certain types of cancer, type 2 diabetes, and other health risks. The higher a person's BMI is above 25, the greater their weight-related risks.

Adipose Indices

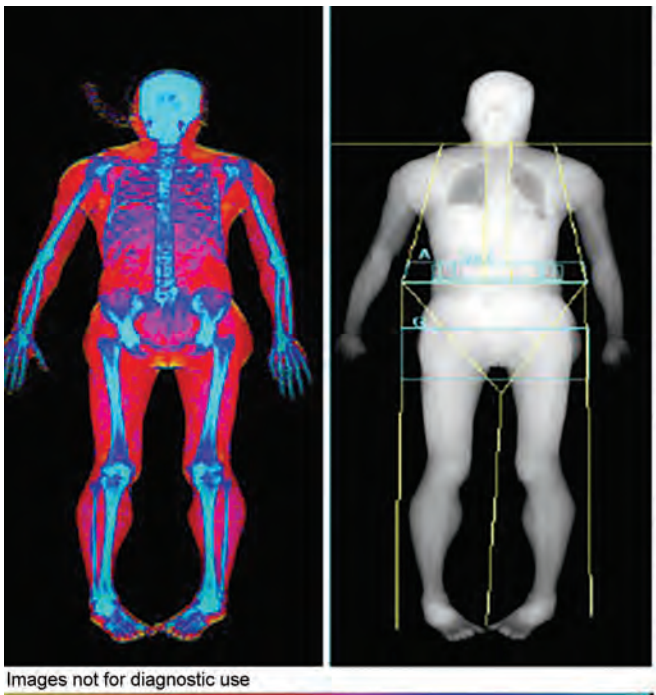
Measure	Result	Percentile YN	Percentile AM
Total Body % Fat	40.5	73	67
Fat Mass/Height (Kg/m²)	9.24	53	47
Android/Gynoid Ratio	0.87		
% Fat Trunk/% Fat Legs	0.85	64	57
Trunk/Limb Fat Mass Ratio	0.81	53	43
Est. VAT Mass (g)	276		
Est. VAT Volume (cm³)	298		
Est. VAT Area (cm²)	57.6		

Lean Indices

Measure	Result	Percentile YN	Percentile AM
Lean/Height² (kg/m²)	12.8	8	7
Appen. Lean/Height² (kg/m²)	5.57	17	16

Est. VAT = Estimated Visceral Adipose Tissue
YN = Young Normal
AM = Age-matched

Fig. 5: Normal weight obesity



Underweight | Normal | Overweight | Obesity I | Obesity II | Obesity III

10 15 20 25 30 35 40 45

BMI has some limitations and an actual diagnosis of overweight or obesity should be made by a health professional. Obesity is associated with heart disease, certain types of cancer, type 2 diabetes, and other health risks. The higher a person's BMI is above 25, the greater their weight-related risks

Adipose Indices

Measure	Result	Percentile YN	Percentile AM
Total Body % Fat	**22.6**	**2**	**2**
Fat Mass/Height² (kg/m²)	4.63	5	3
Android/Gynoid Ratio	0.95		
% Fat Trunk/% Fat Legs	1.15	98	97
Trunk/Limb Fat Mass Ratio	1.37	99	96
Est. VAT Mass (g)	229		
Est. VAT Volume (cm³)	247		
Est. VAT Area (cm²)	47.5		

Body Composition Results

Region	Fat Mass (g)	Lean + BMC (g)	Total Mass (g)	% Fat	%Fat Percentile YN	%Fat Percentile AM
L Arm	539	2128	2668	20.2	1	1
R.Am	685	2348	3033	22.6	3	2
Trunk	6148	19996	26144	23.5	15	9
L. Leg	1566	6334	7899	19.8	1	1
R. Leg	1699	6413	8112	20.9	1	1
Subtotal	10637	37219	47856	22.2	2	1
Head	1213	3318	4531	26.8		
Total	**11850**	**40537**	**52386**	**22.6**	**2**	**2**
Android (A)	725	2571	3296	22.0		
Gynoid (G)	1625	5422	7046	23.1		

Result Summary	: Utilizing the Next Generation Sequencing approach, the patient was found to be positive for a heterozygous pathogenic LMNA (NM_170707.4):c.1445G>A (p.Arg482Gln) variant
Variant classification based on ACMG 2015 guidelines	: Pathogenic

Fig. 6: Lipodystrophy

Table 1: Fat mass index cutoff derived by NHANES data[48]

Ethnicity	*FMI matching BMI (kg/m²)*				
	<18.5	>25	>30	>35	>40
Caucasians					
Male	<2.9	>6	> 8.9	>11.9	>15
Female	<4.9	>9.2	>12.9	>16.8	>20.6
Non-Caucasians					
Male	<3	>6.3	>9.2	>12.3	>15.4
Female	<5.2	>9.4	>12.8	>16.1	>19.2

negative cardiovascular and metabolic outcomes.[49]

In addition to FMI, absolute fat percentages are also mentioned. The ESI defines obesity with a fat percentage >25% in males and >30% in females.[20] This parameter is especially important in the concept of normal weight obesity (NWO), in which BMI falls in the normal range with higher fat percentages (Fig. 5). In an epidemiological study, the Kerala Diabetes Prevention Programme[23] found that the prevalence of NWO was 37%, and they had similar cardiometabolic outcomes as people with higher BMI.

AG fat mass ratio: It is a DEXA analogue of WHR. It is defined as the ratio between the android region (between the last thoracic rib and the upper part of iliac wings) and the gynoid region (includes the gluteofemoral region with an upper horizontal line below the pelvis line, and a lower horizontal line identified by measuring twice the height of the android region).[46] An AG ratio >1 is linked with metabolic syndrome, dyslipidemia, hypertension, and insulin resistance.[50]

- Visceral vs subcutaneous fat:

The newer DXA machines have software CoreScan™ for GE-Lunar and InnerCore™ for Hologic.[46] These measure the subcutaneous fat. The visceral fat is then estimated by subtracting subcutaneous fat from the total FM.

Studies have shown that VAT >100 cm² is associated with adverse medical outcomes.[51] Pickhardt et al. found that VAT >70 cm² in women predicted metabolic syndrome with sensitivity and specificity of 83.7 and 80.0%, respectively.[52] They also showed that subcutaneous fat was a better predictor of metabolic syndrome and its complications in men, with a cutoff of >204 cm².

- Lipodystrophy:

The differential fat distribution in genetic or acquired causes of lipodystrophy can also be studied with DXA (Fig. 6). In a study in patients with HIV,[53] it was found that a trunk fat/lower limb fat mass ratio >2.28 predicted the people who would develop lipodystrophy and metabolic syndrome. It is also important to identify these people in the diabetes cohort to screen for other related diseases like nephrotic syndrome and fatty liver. Additionally, more than half of them can be managed with insulin sensitizers.[54]

Computed Tomography and Computed Tomography Body Composition

CT uses X-ray projections from different angles to give a 3D image of parts of the body, which are differentiated based on attenuation of the rays. It can accurately determine fat in the liver and skeletal muscle.[55,56] The body composition is done using 2D analysis of specific axial slices to minimize the radiation dose and technical difficulties.[57]

Magnetic Resonance Imaging

MRI uses the magnetic properties of nuclei to estimate body composition. The precise measurement of adipose and lean tissue is done using "quantitative fat-water imaging," which is based on Dixon imaging.[58] Since there is no ionizing radiation, it is useful even in infancy. However, like CT, body composition assessment using MRI is done with one- or two-dimensional slices. Since body movement can cause artifacts during image acquisition, infants need to be sleeping while the scan is done.

Conclusion

Body composition analysis has become an essential part in the evaluation of nutritional status, obesity phenotype, and the effect of any intervention. There are various techniques available for each age group, and the choice can be made based on feasibility, accuracy, cost, and the technical skill available.

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ORIGINAL ARTICLE

Spectrum of Thyroid Disorders in Rheumatoid Arthritis

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Abstract

Introduction: Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory arthritis involving 0.5–1% of the global population. Coexistence of RA and thyroid dysfunction is now increasingly being recognized. This is due to the shared factors involved in the pathogenesis of RA and autoimmune thyroid disease. Thyroid disorder is an important amplifier of disease activity, thereby impairing the quality of life.

Objectives: To study the prevalence and pattern of thyroid dysfunction in RA patients, to compare the disease activity among RA patients with thyroid dysfunction and those without thyroid dysfunction, and to study the possible association between severe RA and thyroid dysfunction.

Methodology: A hospital-based analytical cross-sectional study was done in 165 RA patients attending the General Medicine and Rheumatology outpatient facilities of the Department of General Medicine, Government Medical College, Kozhikode, from January to December 2019. Study subjects were selected based on the inclusion and exclusion criteria. Relevant investigations were done, which included serum thyroid stimulating hormone (TSH), free thyroxine (free T4), free triiodothyronine (free T3), and anti-thyroid peroxidase antibody (anti-TPO) antibody levels. Data were analyzed using MS Excel and Statistical Package for the Social Sciences (SPSS) software. The prevalence and pattern of thyroid disorders in RA patients were assessed. The association of thyroid dysfunction with disease activity was tested.

Results: The prevalence of thyroid dysfunction among RA patients was 38.2%. The most common thyroid disorder observed was subclinical hypothyroidism, which was seen in 33.3% (55) of the study population, followed by overt hypothyroidism in 3.6% (6) of patients. Both subclinical hyperthyroidism and clinical hyperthyroidism were found in only 0.6% of RA patients. There was a significant difference in mean age between RA patients with thyroid dysfunction and euthyroid patients (p-value = 0.001). No significant association was found between the duration of RA and thyroid dysfunction (p-value = 0.253). RA patients with thyroid dysfunction had elevated inflammatory markers compared to those with normal thyroid function. The prevalence of autoimmune thyroid disorder in RA patients is 24.8%. There was a significant association between disease activity and thyroid dysfunction (p-value = 0.001). Patients with thyroid disorders had severe disease compared to euthyroid patients. A significant positive correlation was noted between serum TSH and Disease Activity Score-28 (DAS-28) (Pearson coefficient = 0.768, p-value = 0.000), and between anti-TPO antibody and DAS-28 (Pearson coefficient = 0.794, p-value = 0.000).

Conclusion: Thyroid dysfunction is prevalent in 38.2% of RA patients, with subclinical hypothyroidism being the most common thyroid disorder encountered. RA patients with thyroid dysfunction had higher disease activity than euthyroid patients. Hence, thyroid function tests should be a routine investigation in all RA patients, and if found abnormal, they should be treated appropriately.

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by symmetrical synovial inflammation, particularly involving the smaller joints of the hands and feet. It has a lifetime prevalence of 1% among the worldwide population and is associated with substantial functional disability, morbidity, and accelerated mortality.[1] Research has shown that individuals with a history of one autoimmune disease are more likely to develop additional autoimmune disorders, as these conditions often involve common underlying pathological mechanisms.[2] Characteristically, autoimmune thyroid disease involves the production of autoantibodies against thyroid antigens, such as thyroglobulin, thyroid peroxidase, or the thyroid stimulating hormone (TSH) receptor.[3] The global prevalence of autoimmune thyroid disease in RA patients exhibits significant variability, with reported rates spanning from 0.5% in Morocco to 27% in Slovakia.[4] Additionally, studies have revealed an association between RA and thyroid dysfunction, either autoimmune or non-autoimmune in origin, affecting 6–34% of RA patients.[5] According to the study by Dihingia et al. in 2017, the predominant thyroid abnormality detected in RA patients was subclinical hypothyroidism.[6] Thyroid disease is either clinically asymptomatic or has symptoms similar to those found in RA in the majority of cases; hence, thyroid dysfunction may be overlooked. Thus, it also contributes to the persistent joint pain in RA patients despite adequate inflammation control.

Many studies suggest that thyroid disorders and disease severity in RA are correlated. In a study conducted at Government Medical College, Thiruvananthapuram, Kerala, by Kumar and Aruna, it was found that serum TSH positively correlated with Disease Activity Score-28 (DAS-28), and RA patients with thyroid dysfunction had more severe disease compared to the euthyroid group.[7] However, Przygodzka and Filipowicz-Sosnowska showed that RA patients with thyroid abnormalities had lower disease activity than RA patients without thyroid disorders.[8] While numerous studies have investigated the clinical manifestations of thyroid dysfunction in RA patients, relatively few have explored its influence on disease severity and activity. Hence, this study has been undertaken to estimate the prevalence and pattern of thyroid dysfunction in RA patients, as well as to find a possible association of thyroid dysfunction with disease severity.

Methodology

A cross-sectional analytical study was conducted at the General Medicine and Rheumatology Outpatient Department of Government Medical College, Kozhikode, Kerala, from January to December 2019. Ethical clearance was obtained from the Institutional Ethics Committee prior to the commencement of the study. Patients who were diagnosed with RA for a duration of >5 years, according to the 2010 American College of Rheumatology (ACR)/European

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League Against Rheumatism (EULAR) criteria, were included in the study.[9] Exclusion criteria comprised patients aged under 13 years, pregnant or lactating females, patients with a history of thyroidectomy, malignancy on radiotherapy, those on oral contraceptive pills, sepsis, any diseases affecting thyroid function like pituitary mass, and those who were unwilling to undergo blood investigations.

A total of 165 patients satisfied the inclusion and exclusion criteria. Comprehensive medical histories and physical examinations were performed to assess joint involvement and inflammatory signs. Laboratory tests included blood routine, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), TSH, free triiodothyronine (free T3), free thyroxine (free T4), and anti-thyroid peroxidase antibody (anti-TPO) antibodies. The reference range was free T3 = 2.5–3.9 pg/mL, free T4 = 0.58–1.64 ng/dL, TSH = 0.34–5.6 µIU/mL, anti-TPO = 0–75 IU/mL. Patients were categorized as hypothyroid, euthyroid, and hyperthyroid based on the thyroid function tests. The prevalence of each thyroid disorder in RA patients was evaluated. A comparison of disease activity was done between RA patients with thyroid dysfunction and those without, using the DAS-28. The components of the score include the number of swollen joints, number of tender joints, ESR or CRP, and global assessment of health, which were fed into a complex formula.[10] The score range is <2.6—remission, >2.6 to <3.2—low, >3.2 to <5.1—moderate, >5.1—high. Data analysis was performed using MS Excel and Statistical Package for the Social Sciences (SPSS) software. Association between categorical variables was assessed using either Fisher's exact test or Chi-squared test, depending on the data characteristics. Pearson correlation was used to estimate the correlation between parameters. A p-value < 0.05 was considered statistically significant.

Results

Out of 165 patients, 125 were females and 40 were males. The mean age of the study population was 56.65 (+9.717) years. The prevalence of thyroid dysfunction in our study was 38.2% (63). Subclinical hypothyroidism was the most common abnormality detected, constituting 33.3% (55) of the study population. Table 1 demonstrates the pattern of thyroid disorders in RA patients. Patients with thyroid dysfunction had a mean age of 59.68 (+10.13) years, and those with normal thyroid function had a mean age of 54.78 (+9.0) years, and this was found to be statistically significant (p-value 0.001). Among the patients with thyroid dysfunction, 53 (84.1%) were females and 10 (15.9%) were males, and there was a significant difference between gender and thyroid status (p-value 0.049). There was no significant association between the duration of RA and thyroid status (p-value 0.253).

Analysis of Table 2 indicates that 50.8% (32) patients with thyroid disorders had co-positivity for RF and anti-CCP antibodies, whereas 52.9% of the euthyroid patients had positive RF antibodies alone. Thus, the prevalence of thyroid dysfunction is higher in RA patients with both antibodies when compared with their counterparts with a single antibody alone (p-value 0.001). In our study population, 133 (80.6%) patients had swollen and tender joints, 26 (15.8%) had joint deformity, and 3 (1.8%) had goiter. 95.2% (60) of patients with thyroid dysfunction had elevated ESR and CRP, whereas 66.7% (68) of euthyroid patients had elevated ESR alone and 9.8% (10) had normal values. This was found to be statistically significant as evidenced by a p-value of 0.001. Hence, RA patients with thyroid dysfunction had elevated inflammatory markers compared to euthyroid patients. In our study, 41 (65.1%) patients with thyroid dysfunction and 20 (19.6%) euthyroid RA patients had anti-TPO positivity, which is statistically significant (p-value 0.001). Patients with anti-TPO positivity (31.1%) had severe disease activity compared to those without anti-TPO antibody (5.8%) (p-value 0.001). The prevalence of autoimmune thyroid disorder in RA patients is 24.8%.

In our study, out of 165 patients, 47.3% (78) had low disease activity, followed by moderate disease activity in 33.3% (55) of patients. Among the RA patients with thyroid dysfunction, 39 (61.9%) patients had moderate disease activity, and 23 (36.5%) had high disease activity as per the DAS-28 scoring. From Table 3, it is evident that the majority of the euthyroid patients (75.5%) had mild disease activity. Thus, a statistically significant difference in the disease activity of RA between patients with thyroid dysfunction and patients without thyroid dysfunction (p-value 0.001) was obtained. A significant positive correlation was noted between serum TSH and DAS-28 (Pearson coefficient = 0.768, p-value = 0.000) (Fig. 1), anti-TPO and DAS-28 (Pearson coefficient = 0.794, p-value = 0.000) (Fig. 2), a significant negative correlation was noted between free T4 and DAS-28 score (Pearson coefficient = –0.170, p-value = 0.029), and no correlation between free T3 and disease activity (Pearson coefficient = –0.170, p-value = 0.210).

Table 1: Data showing the patterns of thyroid dysfunction in the study population

Thyroid status	*Frequency*	*Percentage*
Subclinical hypothyroidism	55	33.3
Overt hypothyroidism	6	3.6
Euthyroid	102	61.8
Subclinical hyperthyroidism	1	0.6
Clinical hyperthyroidism	1	0.6

Discussion

Our study encompassed 165 RA patients, diagnosed according to the 2010 ACR/EULAR criteria, consisting of 125 females

Table 2: Comparison of RA and anti-CCP antibody status among RA patients with and without thyroid dysfunction

RF and anti-CCP	*Abnormal thyroid function*	*Normal thyroid function*	*Total*
RF positive, anti-CCP positive	50.8% (32)	6.9% (7)	23.6% (39)
RF positive, anti-CCP negative	39.7% (25)	52.9% (54)	47.9% (79)
RF negative, anti-CCP positive	9.5% (6)	3.9% (4)	6.1% (10)
RF negative, anti-CCP negative	0.0% (0)	36.3% (37)	22.4% (37)
	63	102	165

Table 3: Comparison of disease activity among RA patients with and without thyroid dysfunction (p-value 0.001)

DAS-28	*Abnormal thyroid function*	*Normal thyroid function*	*Total*
<2.6	0.0% (0)	6.9% (7)	4.2% (7)
2.6–3.2	1.6% (1)	75.5% (77)	47.3% (78)
3.2–5.1	61.9% (39)	15.7% (16)	33.3% (55)
>5.1	36.5% (23)	2.0% (2)	15.2% (25)
	63	102	165

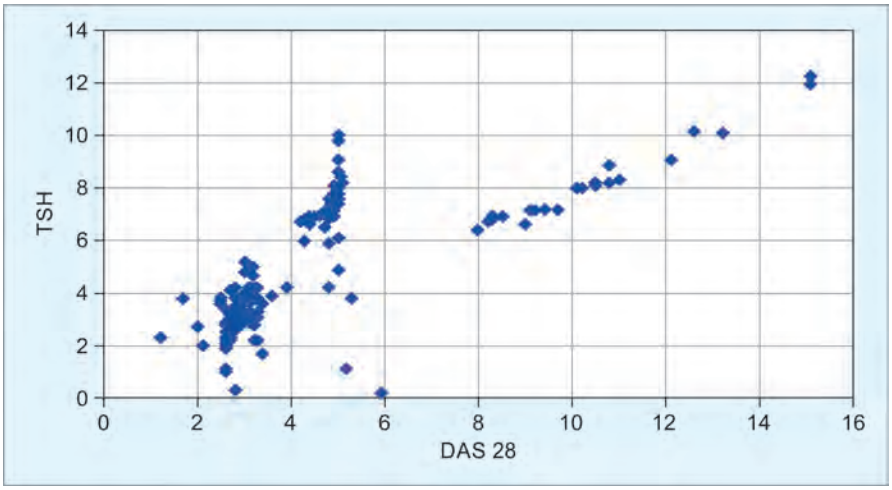

Fig. 1: Scatter diagram showing positive correlation between TSH and DAS-28 (Pearson coefficient = 0.768 and *p*-value = 0.000)

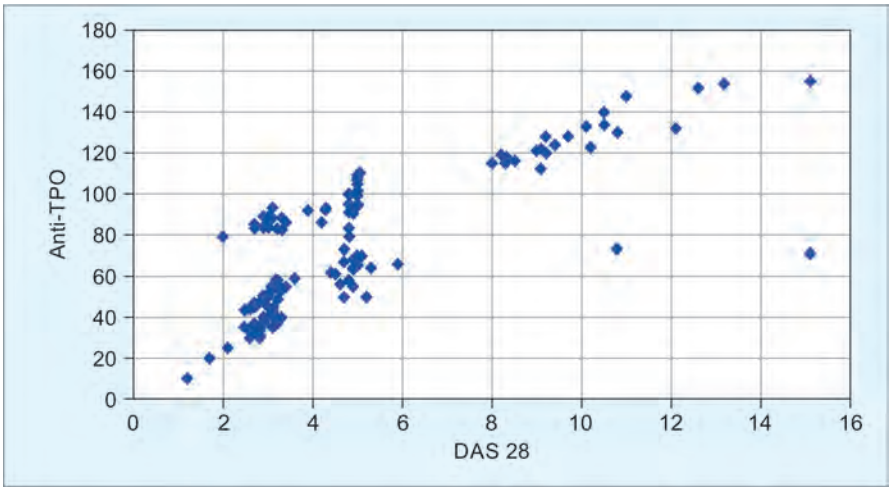

Fig. 2: Scatter diagram showing positive correlation between anti-TPO and DAS-28 (Pearson coefficient = 0.794 and *p*-value = 0.000)

and 40 males. Among those with thyroid dysfunction, 84.1% (53) were females and 15.9% (10) were males, indicating a statistically significant difference (*p*-value = 0.049). The mean age of the study population was 56.65 years (+9.717), which was comparable to Rawdha Tekaya et al.'s study, where the mean age was 55.5 ± 10.5 years.[11] A significant age difference was observed between RA patients with thyroid dysfunction [59.68 (+10.13) years] and those with normal thyroid function [54.78 (+9.0) years], with a *p*-value of 0.001. Consistent with our findings, the general population also displays an age-related escalation in thyroid dysfunction prevalence. There was no significant association between the duration of RA and thyroid disorder (*p*-value = 0.253), which is comparable to the study by Dihingia et al.[6] Hence, thyroid status is not dependent on the duration of RA. It is mainly determined by autoimmunity and the level of inflammation.

Thyroid abnormalities were detected in 38.2% (63) of RA patients, with subclinical hypothyroidism being the most common disorder, constituting 33.3% (55) of the study population, followed by overt hypothyroidism in 3.6% (6) of patients. Subclinical hyperthyroidism and clinical hyperthyroidism were found in only one patient each. Our findings align with Nadeem et al.'s study in Srinagar, which reported a 41.8% prevalence of thyroid dysfunction in RA patients, with the most frequent abnormality observed being subclinical hypothyroidism (37.9%).[12] In contrast to our findings, the most common thyroid dysfunction in the study by Kumar and Aruna was overt hypothyroidism.[7] The prevalence of thyroid dysfunction is higher in RA patients with both antibodies compared to their counterparts with a single antibody alone. This was consistent with the study by Mosli and Attar in 2014, in which a significant association was observed between RF-positive RA and hypothyroidism (*p* = 0.027).[13]

Anti-thyroid peroxidase antibody antibodies were seen in 65.1% (41) patients with thyroid dysfunction, which was statistically significant (*p*-value = 0.001), as in the study by Nadeem et al.[12] Among them, 67% had subclinical hypothyroidism. Twenty (19.6%) euthyroid patients were found to have positive anti-TPO antibodies. Hence, the detection of anti-TPO antibodies in euthyroid individuals may serve as a predictive indicator for the potential onset of overt thyroid disease in the future.

There were significantly higher levels of inflammatory markers among patients with thyroid dysfunction (*p*-value = 0.001). About 95.2% of patients with thyroid dysfunction had both elevated ESR and CRP, whereas among the euthyroid group, 23.5% had raised ESR and CRP. Our findings align with the study by Kumar and Aruna in Government Medical College, Thiruvananthapuram, in which both ESR (*p*-value = 0.01) and CRP (*p*-value = 0.001) had significant associations with thyroid dysfunction. The shared inflammatory pathogenesis of thyroid dysfunction and RA, coupled with the association between thyroid dysfunction and disease severity, provides a rationale for increased inflammatory markers like ESR and CRP.

In our study, 61.9% (39) patients with thyroid disorder had moderate disease activity, and 36.5% (23) had high disease activity as per the DAS-28 scoring. In contrast, the majority of euthyroid patients (75.5%) had mild disease activity, and only 2% had severe disease activity. Thus, RA patients with thyroid dysfunction had higher disease activity compared to those with normal thyroid function (*p*-value = 0.001). This was comparable to the study by Azeem et al., where 60% of patients with thyroid dysfunction had moderate activity, and 20% had severe disease activity, compared to euthyroid patients, in which 45% had mild disease and only 2.5% had high disease activity (*p*-value = <0.01).[14] Studies by Elattar et al.[4] and Dihingia et al.[6] also depicted a significant association of disease activity with thyroid dysfunction. The coexistence of thyroid disorder and RA amplifies the inflammatory process, resulting in exacerbation of disease activity, which is marked by increased joint inflammation and higher DAS-28 scores. Anti-TPO antibody showed a significant association with disease activity (*p*-value = 0.001). This implies that patients with anti-TPO positivity (31.1%) had severe disease compared to those without anti-TPO antibody (5.8%). In our study, a

significant positive correlation was observed between serum TSH and anti-TPO antibody with the DAS-28 scores, indicating that increased serum TSH and anti-TPO antibody titer are associated with higher disease activity. This was consistent with the study by Kumar and Aruna.[7]

Conclusion

The prevalence of thyroid dysfunction among RA patients in our study was 38.2%. The most common thyroid disorder was subclinical hypothyroidism, accounting for 33.3% of the study population. RA patients with thyroid abnormalities had higher disease activity than their counterparts with normal thyroid function. Hence, regular thyroid function tests should be done in all RA patients to detect thyroid dysfunction, enabling timely management and improved disease outcomes.

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ORIGINAL ARTICLE

A Study of Bedside Diagnosis of Bacterial Meningitis Using Urinary Strip Reagent for Semiquantitative Analysis of Cerebrospinal Fluid

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Abstract

Background: Meningitis is an inflammatory disease of the leptomeninges and is defined by the abnormal number of white blood cells (WBCs) in the cerebrospinal fluid (CSF). Meningitis-related mortality and morbidity can be decreased with early diagnosis and antibiotic administration. The most reliable method of diagnosis is still CSF analysis. Yet, a straightforward bedside test would be helpful for early identification due to the absence of experienced staff, laboratory, and transport services at the primary health care level in developing countries.

Materials and methods: Patients fitting the inclusion criteria were admitted to Gandhi Hospital, and a lumbar puncture was performed under aseptic conditions. Using the SEIMENS Multistix 10 SG reagent strip as the index test and CSF microscopy and biochemistry as the gold standard diagnostic test, CSF was examined for proteins, sugars, and leukocytes.

Results: Among 100 CSF specimens evaluated, 52 (52%) were normal and 48 (48%) were considered as having pleocytosis. The overall performance of the urine leukocyte strip when compared to CSF leukocytes had a sensitivity of 95.8%, specificity of 67.3%, negative predictive value (NPV) of 94.6%, and positive predictive value (PPV) of 73.1%. The protein portion of the urine strip was compared to quantitative CSF proteins and showed a sensitivity of 90%, specificity of 70%, PPV of 66.7%, NPV of 91.3%, and diagnostic accuracy of 78%. The glucose portion of the reagent strip also performed better than the standard test, with a sensitivity of 100%, specificity of 93.8%, PPV of 90%, NPV of 100%, and diagnostic accuracy of 96%. For the diagnosis of bacterial meningitis, the strip glucose showed a sensitivity of 100%, specificity of 69.7%, PPV of 35%, NPV of 100%, and diagnostic accuracy of 74%. The significance of the reagent strip test for leukocytes, proteins, and sugars, when compared to the standard test, was established at a 95% confidence interval (CI) using the Pearson Chi-squared test.

Conclusion: The urinary reagent strip is a simple test for a semiquantitative assessment of CSF, which may help with the diagnosis of meningitis at the point of care. It can also assist in deciding whether to begin antimicrobial therapy in settings with limited resources.

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Introduction

Meningitis is an inflammation of the leptomeninges, that is, the dura mater, arachnoid mater, and pia mater, that enclose the brain and spinal cord. The etiology of meningitis can be both infectious and noninfectious. Among the infectious causes, meningitis can be caused by various bacteria, viruses, mycobacteria, parasites, and fungi.[1,2] The most serious form of meningitis is caused by bacteria, although viral meningitis is the most prevalent worldwide; both are important contributors to morbidity and mortality.[2,3] The usual presentation of a patient with acute meningitis is with altered mental status, fever, and neck rigidity.[3,4]

Despite numerous advances in the management of infectious diseases, particularly concerning bacterial meningitis, such as the development of novel vaccines and antibiotics, there hasn't been much advancement in its diagnostic techniques. According to estimates, low-income countries have a larger disease burden than high-income ones. A basic bedside test would be helpful in rural and distant places without adequate transportation facilities.[5] Usually, to establish the diagnosis of meningitis, cerebrospinal fluid (CSF) is collected for cell count, cytology, routine biochemistry, gram stain, culture, antibodies against antigens using polymerase chain reaction (PCR), and immunohistochemistry analysis. In urban centers or tertiary hospitals, a CSF analysis can be easily done. A biochemistry study of the CSF can take up to 24 hours, which emphasizes the need for a bedside diagnostic test that can help with the early commencement of empirical therapy.[6]

Materials and Methods

Sample Size

One hundred patients during the study period in Gandhi Hospital, Secunderabad, Telangana.

Study Setting

Patients admitted to medical wards in Gandhi Hospital, Secunderabad, Telangana. IRB name: Institutional Ethics Committee Approval Number: IEC/GMC/2020/01/34.

Data Collection

All enrolled patients were informed about the nature of the study, and informed consent was obtained before inclusion in the study. Patients admitted were tested for all routine investigations and subjected to CSF analysis. A SIEMENS Multistix 10 SG reagent strip was used as the index test, and CSF microscopy and biochemistry were used as the reference standard for comparison.

Inclusion and Exclusion Criteria

Table 1 shows the inclusion and exclusion criteria considered for the study.

Methods

Patients who met the inclusion criteria and were admitted to Gandhi Hospital during the study period underwent CSF analysis as

Table 1: Inclusion and exclusion criteria

Inclusion criteria	*Exclusion criteria*
Age >18 years	All patients <18 years
Fever or prior history of recent fever	Patients who have been started on antibiotics >48 hours
Any one or more of the following: neck stiffness, vomiting, seizures, altered sensorium	

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well as all other regular investigations. The CSF was examined using CSF microscopy and biochemistry as reference standards and the SEIMENS Multistix 10 SG reagent strip as the index test.

The manufacturer's color grading system[7] for the white blood cell (WBC) count described below was used to interpret the CSF WBC count:

- <10 granulocytes/mm^3 = no color
- 10–100 granulocytes/mm^3 = 1+
- 100–500 granulocytes/mm^3 = 2+
- >500 granulocytes/mm^3 = 3+

Results from the reagent strip for CSF glucose were interpreted as below:

- Glucose <50 mg/dL = no color change
- Glucose >50 mg/dL = color change

Proteins on reagent strip were interpreted as follows:

- <30 mg/dL = no change in color
- 30 and 100 mg/dL = 1+
- 100 and 500 mg/dL = 2+
- >500 mg/dL = 3+

The reference tests done were total and differential CSF cell counts by microscopy (using a Neubauer's chamber), CSF sugars and protein levels by biochemistry, CSF gram stain, culture, and *Mycobacterium tuberculosis*-cartridge-based nucleic acid amplification test (MTB-CBNAAT) for confirmation of diagnosis.

Results

Characterization of Study Population

During the study period between 2019 and 2021, 100 patients fitting the study criteria were included. Sixty-two out of 100 participants were men, and 38 out of 100 were women. The mean age of participants was 43.34, with the minimum being 21 and the maximum being 78. Fever was the most common symptom, with 94 out of 100 patients having fever at the time of hospital admission. Six patients had a history of fever before hospital admission, followed by altered mental status (73%), seizures (46%), irritability (44%), headache (37%), neck stiffness (36%), vomiting (16%), and cranial nerve palsy (4%).

Among the admitted patients, 35 out of 100 (15%) were on antibiotics. Thirty-four patients were on a single antibiotic, and one patient was on two antibiotics.

The baseline lab parameters are shown in Table 2.

Out of 100 patients, 25 were positive for human immunodeficiency virus (HIV). Thirteen were aware of their positive status at admission, but only 4 out of 13 were on treatment. Twelve patients were diagnosed de novo during admission in our hospital, and the remaining 75 were negative for HIV.

The most frequent diagnosis observed among the 100 admitted patients, as demonstrated, was viral encephalitis (18%), followed by bacterial meningitis (14%), tubercular meningitis (8%), and aseptic meningitis (4%). There were nine cases of suspected meningitis, seven bacterial and two tuberculous meningitis, but no microbiological evidence was obtained and they were not included in the study.

Bacterial meningitis cases were confirmed by positive culture or Gram stain. Suspicion of tubercular meningitis was based on clinical features, contact with tuberculosis, raised erythrocyte sedimentation rate (ESR), presence of extrapulmonary tuberculosis elsewhere, and confirmed by positive CSF nucleic acid amplification test (CBNAAT) and significant adenosine deaminase (ADA) levels in CSF. There was one case of fungal meningitis; cryptococcal species was identified by latex agglutination of CSF. Out of 14 viral encephalitis cases, one case was positive for herpes simplex virus (HSV) detected by HSV PCR, and one case was positive for Japanese encephalitis, also detected by PCR. The category "others" includes patients with sepsis, hyponatremia, cerebrovascular accident, alcohol withdrawal, malaria, central pontine myelinolysis, and acute disseminated encephalomyelitis (ADEM).

Table 2: Blood and CSF parameters of study population

Blood parameters	
WBC (mean ± SD)	16.44 ± 10.48 (10.00–19.25)
Neutrophil% (mean ± SD)	62.10 ± 19.08 (49–77)
Lymphocyte% (mean ± SD)	26.21 ± 16.1 (13–39)
Platelets*10^3 (mean ± SD)	353.7 ± 211.7 (175–489)
CSF	
Pleocytosis (defined as WBC >10 cells/mm^3)	48/100
Positive CSF culture	10/100
Positive gram stain	4/100

Results of Cerebrospinal Fluid Analysis

Cerebrospinal Fluid Leukocyte Count

Out of the 100 samples, 52 were considered normal with a CSF count <10 cells/mm^3, and 48 samples were pleocytic (WBC >10 cells/mm^3), shown below in Table 3.

Among the 48 samples with pleocytosis on microscopy (>10 cells/µL), the average cell count was 343.11. Out of these 48 samples, 10 had a positive culture, four had a positive gram stain, and four had a positive CSF CBNAAT for *M. tuberculosis*.

We compared the accuracy of the urinary reagent strip and a laboratory-based CSF WBC cell count performed at two distinct cutoff values: 10 and 100 cells/mm^3 in Tables 4 and 5.

Table 4: Sensitivity, specificity, and diagnostic accuracy of strip leukocytes compared to CSF leukocytes at cutoff above 10 cells (*N* = 100)

Strip leukocytes	*CSF leukocytes*	
	>10 cells/mm^3	*<10 cells/mm^3*
>10 cells/mm^3	46	17
<10 cells/mm^3	2	35
Chi-squared test, *p*-value <0.001, significant		
Sensitivity = 95.8%		
Specificity = 67.3%		
PPV = 73.1%		
NPV = 94.6%		
Diagnostic accuracy = 81.0%		

Table 5: Sensitivity, specificity, and diagnostic accuracy of strip leukocytes compared to CSF leukocytes at cutoff above 100 cells (*N* = 100)

Strip leukocytes	*CSF leukocytes*	
	>100 cells/uL	*<100 cells/uL*
>100 cells/uL	18	2
<100 cells/uL	8	72
Chi-squared test, *p*-value <0.001, significant		
Sensitivity = 69.2%		
Specificity = 97.3%		
PPV = 90.0%		
NPV = 90.0%		
Diagnostic accuracy = 90.0%		

Table 3: Distribution of study subjects on the basis of CSF leukocytes and urinary strip leukocytes

CSF leukocytes	*No.*	*Percent*	*Strip leukocytes*	*No.*	*Percent*
<10 cells/mm^3	52	52.0	1+	43	43.0
10–100 cells/mm^3	22	22.0	2+	20	20.0
>100 cells/mm^3	26	26.0	Negative	37	37.0

The reagent strip fared slightly better than the CSF cell count, with a higher specificity and higher positive predictive value (PPV).

Cerebrospinal Fluid Proteins

According to CSF protein estimation in the laboratory, out of 100 samples, 60 had <100 mg/dL proteins, and 40 had >100 mg/dL proteins. In all 14 patients with established bacterial meningitis, CSF proteins were >100 mg/dL. In 86 patients without bacterial meningitis, CSF proteins were >100 mg/dL in 26 and <100 mg/dL in 60 patients. The standard test for estimation of CSF proteins in our setup had a sensitivity of 100%, specificity of 69.7%, PPV of 35%, negative predictive value (NPV) of 100%, and diagnostic accuracy of 74%, as shown in Table 6.

Reagent Strip Test for Proteins

Among the 100 samples of CSF collected, 80 (80%) showed a positive reaction on the reagent strip. The 2+ reading represents a protein concentration of 100 mg/dL and was adopted because infective meningitis often results in a CSF protein concentration ≥100 mg/dL. Based on this cutoff point at 2+, 54 (54%) were considered positive for protein, and 46 (46%) were considered negative, shown in Table 7.

The reagent strip protein was compared to the standard laboratory test at a cutoff of 100 mg/dL, shown below in Table 8.

The sensitivity of the test was 90%, specificity was 70%, PPV was 66.7%, NPV was 91.3%, and diagnostic accuracy was 78%. There was a significant correlation with a *p*-value < 0.001 [99.9% confidence interval (CI)] using the Pearson Chi-squared test.

Table 6: Results of CSF proteins in adults with and without bacterial meningitis

CSF protein	*Bacterial meningitis*	*No bacterial meningitis*
>100 mg/dL	14	26
<100 mg/dL	0	60
Sensitivity = 100.0%		
Specificity = 69.7%		
PPV = 35.00%		
NPV = 100.0%		
Diagnostic accuracy = 74%		

Table 7: Distribution of study subjects according to reagent strip proteins (*N* = 100)

Strip proteins	*No.*	*Percent*
1+	26	26.0
2+	40	40.0
3+	14	14.0
Negative	20	20.0

Glucose

Cerebrospinal fluid glucose was measured for 100 samples. Thirty-six out of 100 were <50 mg/dL, and 64 out of 100 were >50 mg/dL. The reagent strip was positive for 60 samples and negative for 40 samples, as shown below in Table 9.

Since bacterial meningitis is associated with a CSF glucose level <2/3 of blood glucose levels, we took a negative glucose reading as <50 mg/dL on the strip. A color change on the strip is indicative of a glucose reading >50 mg/dL. We compared the strip glucose results with quantitative CSF glucose readings and found the strip to have a sensitivity of 100%, specificity of 93.8%, PPV of 90%, NPV of 100%, and diagnostic accuracy of 96% when compared to the gold standard test. There was a significant correlation with a *p*-value < 0.001 (99.9% CI) using the Pearson Chi-squared test, as shown in Table 10.

Strip glucose for the diagnosis of bacterial meningitis showed a sensitivity of 100%, specificity of 69.7%, PPV of 35%, NPV of 100%, and diagnostic accuracy of 74%, as shown in Table 11.

Pearson Chi-square was tested among these categorical variables to test for independence. We observed a significant relationship between negative CSF glucose and bacterial meningitis ($\chi^2 > 24.419$, $N = 100$), $p < 0.05$.

Discussion

Bacterial meningitis is an illness that can be fatal. The prognosis of a patient with acute meningitis depends on early diagnosis and treatment. Though diagnostic techniques for bacterial meningitis have been studied extensively, with methods ranging from identification of clinical signs and symptoms to sophisticated tests like latex agglutination tests, PCR, and cytokine levels in CSF, a majority of these tests are not available in areas with limited resources, making it difficult to diagnose meningitis. Clinically, it can be difficult to distinguish between bacterial meningitis and conditions like cerebral malaria, encephalitis, etc., making it challenging for doctors to decide when to prescribe antibiotics. The optimal test for diagnosing bacterial meningitis should be 100% sensitive and 100% specific to guarantee that no cases are overlooked. However, no test has ever been shown to be 100% sensitive and specific, suggesting that clinical and laboratory characteristics must be considered simultaneously to make a diagnosis.

Parmar et al. conducted a prospective clinical single-blinded investigation on 63 children suspected of having meningitis, comparing the results of the CSF with the Combur reagent strip.[8] Godyn's test was employed to assess the accuracy of the reagent strip. In their study, the reagent strips' sensitivity and specificity were

Table 8: Sensitivity, specificity, and diagnostic accuracy of strip proteins compared to CSF proteins at cutoff above 100 mg/dL (+2 on strip) (*N* = 100)

Strip proteins	*CSF proteins*	
	>100 mg/dL	*<100 mg/dL*
>100 mg/dL	36	18
<100 mg/dL	4	42
Chi-squared test, *p*-value < 0.001, significant		
Sensitivity = 90.0%		
Specificity = 70.0%		
PPV = 66.7%		
NPV = 91.3%		
Diagnostic accuracy = 78.0%		

Table 9: Distribution of study subjects on the basis of strip and CSF glucose (*N* = 100)

Glucose	*Reagent strip*	*CSF*
<50 m/dL	40	36
>50 mg/dL	60	64

Table 10: Sensitivity, specificity, and diagnostic accuracy of strip glucose compared to CSF glucose (*N* = 100)

Strip glucose	*CSF glucose*	
	<50 mg/dL	*>50 mg/dL*
<50 mg/dL	36	4
>50 mg/dL	0	60
Chi-square test, *p*-value < 0.001, significant		
Sensitivity = 100.0%		
Specificity = 93.8%		
PPV = 90.0%		
NPV = 100.0%		
Diagnostic accuracy = 96.0%		

Table 11: Frequency of glucose reagent strip results among cases of bacterial meningitis

Strip glucose	*Bacterial meningitis*	*No bacterial meningitis*
<50 mg/dL	14	26
>50 mg/dL	0	60
Sensitivity = 100.0%		
Specificity = 69.7%		
PPV = 35.00%		
NPV = 100.0%		
Diagnostic accuracy = 74%		

97.14 and 96.42% for the diagnosis of meningitis, respectively. The sensitivity and specificity for bacterial meningitis and tuberculous meningitis were 96.55 and 100%, respectively. A score >80 was required, per Godyn's suggested scoring system, to designate the reagent strip method as a valid screening technique. The diagnostic accuracy rates for tuberculous meningitis, aseptic meningitis, bacterial meningitis, and meningitis overall were 96.78, 98.2, 98.27, and 83.0%, respectively.[9] Like the Parmar study,[8] Moosa et al. achieved a sensitivity of 97% for the diagnosis of bacterial meningitis based on the use of a urine strip and a specificity of 100%.[10] Romanelli et al. compared the results of reagent strips and those of the cytological and biochemical assay, and obtained values for sensitivity, specificity, positive and NPVs, and accuracy (90.7, 98.1, 95.1, 96.4, and 96.1%, respectively) for the diagnosis of bacterial meningitis.[11] Studies by Bonev and Gledhill,[12] Kumar et al.,[13] and Schwartz and Parke[14] showed similar results, hence confirming the urine reagent strip to be a good bedside test.

The prevalence of bacterial meningitis among 100 patients admitted in our study was 14%. The number of suspected cases of bacterial meningitis was seven, even though culture and Gram stain didn't reveal positive results. These cases were not included while studying the comparison between the index test and gold standard tests. The prevalence of tuberculous meningitis was 8%, and aseptic meningitis was 4%. The reduced rate of microbe detection in the lab and the administration of antibiotics prior to lumbar puncture may account for the lower culture positivity in our context. As per Kanegaye et al.,[15] CSF sterilization in cases of meningococcal meningitis can happen as soon as 2 hours following the delivery of a single dosage of third-generation cephalosporins.[15] In our investigation, *Neisseria meningitidis* and *Streptococcus pneumoniae* were the most often found pathogens. Our investigation did not turn up any *Haemophilus influenzae*, which may be because of the immunization program in our nation. In individuals with suspected meningitis, fever (94%), changed sensorium (73%), seizures (46%), agitation (44%), and stiff neck (36%) were the most common presenting signs and symptoms.

When we compared the reagent strip's ability to identify CSF leukocytes to microscopy (the gold standard), we found that at a cutoff of 1+, the test's sensitivity was 95.8%, specificity was 67.3%, PPV was 73.1%, NPV was 94.6%, and diagnostic accuracy was 81%. The test's sensitivity was 69.2%, specificity was 97.3%, PPV was 73.1%, NPV was 90.0%, and diagnostic accuracy was 90% at a cutoff of 2+ on the reagent strip. For leukocyte detection by reagent strip, specificity, diagnostic accuracy, and NPV were all improved at a threshold of 2+ (>100 cells/mm).

The reagent strip demonstrated 100% sensitivity, 93.8% specificity, 90% PPV, 100% NPV, and 96% diagnostic accuracy for detection of CSF glucose when compared to quantitative CSF glucose values by biochemistry. The results of using strip glucose to diagnose bacterial meningitis were 100% sensitivity, 69.7% specificity, 35% PPV, 100% NPV, and 74% diagnostic accuracy. Another significant finding from our investigation is the NPV, which indicates the percentage of individuals with negative test results who are disease-free. When evaluating CSF glucose, proteins, and leukocytes, the reagent strip's NPV was noticeably high. Urine reagent strips can reasonably accurately determine CSF leukocyte counts >10 and 100/mm^3, CSF protein levels >100 mg/dL, and CSF glucose levels <50 mg/dL. Even with these results, however, clinicians and laboratories in resource-constrained environments are reluctant to use this bedside test because of the different cutoffs for protein and glucose readings for CSF and urine tests. These strips can be customized to provide CSF analytical cutoffs that are clinically significant. The urine reagent analytical cutoffs for proteins are 30, 100, and 500 mg/dL. CSF protein levels can be adjusted to 45, 100, or 500 mg/dL since anything >45 mg/dL is considered abnormal. Similarly, the present strip's lowest cutoff for CSF sugar detection can be lowered from 50 to 40 mg/dL because a low CSF glucose is more clinically meaningful. The strips may be set up to include just three factors—proteins, glucose, and granulocytes—instead of the 10, which could reduce their cost and improve the efficiency of CSF strip analysis. The test pad's color may change in situations involving bloody taps or lumbar punctures, thus producing false-positive findings. In these situations, care must be taken while interpreting the data.

We conducted this investigation in a blinded manner, and CSF laboratory tests and the reagent strip testing were completed within 30 minutes of receiving the sample. A limitation of the study is its small sample size. Another disadvantage of our study is the inclusion of patients who had already received empirical antibiotics. Administering antibiotics can significantly alter blood leukocyte counts, but not giving empirical antibiotics for suspected cases of meningitis would be lethal to the patients. Since these drugs are given in the emergency as soon as they arrive, it was difficult to draw CSF samples for all patients without prior antibiotic exposure. As previously mentioned, another disadvantage is the variation in clinically significant cutoffs for CSF and urine analysis. Even though this simple test has been described and studied since the early 1970s, the test has not been used extensively till now due to a lack of awareness and results from large trials. Trials in multiple centers across the nation will give us an idea of how this bedside test can have an impact in early intervention in bacterial meningitis. Selecting only confirmed cases of bacterial meningitis for comparison between strip reagent and gold standard testing would have been more beneficial in this study, but at the cost of changes in results due to prolonged exposure to antibiotics and observer bias.

Conclusion

According to our research, urine reagent strips can accurately and swiftly diagnose bacterial meningitis with good specificity and sensitivity. They can help in deciding quickly whether to provide empirical antibiotics to patients with a suspicion of meningitis. While waiting for the results of the standard test, doctors may use urine reagent strips as an additional tool to help them manage the patient. This is particularly crucial in developing nations without laboratory facilities or when a reporting delay is anticipated. Though, while measuring a few parameters such as CSF leukocytes and glucose, the reagent strip functioned better in our environment than the gold standard tests, these strips do have some limitations, which have already been mentioned above. If these limitations are overcome, they will make a very good tool for bedside diagnosis of meningitis.

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ORIGINAL ARTICLE

Comparative Study of Efficacy and Safety of Dapagliflozin vs Basal Insulin in Stabilizing Glycemic Variability in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Triple Drug Combination Therapy

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Abstract

Wide variations in glucose levels may enhance oxidative stress and inflammation, sequentially resulting in endothelial cell damage. Insulin glargine, a basal insulin, is associated with good glycemic control with fewer events of hypoglycemia. Dapagliflozin is a selective inhibitor of sodium-glucose cotransporter 2 (SGLT-2) that reduces blood glucose by enhancing its urinary excretion. Continuous glucose monitoring (CGM) allows continuous assessment of interstitial glucose over time, allowing individualization of diabetes management.

Objective: To compare the efficacy and safety of dapagliflozin vs basal insulin in stabilizing glycemic variability (GV) in patients with type 2 diabetes mellitus (T2DM).

Materials and methods: A 1-year, prospective, randomized, open-label, single-center, double-arm, interventional clinical study was conducted at Deogiri Diabetes Care Centre, Aurangabad. About 100 patients with T2DM who were inadequately controlled on triple drug combination therapy were randomized into group A ($N = 50$), receiving dapagliflozin 10 mg once daily (OD), and group B ($N = 50$), receiving insulin glargine as the fourth glucose-lowering agent for 3 months. The "FreeStyle Libre Pro®" ambulatory glucose monitoring (AGM) sensor was used for the study to evaluate the coefficient of GV, time in range (TIR)%, time below range (TBR)%, time above range (TAR)%, and glucose management index (GMI).

Results: A significant reduction in the values of GV parameters (TIR, TAR, TBR, GMI, and coefficient of GV) and glycemic parameters like fasting blood sugar (FBS), postprandial blood sugar (PPBS), glycated hemoglobin (HbA1C), and change in body weight of patients was observed in both groups after 3 months of therapy.

Conclusion: Insulin glargine, as the fourth glucose-lowering agent on the background of a triple drug regimen, has demonstrated a significant reduction in GV compared to that observed with dapagliflozin.

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Introduction

Diabetes mellitus, a heterogeneous group of metabolic syndromes, is characterized by chronic hyperglycemia. In the Southeast Asian region, with around 74 million people with diabetes, India has emerged as the diabetes capital, with an approximate prevalence of 9.8%.[1]

Being an easily available and accessible methodology, glycated hemoglobin (HbA1c) has been considered the gold standard method to assess glycemic status and overall response to glucose-lowering therapy in patients with diabetes mellitus.[2] During the last three decades, it has been observed through several epidemiological studies that raised levels of HbA1c are a significant point of reference for diabetic complications. Additionally, a reduction in HbA1c levels is correlated with a marked alleviation of cardiovascular complications and diabetes-associated morbidity and mortality.[3]

In accordance with observations from these epidemiological studies, major organizations working on diabetes have established treatment objectives of HbA1c in a range between 6.5 and 7.5% for most patients with diabetes, while emphasizing the disease duration, life expectancy, patient preferences, available resources, and risk of development of hypoglycemia.[4] But the notable limitation is that HbA1c assesses only the cumulative value of glycemic data for the past 3 months and does not reflect day-to-day glycemic excursions.[5]

Wide variations in glucose levels may enhance oxidative stress and inflammation, which sequentially result in endothelial cell damage. Several studies have demonstrated the association of glucose excursions with increased risk of cardiovascular complications, cognitive function decline, ultimately limiting the quality of life. Glycemic variability (GV) is an index of hyper- and hypoglycemia that assesses both the amplitude of the excursion, that is, how far the blood glucose level is out of range, and the time spent in the excursion (for how long the blood glucose is out of the normal range).[6] Thus, in patients with diabetes, GV is rapidly emerging as an independent risk factor for the development of cardiovascular mortality.[7]

While conducting continuous glucose monitoring (CGM), we consider various parameters such as time in range (TIR), time above range (TAR), time below range (TBR), glucose monitoring index (GMI), and coefficient of GV (% CV with a target of ≤36%). TIR could be very useful to clinicians to alleviate the diabetes-associated risks, as it may yield a more precise evaluation of hypoglycemia and assessment of glycemic stability.[8] The TIR metric clearly measures the percentage of time for which the glucose level is within a prespecified target range, and thus systematizes the use of the primary glucose range between 70 and 180 mg/dL as a standard.[9] TAR level I specifies the glucose concentration range between 180 and 250 mg/dL, and a value >250 mg/dL is considered as level II TAR. Similarly, glucose concentration between <70 and >54 mg/dL is considered as level I TBR, and level II TBR is attributed to a value <54 mg/dL. Thus, for reanalyzing the glucose-lowering treatment regimen, time below metrics (<70 and <54 mg/dL) and time above measures (>180 mg/dL) can be considered as very helpful parameters.[9]

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Continuous glucose monitoring allows a continuous assessment of the interstitial glucose over time. Thus, analysis of different variables such as glucose variations, hypoglycemic events, and TIR can be ascertained.[10] In the present practice, real-time CGM (rtCGM) or intermittent scan CGM (isCGM) are both available. Diabetes patients with a high risk of frequent or severe hypoglycemia events, and those with impaired cognizance of hypoglycemia, are the most benefited.[6,11] The most important advantage of continuous glucose monitoring system (CGMS) is that it helps in individualization of diabetes management.

Hence, some investigators are of the opinion that the combined approach with blood glucose variations and HbA1c levels can serve as an essential index for assessment of glycemic control and the risk of development of long-term micro- and macrovascular complications.[12]

Insulin glargine (Lantus; Sanofi Aventis U.S., Bridgewater, NJ), a basal insulin, is one of the injections used in a multiple daily injections (MDI) regimen. As compared with NPH insulin in adults with type 1 or type 2 diabetes, glargine is associated with good glycemic control and fewer events of hypoglycemia. This quality has been attributed to its restricted variations in site absorption and little or no noticeable action peak.[13–15]

Dapagliflozin is a selective inhibitor of sodium-glucose cotransporter 2 (SGLT-2) that enhances urinary excretion of glucose and hence reduces blood glucose. Several studies conducted recently observed that when dapagliflozin was administered in combination with other glucose-lowering drugs, with or without insulin treatment, it improved HbA1c levels by minimizing blood glucose levels.[16] Some researchers also reported that in patients with T2D receiving insulin treatment, SGLT-2 inhibitors could improve GV.[17]

We conducted a 1-year, prospective, randomized, open-label, single-center, double-arm, interventional, clinical study in patients with type 2 diabetes mellitus (T2DM) who were inadequately controlled on three oral glucose-lowering agents. One group received dapagliflozin as the fourth glucose-lowering agent, and the other group received insulin glargine as the fourth glucose-lowering agent for 3 months. The "FreeStyle Libre Pro®" ambulatory glucose monitoring (AGM) sensor was applied to the patients for the study to evaluate glycemic excursions.

Materials and Methods

A 1-year, prospective, randomized, open-label, single-center, double-arm, interventional, clinical study was conducted at Deogiri Diabetes Care Centre, Aurangabad. The study was conducted from November 2022 to October 2023 in patients with T2DM who were inadequately controlled on triple drug combination therapy, aged between 18 and 65 years (N = 100). The inclusion criteria were patients of either sex (male or female) having T2DM, with HbA1c >8.5% despite using three oral glucose-lowering agents, who were willing to give written informed consent. Newly diagnosed T2DM patients, patients with type 1 DM, gestational DM, diabetic ketoacidosis, hyperosmolar hyperglycemic state, patients with recurrent urinary tract infections (UTI), and patients with an estimated glomerular filtration rate (eGFR) value <45 mL/minute/1.73 m^2 calculated by the modification of diet in renal disease (MDRD) formula were not included in the study. Patients with any hepatic or renal disease, pregnant or lactating women, and those with known allergies to drugs were also excluded from the study.

All the patients participating in the study were explained clearly about the purpose and nature of the study in the language they could understand. They were included in the study only after obtaining a written informed consent form (ICF).

Following the approval of the Institutional Ethics Committee, the study was initiated. All information pertaining to the patient visiting the outpatient department, such as the patient's age, gender, occupation, relevant history, past history, and drug therapy given, was recorded in a case record form (CRF). Details of the prescribed drugs for diabetes mellitus, and all other drugs used in the patient during treatment, were recorded. They include the dose, duration, type of dosage form used, frequency of drug administration, etc., and necessary information was recorded in a structured CRF.

The T2DM patients who were inadequately controlled on triple drug combination (N = 100) were randomized into two groups. One group (group A) (N = 50) received Dapagliflozin 10 mg once daily (OD) as the fourth glucose-lowering agent, and the other group (group B) (N = 50) received insulin glargine [started with 10 U at bedtime and gradually doses were escalated depending upon (self-monitoring of blood glucose (SMBG)] as the fourth glucose-lowering agent for 3 months. The "FreeStyle Libre Pro®" AGM sensor was used for the study. Upon receiving voluntary consent from patients, the sensors were applied to the patients for 14 days before initiating the therapy in both groups. Sensor data were recorded and checked accordingly. About 3 months after starting the respective therapies in both groups, the "FreeStyle Libre Pro®" AGM sensors were again applied to the patients for 14 days. Sensor data were recorded and checked at the end of the study to assess the GV. Upon completion of 14 days, the sensors were removed. The AGP report, combining all the data elements including the coefficient of GV, TIR%, TBR%, TAR%, and GMI, were checked in both groups before and after initiating the therapies.

Study assessment was done by evaluating the study visit checklist, which included informed consent, screening for inclusion criteria and exclusion criteria, and general and physical examination. Electrocardiogram (ECG), serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), kidney function test (KFT), urinary microalbumin level, serum creatinine level, and blood pressure with safety assessment were performed at baseline, and changes in glycaemia parameters like fasting blood sugar (FBS), postprandial blood sugar (PPBS), HbA1C, and CGM parameters (TIR, TAR, TBR, GMI, coefficient of GV) were assessed at baseline and at the end of 3 months.

The primary endpoint was the comparison of efficacy of dapagliflozin vs insulin glargine as the fourth GLT on FBS, PPBS, HbA1C, and CGMS parameters in patients with T2DM inadequately controlled on triple drug combination. The secondary endpoint was to study the safety of dapagliflozin and insulin glargine in patients in both treatment groups. Safety assessment was performed by general and systemic examination and as per adverse drug reactions (ADRs) reported by patients.

For the calculation of sample size for the present study, G*Power software was used. Considering α level = 0.01, power = 0.80, and large effect size = 0.8, using G*Power software, the sample size was found to be 50 patients in each group.

Data were entered in Microsoft Excel and analyzed using SPSS version 24.0. The mean and SD were calculated for quantitative variables, and proportions were calculated for categorical variables. Data were also represented in the form of visual impressions, such as bar diagrams, etc. The Z-test was applied to check the significant difference between two groups. The Chi-squared test was applied to check the association between different attributes. A p-value of <0.05 was considered statistically significant.

The instrument used to measure HbA1C was ion-exchange high-performance liquid chromatography with the Bio-Rad Variant II Turbo analyzer (Bio-Rad, Hercules, CA).

Results

We conducted the present study on 100 patients with T2DM inadequately

controlled on triple drug combination therapy. Of these 100 patients, 52 were males and 48 were females. Study participants were divided equally into two study groups, with 50 participants in group A and 50 patients in group B. Patients in group A were prescribed tablet dapagliflozin 10 mg OD with a large amount of water, and those in group B received insulin glargine (started with 10 U at bedtime and gradually doses were escalated depending upon SMBG) as the fourth glucose-lowering agent for 3 months. In group A, 28 patients (56%) were males and 22 (44%) were females. The mean age of group A participants was 41.58 ± 17.09 years. The mean body weight of group A patients was 61.06 ± 8.90 kg. In group B, there were 24 (48%) males and 26 (52%) females. The average age of group B participants was 43.44 ± 17.85 years. The average body weight of group B patients was 60.43 ± 7.60 kg (Table 1).

We observed a reduction in values of glycemia parameters like FBS, PPBS, HbA1C, and a change in body weight of patients in both groups before and after initiating the therapies.

The "Free-style Libre Pro®" AGM sensor was used for the study. Upon receiving voluntary consent from patients, the sensors were applied to the patients for 14 days before initiating the therapy in both groups. Sensor data were recorded and checked accordingly to assess the GV. CGM parameters (TIR, TAR, TBR, GMI, and coefficient of GV) were assessed at baseline before initiating therapy in both groups.

About 3 months after starting the respective therapies in both groups, the "Free-style Libre Pro®" AGM sensors were again applied to the patients for 14 days. Sensor data were recorded and checked at the end of the study to assess the GV. CGM parameters (TIR, TAR, TBR, GMI, coefficient of GV) were reassessed at the end of 3 months.

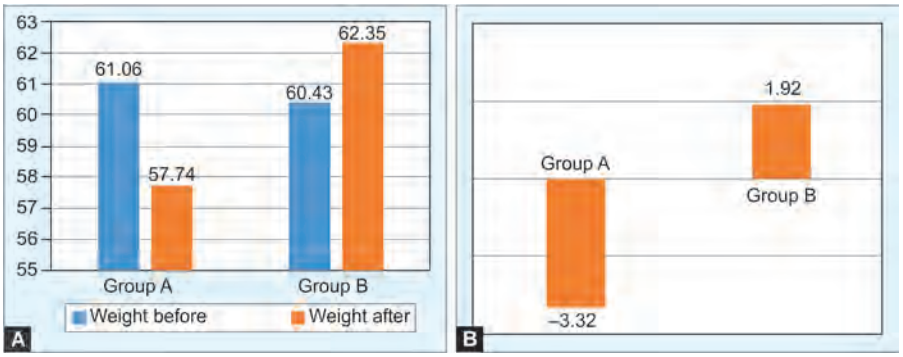
Thus, the AGP report combining all the data elements, including the coefficient of GV, TIR%, TBR%, TAR%, and GMI, was checked in both groups before and after initiating the therapies.

After 3 months of therapy, group A patients who received 10 mg of dapagliflozin OD experienced a reduction of 3.32 kg in body weight from baseline ($p < 0.0001$), while a +1.92 kg weight gain was recorded in patients prescribed with insulin glargine in group B ($p = 0.002$) (Figs 1A and B).

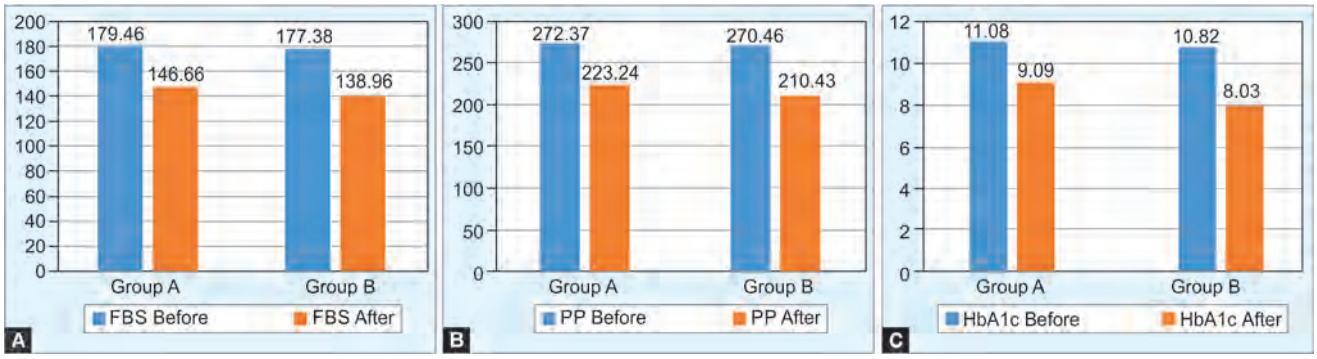
In this study, the mean FBS (mg/dL) at baseline in group A patients was 179.46 ± 23.49, and at the end of 3 months, it was 146.66 ± 19.08 (Fig. 2A), with a mean difference of –32.8 mg% ($p < 0.0001$) (Table 2). The mean PPBS (mg/dL) at baseline in group A was 272.37 ± 37.22, and at the end of 3 months, it was observed to be 223.24 ± 30.32 (Fig. 2B), with a mean difference of –49.13 ($p < 0.0001$) (Table 2).

In the dapagliflozin-treated group A, the mean HbA1C value (gm%) at baseline was 11.08 ± 1.36, which was reduced to 9.09 ± 1.14, 3 months after therapy (Fig. 2C) with a significant mean reduction of 1.99 ($p = 0.002$) (Table 2). Thus, in group A, where 50 T2DM patients inadequately controlled on a triple-drug combination received dapagliflozin 10 mg OD as the fourth glucose-lowering agent, a highly significant reduction ($p < 0.0001$) was demonstrated in all the glycemic parameters 3 months after therapy (Table 2).

Highly significant reduction ($p < 0.0001$) was observed in the values of all the glycemic parameters 3 months after therapy within group B patients prescribed insulin glargine as a fourth glucose-lowering agent. Mean FBS (mg/dL) in group B patients at baseline was 177.38 ± 20.82, and at the end of 3 months, it was 138.96 ± 20.08 (Fig. 2A). With a mean difference of –38.42 in the values of FBS from baseline to the end of the study, a highly significant reduction was recorded ($p < 0.0001$) (Table 2).



Figs 1A and B: (A) Change in weight; (B) Change in weight



Figs 2A to C: (A) Comparison mean FBS; (B) Comparison mean PPBS; (C) Comparison mean HBA1C

Table 1: Demographic variables

Demographic variables	*Group A*	*Group B*	*Z-value*	*p-value*
	Mean ± SD	*Mean ± SD*		
Age	41.58 ± 17.09	43.44 ± 17.85	0.532	$p = 0.596$ NS
Male/female	28/22	24/26	$X^2 = 0.641$	$p = 0.432$ NS
Weight	61.06 ± 8.90	60.43 ± 7.60	1.23	$p = 0.329$ NS

Mean PPBS (mg/dL) in the insulin-treated group at baseline was 270.46 ± 41.56, and at the end of the study, it was reduced to 210.43 ± 37.09 (Fig. 2B), with a mean difference of –60.03 after 3 months, observing a significant reduction ($p < 0.0001$) (Table 2). The mean HbA1C (gm%) at baseline was 10.82 ± 1.27, which was reduced to 8.03 ± 1.19 after 3 months (Fig. 2C), with a highly significant mean difference of –2.79 ($p < 0.0001$) (Table 2). In accordance with the observations from group A patients, in group B patients prescribed insulin glargine as a fourth glucose-lowering agent, a highly significant reduction ($p < 0.0001$) was observed 3 months after therapy in all the glycemic parameters (Table 2).

Above results suggest a highly significant decline in all the glycemic parameters such as FBS, PPBS, HbA1C, and other parameters like body weight from baseline to the end of 3 months in both dapagliflozin-prescribed group A patients as well as insulin glargine-treated group B patients ($p < 0.0001$).

Continuous glucose monitoring is a monitoring system that provides the ability to observe glucose variations and measures interstitial glucose levels continuously over a stipulated time. In the present study, we also assessed the AGP report, combining all the data elements, including the coefficient of GV, TIR%, TBR%, TAR%, and GMI in both groups before and after initiating the therapies.

In group A, where the 50 T2DM patients who were inadequately controlled on a triple drug combination received dapagliflozin 10 mg OD as a fourth glucose-lowering agent, a highly significant reduction ($p < 0.0001$) with mean differences of 6.3 and 5.89% (Table 3) was observed between before (29.16 ± 6.16) and after (22.86 ± 4.63) therapy TAR Level 1 (BSL in the range of 180–250 mg/dL) and before (19.34 ± 4.16) and after therapy (13.45 ± 2.01) TAR level 2 (BSL >250 mg/dL) values, respectively (Figs 3A and B). However, the values were observed to be nonsignificant when comparing before (1.39 ± 0.44) and after (1.28 ± 0.63) therapy TBR level 1 (BSL levels between <70 and >54 mg/dL) and before (0.26 ± 0.44) and after therapy (0.20 ± 0.44) TBR level 2 (BSL <54 mg/dL) (Figs 3C and D), with mean differences of 0.10% ($p = 0.329$ NS) and 0.06% ($p = 0.391$ NS), respectively (Table 3). Meanwhile, a highly significant ($p < 0.0001$) improvement of 12.15% in the mean values of TIR (BSL between 70 and 180 mg/dL) was documented 3 months after therapy (62.13 ± 12.80) from the baseline (49.98 ± 10.86) within group A patients (Fig. 4A and Table 3).

Along with TAR, TIR, and TBR, other parameters of CGM were also recorded. According to the findings, the GMI (Fig. 4B) in group A before (10.84 ± 1.44) and after (9.72 ± 1.30) initiating 10 mg dapagliflozin as a fourth add-on significantly ($p = 0.002$ S) decreased by 1.12% (Table 3). The coefficient of GV, which indicates the excursions in BSL in the form of either hypo- or hyperglycemia, was also significantly ($p < 0.0001$) reduced by 9.45%, allowing the patients to remain within the range of 70–180 mg/dL with minimum excursions from baseline (50.46 ± 6.16) to the end (41.01 ± 6.65) of the treatment period (Fig. 4C and Table 3).

In the present study, when readings of CGM parameters of patients from group B were recorded, similarity was noticed with the findings in group A with regard to TAR values, although the reduction was more in group B patients. A highly significant ($p < 0.0001$) difference in TAR level 1 and TAR level 2 values, before and after therapy, was observed with a mean reduction of 9.96 and 9.81%, respectively. However, the TBR level 1 ($p = 0.032$) and level 2 ($p = 0.021$) observations in group B were significantly reduced from baseline values toward the end of the study, unlike group A, with mean differences of 0.24 and 0.16%, respectively. A highly significant ($p < 0.0001$) rise by 18.67% (Table 3) was reported when we compared the TIR values in group B patients from baseline (48.23 ± 11.74) to the end of 3 months after therapy (66.90 ± 10.23) (Fig. 4A). This enhancement in TIR value is a reflection of improvement in glycemic status of patients to help them remain within the range of 70–180 mg/dL to minimize excursions.

A highly significant ($p < 0.0001$) reduction of 2.10% (Table 3) in the values of GMI from the baseline (10.56 ± 1.38) to the end of therapy (8.46 ± 1.16) was reported in the group of patients receiving insulin glargine as the fourth glucose-lowering agent (Fig. 4B). On comparing the values of the coefficient of GV in group B from baseline (50.62 ± 6.15) to the end (39.12 ± 4.89) of 3 months of therapy (Fig. 4C), a mean reduction by 11.50% (Table 3) significantly ($p < 0.0001$) helped the patients to be in the normal range, protecting them from oxidative stress and further complications of glycemic excursions.

Posttreatment results of both groups demonstrated a significant rise in body weight of patients who received insulin compared to patients prescribed with dapagliflozin, with a mean difference of 4.61 kg (Table 4).

Though the glycemic parameters were reduced in both groups at the end of 3 months, group B patients receiving insulin therapy had a significant reduction in mean values of FBS, PPBS, and HbA1c by 7.7 mg/dL, 12.81 mg/dL, and 1.06 gm%, respectively, as compared to group A patients (Table 4).

Similar observations were documented for CGM parameters also. Except for the TBR level 2, all other parameters, like TAR level 1 (mean difference of 2.64%), TAR level 2 (2.32%), TBR

Table 2: Comparison of mean reduction in FBS, PPBS, and HbA1c

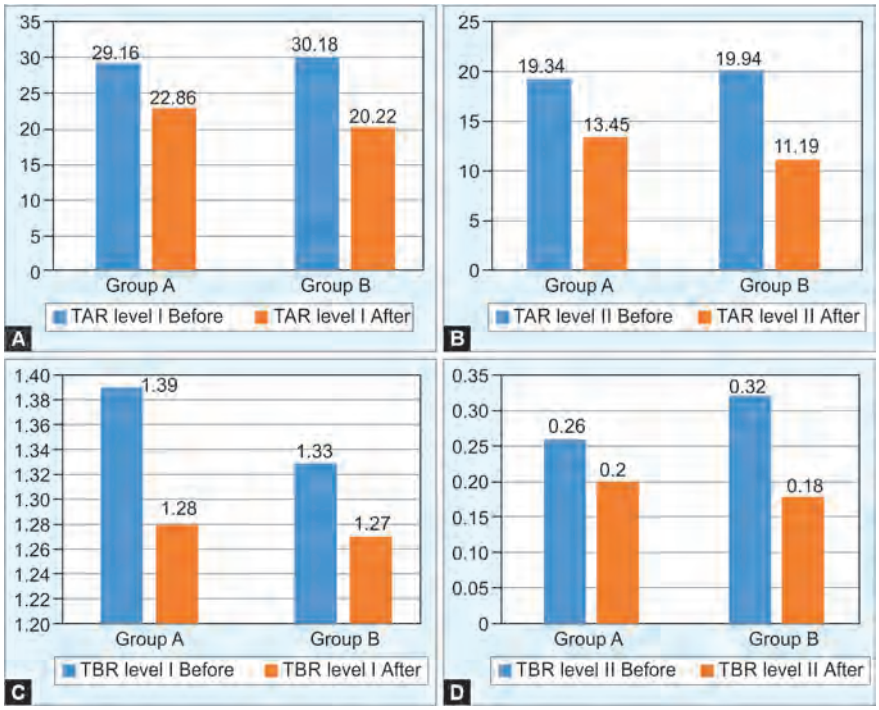
Groups	*Group A*		*Group B*	
Parameters	*Mean difference*	*p-value*	*Mean difference*	*p-value*
Before vs after FBS (mg%)	32.8	$p < 0.0001$ S	38.42	$p < 0.0001$ S
Before vs after PPBS (mg%)	49.13	$p < 0.0001$ S	60.03	$p < 0.0001$ S
Before vs after HbA1C (%)	1.99	$p = 0.002$ S	2.79	$p < 0.0001$ S

Table 3: Comparison of mean difference between CGM parameters

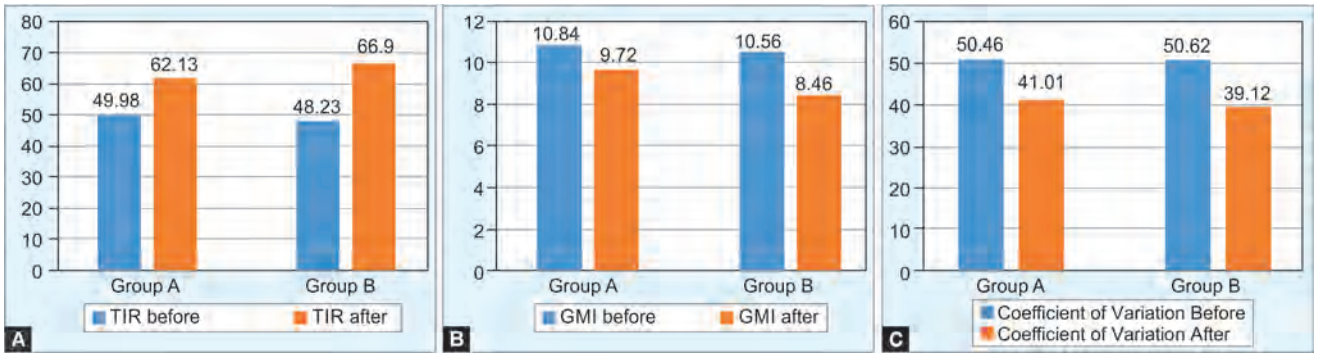
Groups	*Group A*		*Group B*	
Parameters	*Mean difference*	*p-value*	*Mean difference*	*p-value*
Before vs after TAR level 1	6.3	$p < 0.0001$ S	9.96	$p < 0.0001$ S
Before vs after TAR level 2	5.89	$p < 0.0001$ S	9.81	$p < 0.0001$ S
Before vs after TIR	12.15	$p < 0.0001$ S	18.67	$p < 0.0001$ S
Before vs after TBR level 1	0.1	$p = 0.329$ NS	0.24	$p = 0.032$ S
Before vs after TBR level 2	0.06	$p = 0.391$ NS	0.16	$p = 0.021$ S
Before vs after GMI	1.12	$p = 0.002$ S	2.1	$p < 0.0001$ S
Before vs after coefficient of variation	9.45	$p < 0.0001$ S	11.5	$p < 0.0001$ S

level 1 (0.01%), GMI (1.26%), and coefficient of GV (1.89%), were significantly decreased in patients receiving basal insulin as the fourth glucose-lowering agent in group B, as compared to group A patients prescribed with dapagliflozin. There was a significant improvement in TIR percentage in patients in group B than patients in group A, with a mean difference of 4.77%, thus improving the glycemic status of patients with fewer glucose excursions.

When we observed both groups for the occurrence of ADRs, a total of four ADRs were reported from group A patients, which included three cases of genitomycotic infections, and one patient reported hypoglycemia, while in group B, patients also experienced four ADRs, three of which were hypoglycemia, and one was about weight gain. All the patients were appropriately treated for ADRs, and none of them withdrew from the study (Table 5 and Fig. 5).



Figs 3A to D: (A) TAR level I; (B) TAR level II; (C) TBR level I; (D) TBR level II



Figs 4A to C: (A) TIR; (B) GMI; (C) Coefficient of variations

Discussion

Glycated hemoglobin estimated every 3 months for assessment of glycemic control in diabetes mellitus is considered the gold standard method ever. In the past, many comprehensive studies have reported a positive association between higher mean HbA1c levels and the incidence of diabetes-related complications, including the development of major adverse cardiovascular events.[18] Nonetheless, individual factors such as ethnicity, genetics, and hematological conditions significantly affect the HbA1c level.[19]

Reports have shown that variation in glycemia on the background of the same

Table 4: Comparison of after therapy values of parameters between groups

Parameters	*Group A*	*Group B*	*Mean difference*	*p-value*
	Mean ± SD	*Mean ± SD*		
Weight	57.74 ± 8.92	62.35 ± 7.35	4.61	$p = 0.023$ S
FBS	146.66 ± 19.08	138.96 ± 20.08	7.7	$p = 0.012$ S
PPBS	223.24 ± 30.32	210.43 ± 37.09	12.81	$p = 0.031$ S
HbA1C	9.09 ± 1.14	8.03 ± 1.19	1.06	$p = 0.021$ S
TAR level 1	22.86 ± 4.63	20.22 ± 5.70	2.64	$p = 0.012$ S
TAR level 2	13.45 ± 2.01	11.13 ± 3.83	2.32	$p < 0.0001$ S
TIR	62.13 ± 12.80	66.90 ± 10.23	4.77	$p < 0.0001$ S
TBR level 1	1.28 ± 0.631	1.27 ± 0.543	0.01	$p = 0.031$ S
TBR level 2	0.20 ± 0.443	0.18 ± 0.321	0.02	$p = 0.492$ NS
GMI	9.72 ± 1.30	8.46 ± 1.16	1.26	$p < 0.0001$ S
Coefficient of variation	41.01 ± 6.65	39.12 ± 4.89	1.89	$p = 0.041$ S

Table 5: ADRs

Groups	*Genito-mycotic infection and UTI*	*Hypoglycemia*	*Weight gain*	*Device related*
Group A	3 (6%)	1 (2%)	0	0
Group B	0	3 (6%)	1 (2%)	0

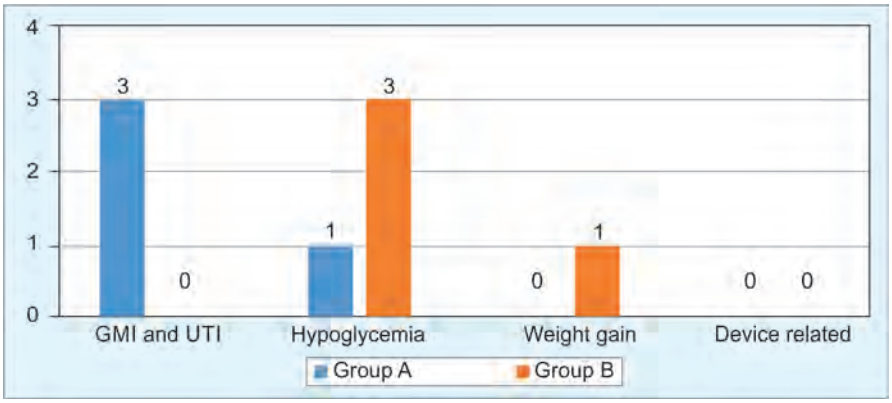


Fig. 5: ADRs

mean blood glucose level is considered an essential risk factor for the development of diabetic neuropathy, where HbA1c assessment fails to reflect that. Compared to HbA1c values, the variations in glycemic levels have a strong and worse impact on the development of cardiovascular disease. Thus, estimation of HbA1c cannot be a single parameter to rely upon in glycemic management.[20]

Continuous glucose monitoring system is a surveillance technology that indirectly reflects the glucose values in the interstitial fluid with the help of a sensor every 5 minutes. This results in the availability of a complete and timely glycemic profile, enabling clinicians to better understand the variation patterns and glycemic excursions.[9]

"DEVOTE 2 study (Degludec vs Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events)" conducted in patients with T2D who are at high risk of development of cardiovascular events evaluated day-to-day fasting glucose level variations.[21] Gerbaud et al. in their study conducted in patients having diabetes mellitus with associated acute coronary syndrome reported that a cutoff value of >2.70 mmol/L (49 mg/dL) of GV was the strongest independent cardiovascular indicator of "MACE (Major Adverse Cardiovascular Events), a composite end point that includes events like nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death."[22]

A positive correlation between GV and incidence of cardiovascular diseases has been reported by previous studies, but some publications have contrasting results. According to the observations from the "HEART2D (Hyperglycemia and Its Effect after Acute Myocardial Infarction on Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus)" study, GV had no role in the occurrence of cardiovascular events in patients with T2DM.[23]

In accordance with the above study, another "DIGAMI 2 study (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction)" conducted in 578 patients with T2DM did not report any relationship between acute cardiovascular complications and glycemic excursions.[24]

In patients with poor glycemic control and existing atherosclerotic cardiovascular disease, the significance of SGLT-2 inhibitors as a constituent of combination therapy has been accentuated by the American Diabetes Association.[4] SGLT-2 inhibitors have been observed to increase beta cell mass and insulin secretion, but they cannot enhance the insulin sensitivity of cells.[25] According to a study conducted by Matthaei et al., subjects who received 52 weeks of dapagliflozin treatment were found to have greater reductions in HbA1c and FPG levels, as compared to those who received the placebo.[26] In another study, Henry et al. observed that when dapagliflozin was used as an add-on therapy for patients with T2DM receiving either insulin or metformin, a beneficial effect on GV was demonstrated.[27] Dandona et al. in their study DEPICT-1 demonstrated that dapagliflozin decreased glycemic excursions, resulting in good glucose control with no hypoglycemia events in patients with type 1 diabetes.[28]

Thus, according to the abovementioned studies, for the management of diabetes, dapagliflozin, when used either as a sole treatment or as an additive to other oral glucose-lowering drugs or insulin, signified a positive effect on GV.

The FLAT-SUGAR trial compared the effect of rapid-acting insulin with the effect of glucagon-like peptide 1 receptor agonist (GLP-1RA) on GV in diabetic patients who were receiving basal insulin therapy. Although, compared with prandial insulin, the CGM demonstrated significant reductions in GV with GLP-1RA, no significant difference was demonstrated in severe hypoglycemia events, cardiac arrhythmias, or cardiovascular risk biomarkers by GLP-1RA.[29]

In a study conducted in pediatric patients with type 1 diabetes, White & Associates described that, as compared to NPH/Lente insulin, glucose variations were less observed with the use of insulin glargine.[30]

Significant reductions (with p-value <0.05) in FBS, PPBS, and HbA1c were observed at the end within both groups, with group B having a statistically significant reduction when compared with group A. The CGM parameters improved significantly within both groups, but group B patients showed statistically significant improvement compared to group A. A weight reduction of 3.32 kg was observed in group A patients receiving dapagliflozin, while group B patients on insulin glargine experienced an average weight gain of 1.92 kg at the end of 3 months.

Conclusion

Since the past three decades, based on the positive association between micro- and macrovascular complications of diabetes and deranged glycemic control, HbA1c has been considered the gold standard parameter to analyze the response to the management of diabetes mellitus. In diabetic patients, a decline in HbA1c levels is thought to be correlated with lower rates of diabetic complications. With the exploration of scientific knowledge in recent years, short-term and long-term glycemic excursions have been linked with the occurrence of detrimental diabetic-related complications. According to various experimental and clinical studies, microvascular and macrovascular complications of diabetes have been observed to develop due to oxidative stress, endothelial dysfunction, and inflammation, which ultimately have been closely linked with glucose fluctuations. Clinical studies that can signify the independent role of GV for the development of diabetic complications are, however, still under process. Thus, a comprehensive antidiabetic strategy focusing on minimizing the assessment of different parameters for blood glucose dysregulation, such as fasting and postprandial glucose, HbA1c, and GV, should be implemented in clinical practice. Minimally invasive CGM sensors provide

periodic measurements of blood glucose levels in a continuous-time fashion. These are now evolving as an increasingly adopted technology for the regularization and therapy of glycemic excursions in patients with diabetes mellitus, to help physicians individualize the management strategies.[31]

Continuous glucose monitoring sensors have demonstrated improved glycemic control by minimizing GV and reducing hypoglycemia events with the help of real-time data on glucose concentrations and their shifts. Recently developed relevant CGM systems have various applications, such as observing blood glucose concentration, patterns of glycemic excursions, along with TIR and GV. Thus, to assess the significance of GV in the development of short- as well as long-term complications in patients with diabetes, more clinical studies using CGM devices should be conducted.[32]

The salient finding of this study was that patients who received insulin glargine as fourth glucose-lowering therapy were observed to experience fewer glucose excursions than patients who received dapagliflozin, as estimated by various parameters.

Minimal glycemic excursions have significant clinical implications, such as a reduced incidence of vascular complications with controlled glycaemia and a lower risk of hypoglycemia.[33] Cox et al. in their study observed that episodes of severe hypoglycemia usually occurred following high GV, indicating that a reduction in GV may curtail the risk of severe hypoglycemia episodes.[34]

Thus, CGMS may serve as an essential implement for analyzing the complete glycemic profile beyond the estimation of A1C levels alone, making it important for clinicians and patients to be updated with the knowledge about GV to make individual choices of therapy.

The study outcomes suggest that the administration of insulin glargine as the fourth glucose-lowering agent on the background of a triple-drug regimen has demonstrated a significant reduction in GV compared to that observed with dapagliflozin. In addition, the use of insulin glargine may confer a reduction in diabetes-associated complications in accordance with the degree to which the number of episodes of glycemic excursions are decreased.[30]

Small sample size and short duration of the study were some limitations of the study. To further confirm the outcomes of the study in the future, these limitations should be taken into consideration. Hence, to establish improvement in GV with dapagliflozin combined with other oral hypoglycemic drugs for long-term benefit in T2D, the study duration as well as the sample size should be increased.

Data Availability

All the data used to support the findings of this study are available from the corresponding author upon request.

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ORIGINAL ARTICLE

Screening for Obstructive Sleep Apnea by Standard Recommended Tools and Its Associated Comorbidities in a Subset of Eastern Indian Surgical Population: An Observational Study

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Abstract

Background and aims: Obstructive sleep apnea/hypopnea syndrome (OSAHS) is underdiagnosed, and patients commonly have a lengthened and difficult hospital stay associated with cardiovascular, respiratory, and neurological complications. Therefore, timely diagnosis using screening tools, especially in resource-poor setups, is essential in preventing an adverse surgical course and delivering optimum patient care. Thus, we intended to highlight the proportion of patients with OSAHS presenting for various surgical procedures and compare the sensitivity of the screening tools when used individually and in various combinations.

Methods: We conducted this prospective observational study with 527 subjects from January 2018 to January 2020. The prevalence of OSAHS was calculated by the simultaneous administration of the Berlin questionnaire, STOP-Bang score, American Society of Anesthesiologists (ASA) checklist, and Preoperative Sleep Apnea Prediction (PSAP) score. These screening tools were also used individually and in combinations of two and three to ascertain the most sensitive combination. Using bivariate logistic regression followed by multivariate logistic regression, associations between OSAHS and various anthropometric measurements were also established.

Results: Four screening tools simultaneously detected the presence of OSAHS in the maximum number of subjects (74.95%), matched by the administration of STOP-Bang, Berlin, and PSAP screening tools in conjunction. Among combinations of any two tools, STOP-Bang and PSAP established OSAHS in 74.38% of respondents, whereas individually, the highest number of cases was observed using the PSAP score (67.17%).

Conclusion: OSAHS is frequently encountered in surgical patients. The STOP-Bang and PSAP screening tools, in combination, are the most sensitive and convenient choice for detecting OSAHS.

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Introduction

Obstructive sleep apnea/hypopnea syndrome (OSAHS) is often underdiagnosed in patients presenting for surgical procedures.[1] The estimated prevalence of OSAHS in India ranges from 13 to 19%.[2] However, studies estimate that up to 92% of women and 82% of men with moderate to severe sleep apnea remain undiagnosed.[3] In these patients, general anesthesia and deep sedation can predispose them to upper airway obstruction, resulting in perioperative and postoperative complications such as rapid desaturation. These patients are more sensitive to anesthetic agents and are associated with an increased risk of perioperative cardiovascular events.[3] They typically have a longer postanesthesia care unit (PACU) and hospital stay, unexplained intensive care unit (ICU) admissions, and higher mortality rates, in addition to cardiac, respiratory, and neurological complications.[4] Hence, early diagnosis is crucial in modifying anesthetic management and utilizing specific means by which complications can be decreased and patient outcomes can be improved.[4]

The standard diagnostic test for identifying OSAHS is polysomnography (PSG).[5] OSAHS is diagnosed by the presence of at least five episodes of apnea or hypopnea per hour, with associated symptoms attributed to sleep-disordered breathing.[5] By consensus, mild sleep apnea is an apnea-hypopnea index (AHI) of 5–15 events per hour, moderate is 15–30 events per hour, and severe is >30 events per hour.[5] However, due to a scarcity of technical resources, sensitive screening tools are heavily depended on for making a preliminary diagnosis. The sensitivity of screening increases with the combination of screening tools.[6] This combination can help identify high-risk patients and prioritize them for PSG so that they can receive early treatment. Hence, it is pertinent to administer fast screening of OSAHS as part of a patient's preanesthetic checkup (PAC) using standard tools individually or in combination.

This study seeks to highlight the proportion of patients with OSAHS presenting to our institution for various surgical procedures by simultaneously administering four internationally recommended questionnaires, following which we compared the sensitivities of the screening tools when used individually and in various combinations of two and three tools. Additionally, we attempt to evaluate the relationship between OSAHS and several demographic factors, anthropometric measurements, and comorbidities.

Methods

This cross-sectional observational study was conducted after obtaining approval from the Ethics Committee of our institution (Institutional Ethics Committee, R.G. Kar Medical College; approval number: RKC/Ethics/34; approved date: 5th December 2017), following the principles of the Declaration of Helsinki, 2013, and good clinical practice. A total of 527 subjects attending PAC clinics or admitted for various in-hospital surgical procedures from January

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2018 to January 2020 were included in our study. The age-group for inclusion in the study was 30–60 years. Pregnant patients and patients posted for neurosurgery and head-neck surgery were excluded. Written informed consent was obtained from every participant for participation in the study and use of patient data for research and educational purposes.

A patient's OSAHS status, whether present or absent, was evaluated by four standard screening tools: the Berlin questionnaire,[7,8] STOP-Bang score,[9] ASA checklist,[8] and PSAP score.[6] The OSAHS status of each patient was assessed by administering the aforementioned screening tools singly and then simultaneously in combinations of two, three, and four. Patients were marked as "OSAHS present" when any one of the tests showed positive for OSAHS while using the tools singly or simultaneously in any combination.

The standard diagnostic test for identifying OSAHS is PSG.[5,10] However, due to a scarcity of technical resources, the proportion of OSAHS diagnosed using four screening tools together was taken as the reference standard for our study because maximum detection of OSAHS is possible through the simultaneous administration of the four screening tools.[6,11,12] Other data collected included anthropometric measurements such as body mass index (BMI), neck circumference, thyromental distance (<6 cm/>6 cm), and Mallampati score (1/2/3/4), along with age, gender (male/female), history of type 2 diabetes mellitus (present/absent), and hypertension (present/absent).

The STOP-Bang questionnaire considers the history of snoring, daytime sleepiness, tiredness, observed pauses in breath during sleep, and high blood pressure, as well as variables based on physical examination such as BMI, age, neck circumference, and gender.[9] The Berlin questionnaire considers the history, intensity, and frequency of snoring, as well as the presence of daytime tiredness, the tendency to fall asleep while driving, and high blood pressure.[7,8] The ASA checklist contains Category 1, which includes BMI, neck circumference, craniofacial abnormalities affecting the airway, nasal obstruction, and tonsils touching/nearly touching the midline; Category 2, which includes snoring, awakening from sleep, choking sensation, and its frequency; and Category 3, which includes somnolence, mainly for the assessment of daytime sleepiness or tiredness.[8] The PSAP score considers the history of snoring along with gender, neck thickness, Mallampati score, treated or untreated hypertension and type 2 diabetes mellitus, BMI, age, and thyromental distance.[7]

The sample size was calculated considering a 95% confidence interval, a 22% prevalence of OSA, an absolute precision of 5%, and a design effect of 2 (as systematic random sampling was employed to select study participants).[13] Data were analyzed using MS Excel and International Business Machines Statistical Package for the Social Sciences (IBM SPSS) version 23 for Windows (Chicago, IL, USA). The proportion of OSAHS was calculated for each screening tool, used individually and in combinations of two, three, and four. The proportion of OSAHS diagnosed using four screening tools together was taken as the reference standard for the study. The kappa statistic was calculated as a measurement of agreement between the screening tools used individually and simultaneously in combinations of two and three and the combination of the four screening tools.

Numerical variables were checked for normality of distribution using the Kolmogorov-Smirnov goodness-of-fit test. Data were summarized by mean and standard deviation for normally distributed continuous numerical variables (e.g., age, BMI, neck circumference) and frequency and percentage for categorical variables (e.g., gender, Mallampati score). The association between OSAHS status (assessed by four screening tools in combination) and other anthropometric, demographic, and comorbidity-related factors was established through bivariate logistic regression followed by multivariate logistic regression using the Chi-squared test. *p*-values <0.05 were considered statistically significant.

Results

If four tools were used simultaneously, the presence of OSAHS was observed in the maximum number of subjects. Individually, the PSAP tool identified OSAHS in the maximum number of subjects, followed by STOP-Bang, Berlin, and the ASA checklist. Considering different combinations of any two tools, STOP-Bang and PSAP detected the maximum proportion of OSAHS among study subjects. Using different combinations of any three tools, STOP-Bang, Berlin, and PSAP identified OSAHS in 74.95% of subjects, which was similar to the reference standard of our study, that is, screening by all four tools (Table 1).

Maximum OSAHS detection is possible through the simultaneous administration of the four screening tools. Furthermore, the kappa statistical value was calculated as a parameter of agreement between the results of using four tools simultaneously and each tool individually or in combinations of two or three tools. Individually, the PSAP tool showed the highest and strongest agreement among the screening tools under study. While using two tools simultaneously in different combinations, STOP-Bang and PSAP produced strong agreement, followed by Berlin and PSAP, and finally, PSAP and ASA. While using three tools simultaneously in different combinations, STOP-Bang, Berlin, and PSAP showed the highest and strongest agreement, followed by STOP-Bang, ASA, and PSAP, and Berlin, ASA, and PSAP. The agreement between OSAHS screening tools has been described in Table 2.

Table 1: Proportion of OSA screened by different tools—using individually and simultaneously

Screening tools	*Normal or low risk of OSA (%)*	*OSA (%)*
STOPBANG	36.24	63.76
Berlin	56.74	43.26
ASA	67.36	32.64
PSAP	32.83	67.17
Stopbang and Berlin	35.10	64.90
Stopbang and ASA	35.67	64.33
Stopbang and PSAP	25.62	74.38
Berlin and ASA	55.60	44.40
Berlin and PSAP	32.26	67.74
PSAP and ASA	32.83	67.17
Stopbang, Berlin andPSAP	25.05	74.95
Stopbang, Berlin and ASA	35.10	64.90
Stopbang, PSAP and ASA	25.62	74.38
Berlin, PSAP and ASA	32.26	67.74
Any 4 tools	25.05	74.95

Data expressed as percentage. ASA, American Society of Anesthesiologists checklist; OSA, obstructive sleep apnea; PSAP, perioperative sleep apnea prediction score

Therefore, it was inferred that using STOP-Bang, Berlin, and PSAP tools in conjunction helped screen the highest number of OSAHS cases with maximum agreement with the existing four screening tools, followed by STOP-Bang and PSAP simultaneously.

The mean age (in years) of study subjects recorded was 51.29 ± 11.83. The proportions of males and females were 265 (50.28%) and 262 (49.72%), respectively. The participants' mean BMI (in kg/m^2) and neck circumference (in mm) were 30.67 ± 4.22 and 41.29 ± 2.85, respectively. Out of 527 study subjects, 55.03% were hypertensive, 40.99% suffered from type 2 diabetes, and 57.87% had a thyromental distance of less than 6 cm. On the Mallampati score assessment, 45.35% had a score of 4, while 37% had a score of 3.

On bivariate analysis, OSAHS was significantly associated with aging, higher BMI, and increased neck circumference. It was also associated with a thyromental distance of <6 cm, type 2 diabetes mellitus, hypertension, and a Mallampati score of 4. On multivariate analysis, OSAHS was associated with age, BMI, neck circumference, and a thyromental distance of <6 cm, as shown in Table 3.

Table 2: Agreement between OSA screening tools (using individually and simultaneously)

OSA screening tools	*Agreement with result of simultaneous use of 4 tools (kappa statistic value)*	*p-value*	*Agreement status*
STOPBANG	0.74	<0.001	Moderate
Berlin	0.406	<0.001	Moderate
ASA	0.279	<0.001	Poor
PSAP	0.812	<0.001	Strong
Stopbang and Berlin	0.764	<0.001	Moderate
Stopbang and ASA	0.752	<0.001	Moderate
Stopbang and PSAP	0.985	<0.001	Strong
Berlin and ASA	0.42	<0.001	Moderate
Berlin and PSAP	0.825	<0.001	Strong
PSAP and ASA	0.812	<0.001	Strong
Stopbang, Berlin and PSAP	1	<0.001	Strong
Stopbang, Berlin and ASA	0.764	<0.001	Moderate
Stopbang, PSAP and ASA	0.985	<0.001	Strong
Berlin, PSAP and ASA	0.825	<0.001	Strong

Kappa statistics value of agreement between 2 tools signifies as follows: <4 means poor agreement, ≥4 means moderate agreement, ≥8 means strong agreement. ASA, American Society of Anesthesiologists checklist; OSA, obstructive sleep apnea; PSAP, perioperative sleep apnea prediction score

Discussion

The present study identified 74.95% of patients with OSAHS using all four screening tools. Individually, PSAP identified OSAHS among 67.17% of subjects, followed by STOP-Bang (63.76%), Berlin (43.26%), and ASA (32.64%). Considering different combinations of any two tools, STOP-Bang and PSAP identified maximum OSA among 74.38% of subjects. Considering different combinations of any three tools, STOP-Bang, Berlin, and PSAP identified maximum OSAHS among 74.95% of subjects, which is comparable to screening by all four tools. OSAHS was significantly associated with aging, higher BMI, and increased neck circumference. It was also associated with thyromental distance <6 cm [unadjusted odds ratio (UOR) 0.02, 0.01–0.07], type 2 diabetes mellitus (UOR 8.82, 4.9–15.88), hypertension (UOR 5.59, 3.58–8.72), and Mallampati score 4 (UOR 28, 3.9–201.1).

Table 3: Assessment of the relationship between OSAHS (screened by any of 4 tools) and relevant risk factors

Variables	*OSA [mean (SD) or frequency (%)]*		*Bivariate analysis*		*Multivariate analysis*	
	Present	*Absent*	*UOR (95% CI)*	*p-value*	*AOR (95% CI)*	*p-value*
Age (in years)	53.06 (11.1)	45.97 (12.41)	1.05 (1.03, 1.07)	<0.001	1.05 (1.02, 1.08)	<0.001
Gender						
Male	190 (48.1)	75 (56.8)	1.42 (0.95, 2.11)	0.84	1.41 (0.79, 2.52)	0.236
Female	205 (51.9)	57 (43.2)	1		1	
BMI	31.73 (3.68)	27.41 (3.89)	1.29 (1.22, 1.36)	0.00	1.17 (1.07, 1.28)	<0.001
Neck circumference	41.9 (2.81)	39.48 (2.08)	1.42 (1.3, 1.55)	0.00	1.2 (1.08, 1.34)	<0.001
Thyromental distance (cm)						
>6	218 (55.2)	4 (3)	1		1	
<6	177 (44.8)	128 (97)	0.02 (0.01, 0.07)	0.00	0.07 (0.02, 0.22)	<0.001
Type II DM						
Absent	193 (48.9)	118 (89.4)	1		1	
Present	202 (51.1)	14 (10.6)	8.82 (4.9, 15.88)	0.00	1.07 (0.46, 2.45)	0.878
Hypertension						
Absent	138 (34.9)	99 (75)	1		1	
Present	257 (65.1)	33 (25)	5.59 (3.58, 8.72)	0.00	1.57 (0.83, 2.96)	0.162
Mallampati score						
1	3 (50)	3 (50)	1		1	
2	110 (56.4)	85 (43.6)	1.29 (0.25, 6.57)	0.76	1.82 (0.31, 10.55)	0.511
3	198 (82.8)	41 (17.2)	4.83 (0.94, 24.78)	0.06	3.19 (0.53, 18.98)	0.200
4	84 (96.6)	3 (3.4)	28 (3.9, 201.1)	0	3.99 (0.45, 35.71)	0.223

Data expressed as mean (standard deviation) or frequency (percentage); AOR, adjusted odd ratio; BMI, body mass index; CI, confidence interval; OSAHS, obstructive sleep apnea/hypopnea syndrome; SD, standard deviation; UOR, unadjusted odd ratio

A study by Mador et al. reported that the incidence of total complications was a staggering 48.9% in patients with OSA compared to 31.4% among controls.[14] A meta-analysis by Kaw et al. showed that patients with OSA had an appreciably higher risk of adverse postoperative cardiac outcomes (3.76%), respiratory failure (1.96%), desaturation (10.71%), and ICU transfer (5.09%).[15] Gaddam et al. additionally reported significantly higher chances of neurological complications in OSA patients.[16] Furthermore, a study by Gali et al. noted that OSA patients undergoing cardiac surgery suffered a longer median length of stay, lower discharge rates, and higher readmission rates within the first 30 days of discharge to home.[17] A higher incidence of acute kidney injury was also reported in OSA patients undergoing cardiac surgery compared to controls.

Therefore, diagnosing OSA preoperatively is imperative to prevent adverse surgical outcomes. The combination of questionnaires improves detection sensitivity by up to 95%, and when all of them are negative, OSAHS is ruled out with around 65% confidence.[11] The present study identified 74.95% of patients with OSAHS using all four screening tools. This proportion of OSAHS is very close to the finding of Saxena et al.[6] Individually, PSAP identified OSAHS among 67.17% of subjects, followed by STOP-Bang (63.76%), Berlin questionnaire (43.26%), and ASA checklist (32.64%), observations similar to those by Chung et al.[18] A study by Sharma et al. found high sensitivity of the Berlin questionnaire, which does not support corresponding observations in our study pertaining to the screening tool in question.[7]

Considering different combinations of any two tools, STOP-Bang and PSAP identified maximum OSA among 74.38% of subjects. Considering different combinations of any three tools, STOP-Bang, Berlin, and PSAP identified maximum OSAHS among 74.95% of subjects, which is comparable to screening by all four tools. These findings also corroborate the study of Saxena et al. using three screening tools.[6]

Quintana et al. concluded that a neck circumference of >41 cm was associated with obstructive sleep apnea syndrome.[18] Our study observed a mean neck circumference of 41.9 cm in subjects with OSA. A correlation between thyromental distance and the development of OSAHS was also concluded, a finding corroborated by a study by Lam et al.[19] The mean BMI (kg/m^2) of patients screened as high risk for future development of OSA was 30.67 ± 4.22, an observation verified by a study by Udwadia et al.[20] Furthermore, such patients were not associated with hypertension on multivariate analysis. However, an association of severe OSA with untreated hypertension (37.3%) was found by Marin et al.[21] Moreover, OSAHS, hypertension, and depression were reportedly more prevalent in women with OSA compared to non-OSA subjects, according to Bonsignore et al.[22]

A previous study by Priou et al. concluded that among adults without known diabetes, increasing OSA severity is independently associated with impaired glucose metabolism.[23] Our study, however, revealed no association between OSA and diabetes [adjusted odds ratio (AOR) 1.07, 0.46–2.45]. A major limitation of our study is the inability to employ PSG even though PSG is the gold standard test for detecting OSA. Four screening tools were used simultaneously to detect OSA because maximum detection of OSAHS is possible by simultaneous administration of the four screening tools.[6,11,12] Hence, the possibility of inflated study findings cannot be excluded entirely. However, an attempt has been made to identify the best combination of tools for screening OSA through our study.

Some studies have validated the OSA screening tools individually and in combination with the AHI derived from PSG. Chung et al. observed that the sensitivities of the STOP-Bang questionnaire at AHI of >5, >15, and >30 were 83.6, 92.9, and 100, respectively.[9] In another study by Chung et al., the sensitivities of the Berlin questionnaire at AHI of >5, >15, and >30 were 68.9, 78.6, and 87.2%, respectively. For the ASA checklist, the sensitivities at AHI of >5, >15, and >30 were 72.1, 78.6, and 87.2%, respectively.[8] Bernhardt et al., in their meta-analysis, observed that the Berlin questionnaire's pooled sensitivity for AHI ≥5, ≥15, and ≥30 was 85, 84, and 89%, and pooled specificity was 43, 30, and 33%, respectively. The pooled sensitivity of the STOP-Bang questionnaire for AHI ≥5, ≥15, and ≥30 was 92, 95, and 96%, and pooled specificity was 35, 27, and 28%.[24] Saxena et al. found that for AHI >15, PSAP had a sensitivity of 81% and a specificity of 59%. When three questionnaires, that is, PSAP, STOP-Bang, and Epworth Sleepiness Scale score (ESS), were combined, their sensitivity was 91.66% and specificity was 58.8%.[6]

Ramachandran et al. observed that a PSAP score ≥2 showed excellent sensitivity (0.939) but poor specificity (0.323), whereas for a PSAP score ≥6, sensitivity was 0.239 with excellent specificity (0.911).[25] Pereira et al. found that for AHI ≥10, the combination of Berlin, STOP-Bang, and Sleep Apnea Clinical Score (SACS) had a sensitivity of 71% and specificity of 89% for detecting OSA.[26] Mahismita et al. observed that the combination of STOP-Bang, ESS, and PSAP had a sensitivity of 95.76% and specificity of 24.59% for predicting OSA.[11]

Our study had several strengths. It is one of the few studies that have attempted to highlight the proportion of patients with OSAHS for various surgical procedures by simultaneously administering four internationally recommended screening tools, especially in the Indian population. In a country like India, there is still a lack of awareness regarding OSA among the general population, and a large proportion of patients remain undiagnosed.

Our study aimed to identify the patients who had undiagnosed OSA, attending our hospital for elective surgery during PAC. Our objective was to assess the burden of this probable disease in the preoperative population in a part of India so that at least some less time-consuming tools can be incorporated in PAC to plan intra- and postoperative management. This approach would also educate patients regarding the disease, its complications, and the need for treatment. Anesthesiologists, in this way, can contribute at the community level.

Considering the current burden on sleep laboratories in resource-limited settings, combining screening tools is a suitable option. We presumed that combining these tools might provide a cost-effective, easy method to improve the detection rate of OSA when implemented. This is an endeavor to provide a practical solution to a widely ignored screening practice for this important comorbidity.

Conclusion

The proportion of OSAHS is high in patients attending our institute for different surgical procedures. During the screening of OSAHS, the PSAP screening tool individually shows strong agreement when used alongside four internationally recommended screening tools simultaneously. The highest agreement between two- and three-tool combinations is observed with STOP-Bang and PSAP, as well as STOP-Bang, Berlin, and PSAP. OSAHS is associated with aging, increased BMI, increased neck circumference, and thyromental distance <6 cm.

Therefore, we suggest that the STOP-Bang and PSAP combination is the best and most convenient choice for screening OSAHS, as it is less time-consuming, highly sensitive, and should be routinely incorporated in PAC. This approach would lead to better perioperative outcomes for a large number of patients with undiagnosed OSA, particularly in resource-poor settings with high patient loads, where implementing sophisticated screening tools is challenging.

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ORIGINAL ARTICLE

A Retrospective Study of Clinical Characteristics and Serological Profile of Male Systemic Lupus Erythematosus Patients in India

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Abstract

Objective: Systemic lupus erythematosus (SLE) is a female-preponderant disease, and a few studies from outside India have observed that the clinical characteristics of SLE in male patients vary from those of females. There is a lack of data about SLE in male patients in the Indian subcontinent. Hence, we have reported our observations on the various clinical characteristics of SLE in male patients in this retrospective 5-year cohort study.

Methods: This was a retrospective case record-based study at a tertiary care rheumatology center in North India. Records of all the SLE patients of all age-groups maintained with the department over 5 years were perused. All the patients fulfilling either of the classification criteria, viz., American College of Rheumatology (ACR) 1997 criteria and Systemic Lupus International Collaborating Clinics (SLICC) 2012, were included in the study. Data on clinical features were retrieved at the presentation and during the follow-up, immunological profile, treatment received, and long-term complications.

Results: Records of 45 patients were included in the study, of which two were juvenile lupus. Mucocutaneous manifestations were the most common clinical presentation and minor organ involvement. Among the major organs, renal involvement was the most common, followed by hematological manifestations. Two patients had thrombotic manifestations. Four patients had overlap with other connective tissue disorders. Hypertension was the most common complication developed during follow-up, followed by avascular necrosis (AVN) of the femoral head. Two patients died during follow-up. Eleven patients were tested for antiphospholipid syndrome (APS) antibodies, of which one lupus anticoagulant (LAC)-positive patient had thrombotic complications. All patients were antinuclear antibodies (ANA) positive, with a speckled pattern being common, and anti–double-stranded deoxyribonucleic acid (anti-dsDNA) was the common antibody. All patients received hydroxychloroquine and low-dose steroids, and up to 35% received steroid-sparing agents. Most patients with lupus nephritis (LN) took >1 year to achieve clinical remission.

Conclusion: Our study showed that male SLE patients are at high risk of severe organ damage at an early age and are susceptible to various other complications during follow-up. This may differ from female SLE patients, and larger studies in the future can further enlighten tailored treatment approaches in male patients.

Ethical consent was taken wide letter no. IEC Reg. no. 54/2024 AH RR.

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Introduction

Systemic lupus erythematosus (SLE) is a worldwide chronic autoimmune disease that may affect every organ and tissue with diverse manifestations. Genetic predisposition, environmental triggers, and the hormonal milieu interplay in disease development and activity.[1] SLE is often called a disease of women because of the striking differences in prevalence related to sex. Since the disease is relatively less prevalent in males than in females, one of these challenges is managing these subsets of patients.[2] Male SLE has distinguishing characteristics in etiology, clinical manifestations, outcomes, and drug management. Over the past few decades, rheumatologists and lupus experts have studied male lupus to determine the distinctive and unique clinical features in male SLE patients. According to the available literature, approximately male patients constituted about 4–22% of SLE patients in reported lupus series or lupus populations.[3] Only a few studies have been done in the male population from India due to the relatively infrequent incidence of the disease in males. Our study aims to characterize the clinical features, including the symptoms at presentation and follow-up, serological profile, organ involvement, and treatment in an Indian cohort with SLE.

Methodology

It was a retrospective case-record-based observational study conducted at a tertiary care rheumatology center in North India between 2017 and 2022. The record of all the male patients diagnosed with SLE at the Department of Rheumatology was meticulously perused. Data of all the patients meeting either the American College of Rheumatology (ACR) 1997 criteria or Systemic Lupus International Collaborating Clinics (SLICC), 2012, were included in the study. Data from the case records were transferred to an Excel sheet and analyzed. The main objective was to study the clinical profile of male SLE. Case records were perused by the rheumatologists, and the following data were collected: symptoms and organ system involvement at initial presentation and at any point of follow-up, serological profile, treatment provided to the patients, and outcome of major manifestations. Patients were categorized as juvenile (≤16 years) or adults as per age of disease onset. Data were entered into the Excel sheet and checked by a separate person for correctness. Continuous variables were expressed as a

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mean with standard deviation (SD) or median with interquartile range (IQR). Categorical variables were expressed as numbers (n) or percentages. Data were analyzed using IBM-SPSS version 25 (IBM SPSS Statistics for Mac, Version 25.0. Armonk, NY: IBM Corp.) software.

Results

The study included 45 patients. Three patients were in the juvenile age-group, while the rest, 42, were in the adult age-group at the disease onset and last follow-up. The mean age of the adult patients at the onset of symptoms was 29.1 years (SD 8.1, range 20–57 years). The mean age of all adult patients at the time of last follow-up was 33.5 years (SD 8.5 years, range 22–66 years). The mean follow-up period for all adult patients was 52.9 months (SD 51.4, range 2–201 months). Two of the three patients with juvenile SLE had reached the adult group during follow-up. One patient presented at 9 years; follow-up data was available for 1 year since diagnosis. The other two presented at age 14; they were 17 and 23 years old at the time of the last follow-up.

As a constellation, mucocutaneous manifestations of SLE were the most common presenting feature reported in 30 (66.7%) patients, followed by constitutional symptoms in 29 (64.4%) and musculoskeletal manifestations in 28 (62.2%) patients. The presenting features are further elaborated in Table 1. If accounted for individually, fever was the most common symptom present in 26 (57.8%) patients, followed by polyarthritis in 19 (42.2%) and oral ulcers in 13 (28.9%) patients. Neurological and cardiopulmonary symptoms were reported in seven (15.6%) and five (11.1%) patients.

Table 1: Clinical manifestations and organ system involvement at presentation

1A. Presenting symptoms				*1B. Internal organ involvement at presentation*			
	Symptoms	*N*	*%*	*Organ system*	*Manifestations*	*No.*	*%*
Constitutional	Total	29	64.4	Respiratory	Total	14	31.1
	Fever	26	57.8		Pneumonitis	6	13.3
	Weight loss	11	24.4		ILD	2	4.4
	Fatigue	13	28.9		Pleural effusion	6	13.3
Musculoskeletal	Total	28	62.2		PTE	1	2.2
	Arthritis	19	42.2		PAH	2	4.4
	Arthralgia	9	20.0		DAH	2	4.4
	myalgia	5	11.1	Cardiovascular	Total	11	24.4
	Myositis	2	4.4		Pericarditis	7	15.6
Mucocutaneous	Total	30	66.7		Myocarditis	4	8.9
	Malar rash	8	17.8		Pancarditis	1	2.2
	Alopecia	9	20.0	Gastrointestinal	Total		
	Oral ulcers	13	28.9		Hepatosplenomegaly	12	26.7
	Photosensitivity	9	20.0		Transaminitis	6	13.3
	ACLE	11	24.4		Pancreatitis	1	2.2
	SCLE	4	8.9	Hematological	Total	19	42.2
	DLE	3	6.7		Anemia	6	13.3
	Chill blain	2	4.4		Leukopenia	7	15.6
	Raynaud's	8	17.8		Thrombocytopenia	3	6.7
Neurological	Total	7	15.6		Pancytopenia	9	20.0
	Headache	2	4.4		MAS	4	8.9
	Crania neuritis	1	2.2	Renal	Total	21	46.7
	Psychosis	1	2.2		Nephrotic proteinuria	2	4.4
	Seizures	3	6.7		Sub-nephrotic proteinuria	16	35.6
Cardiopulmonary	Total	5	11.1		Micro hematuria	2	4.4
	Pleurisy	1	2.2		Pyuria	1	2.2
	Hemoptysis	2	4.4		Casts	1	2.2
	Cough	2	4.4		Azotemia	2	4.4
	Dyspnea	2	4.4		LN	15	33.3
Others	Vomiting	5	11.1		Pigment cast nephropathy	1	2.2
	Thrombosis	2	4.4	Others	Intraabdominal/ retroperitoneal/mediastinal lymphadenopathy	6	13.3
					Cutaneous vasculitis lesions	3	6.7

After initial clinical evaluation and assessment of the extent of internal organ system involvement, renal abnormalities were most common in 21 (46.7%) patients. Lupus nephritis (LN) was present in 15 (71.4%) patients. Seven patients had class II LN, two had class III LN, and one had class IV LN. Four patients had class IV/V LN, and one had class III/V LN. The available data on the treatment and outcome of 14 patients have been presented in Table 2. Nephrotic range proteinuria was present in two patients, and both had class IV/V LN. Sub-nephrotic range proteinuria was present in 16 (76.2%) patients, of which ten patients were detected to have LN. This data is summarized in Table 1.

Hematological abnormalities were the next most common organ involved in 19 (42.2%) patients, and among them, the most common abnormality was pancytopenia, which was present in nine (20%) patients. Pleuropulmonary manifestations were present in 14 (31.1%) patients. The cardiovascular system was involved in 11 (24.4%) patients. Pneumonitis and pleural effusion were the most common pleuropulmonary manifestations detected in six (13.3%) patients each. Two patients presented with thrombotic episodes, of which one had recurrent pulmonary thromboembolism and another had deep vein thrombosis of the lower limb.

Overlap of SLE with another connective tissue disease was found in four patients, and, incidentally, in all these patients, SLE followed the onset of overlapping connective tissue disease manifestations. One patient had dermatomyositis (preceded SLE by 5 years), one had diffuse cutaneous systemic sclerosis (preceded SLE by 7 years), one had rheumatoid arthritis (preceded SLE by 17 years), and another had Sjögren syndrome and limited cutaneous systemic sclerosis (preceded SLE by a year).

Analysis of follow-up data revealed additional symptoms, internal organ involvement, and development of treatment-related complications, which are summarized in Table 3. Four patients developed hypertension, requiring antihypertensive therapy. The first patient was detected to have hypertension at the age of 23 years and 14 months of disease duration. He had class II LN and was on low-dose glucocorticoid (5 mg daily) at the time of diagnosis of hypertension, and no other contributory factor was detected. The second patient was detected to have hypertension at 2 years of disease onset. He also had LN class II detected during evaluation at the onset of the disease and continued to have sub-nephrotic range proteinuria when hypertension was detected. The third patient to develop hypertension was a case of juvenile SLE, detected at 12 months of disease duration (age 10 years), and was also detected to have LN IV simultaneously. The fourth patient developed hypertension at 4 years of disease onset, and no apparent cause for it could be elucidated from his records. Among 14 patients with LN, with follow-up data, most patients achieved remission within >1 year.

Three patients developed avascular necrosis (AVN) of the femoral head; one patient was detected to have SLE at 22 years of age and had LN class II at onset and was initially managed with glucocorticoids for 6 months. He developed disease flare (mucocutaneous manifestations and

Table 3: Additional clinical manifestations or organ system involvement during follow-up

	No.	*%*
Hypertension	4	8.9
AVN	2	4.4
Lymphadenopathy	1	2.2
Fever	1	2.2
Malar rash	1	2.2
Bullous rash	1	2.2
Oral ulcers	1	2.2
Cutaneous vasculitis	2	4.4
Anemia	3	6.7
Leukopenia	2	4.4
Pancytopenia	1	2.2
ILD	1	2.2
Bronchiolitis	1	2.2
Pneumonitis	1	2.2
Psychosis	1	2.2
Mononeuritis	1	2.2
Peripheral neuropathy	1	2.2
Pericarditis	1	2.2
Glaucoma	1	2.2
Myositis	1	2.2
Shrinking lung syndrome	1	2.2

Table 2: LN outcomes

1.	Class II	Azathioprine and pulse MP	Remission at 14 months
2.	Class II, CNS manifestations with pancytopenia	MMF and pulse MP	Remission at 64 months
3.	Class II	Pulse MP	Remission at 32 months
4.	Class IV/V	Pulse MP and cyc (NIH regime)	Remission at 42 months
5.	Class IV/V	Pulse MP and cyc (NIH regime) changed to MMF and later added tacrolimus due to persistent proteinuria	Persistent nephrotic range proteinuria at 18 months
6.	Class II	Medium dose GC, HCQS	Remission at 195 months
7.	Class III	MMF and high-dose glucocorticoids	Proteinuria reduced from 2.5 gm to 440 mg at 6 months
8.	Class III and pigment cast nephropathy	Pulse MP and MMF	Remission at 37 months
9.	Class III/V	Pulse MP, rituximab	Remission at 6 months
10.	Class II and CNS with myocarditis	Pulse MP, rituximab, followed by azathioprine	Remission at 201 months
11.	Class IV	Pulse MP and cyclophosphamide NIH, class IV/IV with azotemia, given rituximab. Progressed to ESRD	Died
12.	Class IV	Pulse MP and Cyc euro lupus regime	Remission at 1 year. Proteinuria at 60 months, azathioprine changed to MMF
13.	LN class IV/V with AIHA	Pulse MP and rituximab followed by MMF	Proteinuria 550 mg at 8 months
14.	LN class II	Medium dose GC, HCQS	Class IV at 12 months, given MMF. Remission at 111 months

arthritis) at 3 years of disease duration and, during evaluation, was also found to have AVN of the bilateral femoral head. The second patient had multiple major organ involvement at the onset of the disease (pneumonitis, LN class IV/V). He had received pulse methylprednisolone (MP) followed by high-dose oral glucocorticoid in a 6-month tapering schedule initially, and he also had exposure to glucocorticoids in low to moderate doses subsequently for disease flares. He was detected with AVN of the left femoral head at 30 months of disease duration. The third patient had overlap syndrome with dermatomyositis and SLE. He was also exposed to protracted courses of medium to high doses of glucocorticoid for varied disease manifestations.

One patient developed glaucoma, and he had exposure to high-dose glucocorticoids indicated by LN class IV/V and hemolytic anemia. One patient was reported to have psychosis when he was not on glucocorticoids. Another patient developed peripheral neuropathy, which responded partially to glucocorticoids and rituximab. Myositis was detected in one patient. Anemia was detected in an additional three patients during follow-up, the cause of which was not recorded.

Immunological Profile

All 45 (100%) patients were reported to be antinuclear antibodies (ANA)-positive. In 44 patients, ANA was performed using the indirect immunofluorescence method. anti–double-stranded deoxyribonucleic acid (Anti-dsDNA) antibodies were the most prevalent in 30 (66.7%) patients. It was followed by anti-Sm antibodies in 21 (46.7%), anti-SSA Ro (60 kD) antibodies in 18 (40%), anti-U1RNP antibodies in 14 (31.1%), and anti-ribosomal P antibodies in 11 (24.4%) patients. Direct Coombs' test was positive in 10 (22.2%) patients. Hypocomplementemia was reported in 30 patients; in 16 patients, both C3 and C4 were low; in 13 patients, only C3 was low; and in one patient, only C4 was low.

Direct Coombs test (DCT) was positive for 10 patients. Of these 10 patients, six had anemia, and only three had features of autoimmune hemolytic anemia. Recorded evidence of screening for antiphospholipid antibodies was found in only 11 patients, and three of them tested positive. One patient was lupus anticoagulant (LAC) positive; another had immunoglobulin G anticardiolipin antibody (IgG aCL), and the third tested positive for both IgG aCL and IgG β2-glycoprotein I (IgG B2GPI). The patient with positive LAC had recurrent pulmonary thromboembolism, and no thrombotic episode was recorded in the other two patients. This is summarized in Table 4.

Table 4: Immunological profile

ANA IIF patterns (N 39)	Speckled	21	53.8
	Homogenous	13	33.3
	Nucleolar	2	0.05
	Nuclear rim	1	0.02
Antibodies profile	dsDNA	30	66.7
	Histone	10	22.2
	Nucleosome	8	17.8
	Anti Sm	21	46.7
	U1RNP	14	31.1
	SSA Ro 60	18	40.0
	SSA Ro 52	5	11.1
	SSB La	4	8.9
	Ribosomal P	11	24.4
	PCNA	2	4.4
	Jo1	1	2.2
	Ku	3	6.7
	RF	2	4.4
	ACPA	3	6.7
	PMScl	1	2.2
	mi2	0	0.0
	DCT	10	22.2
Complement	Low C3	29	64.4
	Low C4	13	28.9
Antiphospholipid antibodies	IgM aCL	2	4.4
	IgG aCL	2	4.4
	IgM B2GP1	1	2.2
	IgG B2GP1	0	0.0
	LAC	1	2.2

Table 5: Clinical manifestations with prevalence of common antibodies

Symptom/organ		*Anti-dsDNA (N 30)*		*Anti Sm (N 21)*		*U1RNP (N 14)*		*SSA Ro 60 (N 18)*		*RibosomalP (N 11)*	
	N	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Mucocutaneous	30	21	70.0	14	46.7	9	30	13	43.3	9	30.0
Constitutional symptoms	29	17	56.7	13	44.8	10	34.5	14	48.3	9	31.0
Musculoskeletal	28	20	71.4	12	42.9	9	32.1	12	42.9	7	25.0
Renal	21	12	66.7	12	57.1	7	33.3	9	42.9	9	42.9
Hematological	19	11	57.9	7	36.8	5	26.3	7	36.8	4	21.1
Pleuropulmonary	14	8	57.1	7	50	4	28.6	7	50	5	35.7
Cardiovascular	11	5	45.5	5	45.5	4	36.4	5	45.5	3	27.3
Neurological	7	3	42.9	5	71.4	3	42.9	5	71.4	1	14.0

Table 6: DMARDs prescribed with indications

CsDMARDS/tsDMARDS	*No.*	*%*	*Indications*
Hydroxychloroquine	45	100	
Prednisolone	45	100	
Methotrexate	8	17.8	Arthritis, mucocutaneous manifestations, constitutional symptoms
Azathioprine	15	33.3	LN class II, maintenance phase LN class III and IV, cranial neuritis, hematological, mucocutaneous, arthritis
Mycophenolate	16	35.6	Class III, IV, and mixed LN, CNS lupus, articular, hematological, mucocutaneous
Rituximab	7	15.6	ILD, peripheral neuropathy, cytopenia, LN class III/V and class IV/V, CNS lupus, shrinking lung syndrome
Tacrolimus	1	2.2	Class V LN, in combination with MMF
Cyclophosphamide	9	20.0	LN class IV/V*, LN class IV, ILD, CNS lupus, ILD (DM and SSc associated), cranial neuritis
Pulse MP	20	44.4	LN class III, IV, IV/V, MAS, CNS lupus, pneumonitis, myocarditis, AIHA, pancytopenia, DAH
IVIG**	5	11.1	MAS, DAH, pancytopenia

*One patient had concomitant cavitating pulmonary nodules and responded to treatment; **apart from MAS, IVIG was used in hemodynamically unstable patients with major organ involvement viz. myocarditis, DAH, pancytopenia, and CNS lupus

Clinicoimmunological Profile

Due to the small sample size, the correlation between the clinical manifestations and antibody profile has not been attempted. However, the frequency of the most common organ system involvement and clinical manifestations associated with the most common antibodies found in the study has been summarized in Table 5.

Treatment

All the patients were prescribed hydroxychloroquine and a glucocorticoid in low doses, as shown in the available records. Disease-modifying antirheumatic drugs (DMARDs) and common indications are summarized in Table 6.

Two patients out of 45 had a fatal outcome: one patient succumbed to severe macrophage activation syndrome (MAS) at presentation, and in another patient, class III/V LN progressed to class V, followed by end-stage renal disease requiring renal replacement therapy. He died of pneumonia and sepsis while under pre-renal transplant evaluation.

Discussion

In this retrospective study, we analyzed the clinical presentations, organ involvement, immunological profile, and disease follow-up in male SLE patients. Two of the 45 patients whose data were analyzed were children, and the rest were adults. In our study, mucocutaneous involvement was the most common minor organ manifestation. Renal involvement was the most common major organ manifestation, followed by hematological involvement. One patient had thrombotic manifestations. Four patients had overlap with other connective tissue disorders. Hypertension was the most common complication developed during follow-up, followed by AVN of the femoral head. Two patients died during follow-up. Eleven patients were tested for antiphospholipid syndrome (APS) antibodies, of whom the LAC-positive patient had thrombotic complications. All patients received hydroxychloroquine and low-dose steroids, and up to 35% received multiple immunosuppressants, reflecting the refractory nature of lupus in males.

The mean age of disease onset in males is in the second decade, similar to another study conducted in Indian cohorts of 39 patients.[4,5] This is a decade earlier than in the Caucasian population.[6] Constitutional symptoms were common in their study, while mucocutaneous features were predominant in our study. Renal involvement was the major organ involvement in their study and in various other studies as well.[4,6] In another small retrospective study conducted by Dey et al. among 13 patients, mucocutaneous manifestations were the common findings.[7] Renal involvement was a common major organ involvement along with central nervous system (CNS) involvement. In our study as well, renal involvement was the major manifestation, and among 14 patients with follow-up data available, most patients took >1 year for remission. This was consistent

with other studies that revealed early organ involvement in male SLE and the aggressive nature of the disease.[8–12] Mortality has been reported to be higher in male SLE in other studies.[13] In our study as well, two patients out of 45 succumbed to the illness, one due to MAS and another due to progressive renal involvement.

The serological profile revealed 100% ANA positivity, with anti-dsDNA antibodies being common, similar to other studies.[8] Anti-dsDNA positivity was mostly associated with systemic complications. Higher APS antibody levels are reported in male SLE patients; in our cohort, only 11 patients' reports were available, of which three were positive.[6]

While all patients received hydroxychloroquine, patients with major organ manifestations received cyclophosphamide or mycophenolate as induction agents. Seven patients received rituximab, and five patients received intravenous immunoglobulin for organ-threatening manifestations. Mycophenolate mofetil (MMF) and azathioprine were the agents most commonly used for maintenance therapy.

Lupus patients develop numerous complications during follow-up; in our cohort, hypertension and AVN, probably related to steroids, were the most common adverse effects, similar to other studies.[14] Four of our patients had overlap with other connective tissue disorders, which is well documented in the literature.[15]

The strength of our study is the retrieval and analysis of data from a cohort of male SLE patients in terms of their clinical and serological profiles from various ethnic groups in India. Additionally, we were able to gather information about additional complications over a long follow-up period.

The limitations of our study include its retrospective design and relatively small sample size due to the rarity of the disease, especially in males. Adherence to therapy also could not be ascertained in this cohort.

Conclusion

Our study showed that male SLE patients are at high risk of severe organ damage at an early age and are susceptible to various other complications during follow-up. This may differ from female SLE patients, and larger studies in the future can further elucidate tailored treatment approaches for male patients.

Acknowledgment

We wish to thank all the patients who participated in this study.

Ethical Approval

This study was approved by the Institutional Ethics Committee of Army Hospital research and Referral IEC Reg. no. 54/2024 AH RR.

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ORIGINAL ARTICLE

Correlation of Serum Vitamin B_{12} and Muscle Enzyme (CK-NAC) Level with Severity of Guillain-Barre Syndrome and Its Prediction in Respiratory Failure

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Abstract

Background: Guillain-Barré syndrome (GBS) is an acute-onset polyneuropathy. Several biomarkers have been identified to monitor prognosis in GBS, including serum folate, serum albumin, blood glucose, serum sodium, and plasma cortisol levels.

Objectives: To study the prevalence of serum vitamin B_{12} deficiency and increased creatine kinase (CK-NAC) levels in GBS patients and ascertain if the levels of serum CK-NAC and vitamin B_{12} can serve as prognostic indicators in GBS patients.

Materials and methods: The research recruited 50 patients with GBS from the neurology department of a tertiary care hospital between 2020 and 2021. The study assessed the patients' motor function deficits using the MRC (Medical Research Council) scale as well as the HDS (Hughes Disability Scale). Vitamin B_{12} and CK-NAC levels were measured, and patients were divided into four groups, one of which had a deficiency in vitamin B_{12} and a raised CK-NAC level, while another group had normal serum vitamin B_{12} and CK-NAC levels. Clinical characteristics were compared. Serum vitamin B_{12} and CK-NAC levels were associated with GBS severity based on HDS and MRC scales, autonomic dysfunction, and respiratory failure.

Results: Serum vitamin B_{12} deficiency along with elevated CK-NAC levels was discovered in 44 and 14% of GBS patients, respectively. Serum vitamin B_{12} deficiency correlated significantly with GBS severity, including progression duration, admission and nadir HDS scores, and autonomic dysfunction ($p < 0.05$). CK-NAC level did not correlate with the severity of GBS ($p > 0.05$).

Conclusion: Vitamin B_{12} levels can predict prognosis in GBS patients.

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Key Message

The level of serum vitamin B_{12} may be used in GBS patients as a predictor of prognosis.

Introduction

Guillain-Barré syndrome (GBS) is a polyneuropathy with rapid onset that causes weakness of the arms and legs. It reaches maximal deficit, commonly within 2 weeks from the onset of symptoms.[1,2] Electrodiagnostic tests and cerebrospinal fluid analysis are utilized to assist in the clinical suspicion of GBS. Multiple variables are used to determine the disease's severity as well as the prognosis of GBS, for example, serum folate levels for disease progression prediction,[3] serum albumin levels for responsiveness to treatment,[4] blood glucose levels for predicting early outcome,[5] serum sodium concentrations for predicting 1-year prognosis,[6] and plasma cortisol levels for predicting respiratory failure.[7]

Aims and Objectives

The purpose of this study was to examine the potential use of serum levels of CK-NAC and vitamin B_{12} as prognostic indicators in GBS patients. Our study examined the prevalence of serum vitamin B_{12} insufficiency and increased creatine kinase levels in GBS patients and also studied the relationship between serum vitamin B_{12} level, serum CK-NAC level, and disease severity in GBS.

Materials and Methods

According to the Asbury and Cornblath criteria, 50 individuals with GBS were included in this research. Numerous epidemiological, clinical, and electrophysiological data, along with serum levels of CK-NAC and vitamin B_{12}, were assessed at the time of admission. A vitamin B_{12} deficiency is characterized by a vitamin B_{12} level of <200 pg/mL, and a CK-NAC level above 200 IU is considered increased.[8,9] We also assessed laboratory features of vitamin B_{12} deficiency, such as raised mean corpuscular volume (MCV) and macrocytosis. Lactate dehydrogenase (LDH) or hyperbilirubinemia were not assessed. Additionally, other factors that may lead to a higher serum CK-NAC level due to injury, trauma, or EMG were excluded from our study.

A total of four groups of patients were analyzed—those with or without vitamin B_{12} deficiency, as well as those with or without elevated CK-NAC. We used the sum scores from the MRC (Medical Research Council) scale, ranging from 60 (normal) to 0 (quadriplegic),[10] and the lowest MRC scale score was identified as the GBS nadir. The course of the disease was characterized by the number of days from the onset of symptoms to the peak deficit of the illness.[11]

Exclusion Criteria

- Infectious polyradiculopathy.
- Vasculitic neuropathy.
- Patients with toxic neuropathy.

Statistical Analysis

A paired Student *t*-test was employed to analyze continuous data, whereas a Chi-squared test was utilized to examine categorical data. Pearson correlation coefficients (*r*) were used to examine the associations between serum vitamin B_{12} levels or serum CK-NAC levels and disease severity. The mean along with the standard deviation was used for numerical data, while the percentage and number were used for categorical data. A probability value (*p*) of <0.05 was considered statistically significant. Version 22.0 of IBM Statistical Package for the Social Sciences (SPSS) was used to analyze the data.

Results

Following an analysis of 50 GBS patients, we found that 44% of these individuals had low

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serum vitamin B_{12} levels. Fifty patients in total were divided into two groups: 44% had serum vitamin B_{12} deficiencies (≤200 pg/mL), while 56% had normal levels (>200 pg/mL). In both groups, the average age at presentation was 38.63 ± 18.95 years, with a standard deviation of 39.25 ± 21.42 years, respectively. Males and females comprised 68.18 and 31.82%, respectively, in the group with low serum vitamin B_{12} levels, while 71.43 and 28.57%, respectively, were in the group with normal serum vitamin B_{12} levels.

In both groups, the mean and standard deviation of the MCV were 98.36 ± 7.21 and 79.75 ± 5.78, respectively, with macrocytosis present in 95.45% of individuals with low serum vitamin B_{12} levels (Table 1).

AIDP and AMAN subtypes made up 77.27 and 22.73%, respectively, of the low serum vitamin B_{12} group, whereas 82.14 and 17.86% of the normal serum vitamin B_{12} group had AIDP and AMAN subtypes.

The low vitamin B_{12} group had a mean serum vitamin B_{12} level of 143.40 ± 40.32 pg/mL, while the other group had a mean level of 647.46 ± 436.36 pg/mL. Diarrhea was the most prevalent antecedent infection in each group, accounting for 40.90% in the low vitamin B_{12} group and 21.42% in the normal serum vitamin B_{12} group.

Individuals with serum vitamin B_{12} deficiency showed a higher prevalence of cranial nerve dysfunction and autonomic dysfunction, which were 40.90 and 59.09%, respectively ($p < 0.05$), compared to the other group.

This study also showed that, in comparison to the other group, the group with vitamin B_{12} deficiency had higher mean HDS (Hughes Disability Scale) scores at admission and nadir and lower mean MRC scores at admission and nadir. These differences were statistically significant.

Additionally, the group with low serum vitamin B_{12} levels had a longer disease course, including duration of progression and days of hospitalization, with mean values of 6.68 ± 1.32 and 7.5 ± 1.5 days, respectively (Table 2).

We observed that the duration of disease progression, the HDS score at admission, and the HDS score at nadir were all positively correlated with serum vitamin B_{12} deficiency ($p < 0.001$) (Table 3).

The 50 GBS patients were also divided into two other groups: one with normal CK-NAC levels (≤200 U/L) and another with elevated CK-NAC levels (>200 U/L), comprising 86% and 14% of patients, respectively.

In both groups, the mean age at presentation was 33.71 ± 22.34 years, with a standard deviation of 39.83 ± 19.94 years. Male and female patients in the group with elevated serum CK-NAC levels comprised 71.43 and 28.57%, respectively, whereas in the group with normal serum CK-NAC levels, males and females comprised 69.77 and 30.23%, respectively (Table 4).

Notably, all patients (100%) in the group with elevated serum CK-NAC levels belonged to the AMAN subtype, whereas in the group with normal serum CK-NAC levels, patients with AMAN and AIDP subtypes comprised 6.98 and 93.02%, respectively.

In the groups with elevated and normal serum CK-NAC levels, the mean serum CK-NAC level with standard deviation was 238.71 ± 31.39 U/L and 95.65 ± 44.65 U/L, respectively.

In both groups, the most frequent antecedent infection was diarrhea, occurring in 71.42% of one group and 23.25% of the other.

Patients with elevated serum CK-NAC levels were more likely to have autonomic dysfunction, respiratory failure, and cranial nerve involvement (28.57, 28.57, and 42.85%, respectively), though these associations were not statistically significant ($p > 0.05$).

Table 1: Demographics characteristics with serum vitamin B_{12} level

	With serum vitamin B_{12} deficiency N = 22 (44%)	*Normal serum vitamin B_{12} level N = 28 (56%)*	
Mean age	38.63 ± 18.95	39.25 ± 21.42	
Female sex	7 (31.82%)	8 (28.57%)	
Serum vitamin B_{12} level	143.40 ± 40.32	647.46 ± 436.36	**0.0001**
MCV	98.36 ± 7.21	79.75 ± 5.78	**<0.001**
Macrocytosis	21 (95.45%)	0 (0%)	

p-value<0.05 considered as statistically significant

Table 2: Characteristics of GBS patients with and without vitamin B_{12} deficiency

Group	*With serum vitamin B_{12} deficiency (n = 22)*	*With normal serum vitamin B_{12} level (n = 28)*	*p-value*
Antecedent infection			
Diarrhea	9 (40.90%)	6 (21.42%)	0.21
URI	2 (9.09%)	3 (10.71%)	
Both	0 (0%)	0 (0%)	
Cranial nerve	9 (40.90%)	4 (14.28%)	**0.005**
Respiratory failure	7 (31.82%)	3 (10.71%)	0.09
Autonomic deficit	13 (59.09%)	5 (17.85%)	**0.009**
Motor weakness			
At admission			
HDS	3.77 ± 0.53	3.28 ± 0.81	**0.04**
MRC score	33.45 ± 8.35	40.36 ± 9.29	0.06
At nadir			
HDS	3.97 ± 0.81	3.04 ± 0.77	**0.03**
MRC	32.53 ± 7.36	39.58 ± 9.21	0.06
At discharge			
HDS	3.32 ± 0.72	3.21 ± 0.79	0.69
MRC	37. 82 ± 9.52	41.43 ± 9.15	0.34
At first month			
HDS	2.73 ± 0.83	2.71 ± 0.76	1.00
MRC	45.73 ± 9.42	46.64 ± 8.41	0.95
Disease course			
Hospital days	6.68 ± 1.32	6.07 ± 1.51	0.17
Progression duration	7.5 ± 1.5	5.35 ± 1.37	**<0.001**

p-value<0.05 considered as statistically significant.

Table 3: Pearson correlation of serum vitamin B_{12} level

Correlation	*Correlation–r*	*p-value*
Progression duration	–0.4704	**<0.001**
Respiratory failure	0.4471	0.17
HDS score at admission	–0.3659	**0.009**
HDS score nadir	–0.3659	**0.009**
MRC score at admission	0.2505	0.08
MRC score nadir	0.2505	0.08

p-value<0.05 considered as statistically significant

Table 4: Demographics and clinical characteristics of GBS patients with raised muscle enzyme (CK-NAC level)

	With raised serum CK-NAC level (N = 7)	*With normal serum CK-NAC level (N = 43)*	*p-value*
Mean age	39.83 ± 19.94	33.71 ± 22.34	
Female sex	2 (28.57%)	13 (30.23%)	
Serum CK-NAC level	238.71 ± 31.39	95.65 ± 44.65	**0.0001**
Antecedent infection			
Diarrhea	5 (71.42%)	10 (23.25%)	0.08
URI	1 (14.28%)	4 (9.30%)	
Both	0 (0%)	0 (0%)	
Pain	6 (85.71%)	16 (37.20%)	0.17
Cranial nerve	2 (28.57%)	11 (25.58%)	1.00
Respiratory failure	2 28.57%)	8 (18.60%)	1.00
Autonomic deficit	3 (42.85%)	15 (34.88%)	0.60
Weakness			
At admission			
HDS	3.14 ± 0.90	3.56 ± 0.70	0.10
MRC score	39.71 ± 11.34	36.93 ± 9.21	0.32
At nadir			
HDS	3.21 ± 0.78	3.67 ± 0.73	0.10
MRC	39.01 ± 10.66	36.11 ± 9.60	0.33
At discharge			
HDS	3.0 ± 0.82	3.30 ± 0.74	0.46
MRC	42.0 ± 10.26	39.49 ± 9.33	0.63
At first month			
HDS	2.86 ± 0.90	2.70 ± 0.77	0.74
MRC	44.28 ± 10.03	44.55 ± 8.67	0.67
Disease course			
Hospital days	5.86 ± 0.90	6.42 ± 1.51	0.38
Progression duration	6.28 ± 1.25	6.30 ±1.86	0.53

p-value<0.05 considered as statistically significant

Table 5: Pearson correlation of serum CK-NAC level

Correlation	*Correlation–r*	*p-value*
Progression duration	0.0024	0.99
Respiratory failure	–0.09876	0.77
HDS score at admission	–0.06779	0.64
HDS score nadir	–0.06779	0.64
MRC score at admission	–0.08478	0.56
MRC score nadir	–0.08478	0.56

In the group with elevated serum CK-NAC levels, the mean HDS score at admission was 3.14 ± 0.90, and the mean MRC score at admission was 39.71 ± 11.34, compared to the other group ($p > 0.05$).

The disease progression and duration of hospitalization were shorter in the group with elevated serum CK-NAC levels, with mean values of 6.28 ± 1.25 days and 5.86 ± 0.90 days, respectively, compared to the other group ($p > 0.05$) (Table 4).

The relationship between serum CK-NAC levels and disease progression duration, as well as HDS scores at admission and nadir, did not reach statistical significance ($p > 0.05$) (Table 5).

Discussion

Serum vitamin B_{12} is essential for nerve myelination and axonal regeneration. Its deficiency can lead to peripheral neuropathy, and minor elevations in CK-NAC levels can occur in GBS patients. This formed the basis for including these parameters in our study to examine their relationship with disease severity.

We conducted an extensive literature search to explore the association between serum vitamin B_{12} levels and GBS severity, as well as the relationship between serum CK-NAC levels and GBS severity. However, we were unable to find any prior research investigating these connections.

The prevalence of vitamin B_{12} deficiency in our study was 44%, which is comparable to a previous study conducted in the North Indian population, where the prevalence was 47.19% (defined as serum vitamin B_{12} levels < 200 pg/mL).[12] In our study, low serum vitamin B_{12} levels were found more frequently in males (71.43%) than in females, which is consistent with previous research showing a prevalence of 74.8% in males.[13]

A significant correlation was observed between serum vitamin B_{12} levels at admission and the duration of illness. This may be explained by the role of vitamin B_{12} in immune function, as it is essential for B cell immunoglobulin production, T cell proliferation, and DNA synthesis.[14] A deficiency in vitamin B_{12} may impair immune responses, potentially leading to a prolonged disease course.

Our study also found a relationship between GBS severity—assessed in terms of motor function deficits and autonomic dysfunction—and serum vitamin B_{12} levels at admission. This may be attributed to the crucial role of vitamin B_{12} in peripheral nerve function. A deficiency can contribute to axonal damage, motor and sensory demyelination, and autonomic polyneuropathy.[15,16] Although respiratory involvement was more common in the vitamin B_{12}-deficient group, the difference was not statistically significant.

In our study, 14% of GBS patients had elevated CK-NAC levels. Notably, all patients with the AMAN subtype (100%) had increased CK-NAC levels, similar to findings in previous studies.[9] Our analysis also revealed that patients with elevated CK-NAC levels had a higher incidence of antecedent infections, such as gastroenteritis, compared to those with normal CK-NAC levels. However, the precise mechanism leading to elevated CK levels in GBS remains unclear. One hypothesis suggests that axonal injury in AMAN subtypes results in the release of muscle enzymes from muscle cells.

Our study further demonstrated that most GBS patients (85.71%) with elevated CK-NAC levels experienced painful muscle cramps, suggesting a potential link between CK elevations and muscle cramps.[17,18] However, no significant correlation was found between serum CK-NAC levels at admission and disease duration or the severity of respiratory involvement.

This study has some limitations, including a relatively small sample size and a lower percentage of patients with vitamin B_{12} deficiency, making it challenging to determine the full extent of the association between vitamin B_{12} levels and disease severity. To confirm vitamin B_{12} as a prognostic marker, larger studies with control groups are needed.

Conclusion

Our study's findings suggest that low serum vitamin B_{12} levels independently predict the severity of GBS and disease progression. Further research is necessary to validate this hypothesis.

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ORIGINAL ARTICLE

Role of Sequential Approach to Sample Collection in Microbiological Diagnosis of Smear Negative Pulmonary Tuberculosis

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Abstract

Background: The current diagnostic tools for pulmonary tuberculosis (PTB) fail in detecting up to 43% of cases, leading to inappropriate use of antibiotics and delayed diagnosis. Induced sputum and bronchoalveolar lavage (BAL) are more accurate samples, but their use is not clearly recommended. This study evaluates the real-world feasibility and effectiveness of using a sequential collection of respiratory samples to diagnose PTB.

Materials and methods: PTB cases with sputum-scarce or smear-negative status were included. Sputum induction (SI) and BAL samples were collected. We used a composite reference standard (CRS) method as the reference.

Results: Of 220 cases screened, 156 were enrolled. Eighty cases underwent successful SI (group A), and 76 cases failed induction (group B). In group A, 53.75% of cases were positive for *Mycobacterium tuberculosis* (MTB) by cartridge-based nucleic acid amplification test (CBNAAT). Of the 112 cases that underwent flexible optic bronchoscopy (FOB), 85 were detected positive for PTB, of which eight were detected rifampicin-resistant by CBNAAT in BAL samples. The remaining cases were found to have an alternative diagnosis. Using the sequential approach, CBNAAT had a higher cumulative sensitivity (97.72%), specificity (100%), and diagnostic accuracy (DA) (98.08%) with a *p*-value < 0.001, as compared to either smear examination or culture. 27.56% of cases were able to avoid bronchoscopy using the sequential technique.

Conclusion: The sequential technique of sample collection increased the bacteriological confirmation of PTB.

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Introduction

Tuberculosis (TB) is one of the most rampant infectious diseases of the modern era, with the majority of the burden in developing countries, and the lung being the most commonly affected organ. A quarter of the world's population is estimated to be infected by *Mycobacterium tuberculosis* (MTB). TB is a treatable and curable disease; however, relapse and mortality rates remain high after the initial treatment.[1] One of the important reasons behind poor control rates is the inappropriate use of anti-TB medications, which includes starting anti-TB treatment (ATT) without a bacteriologically confirmed diagnosis. Among other reasons are the inappropriate prescription by health care providers, emergence of drug resistance, ineffective treatment, and premature cessation of treatment by patients.[2]

In India, 85% of TB cases are pulmonary tuberculosis (PTB), and despite multiple methods available to diagnose it, microbiological confirmation is not uniformly sought before ATT initiation.[1] In a significant proportion of subjects, ATT is initiated based on clinical suspicion and/or radiological grounds. Traditionally, sputum smear examination is the first screening test. After initial screening (with sputum smear examination using Ziehl–Neelsen staining), it has been reported that up to 60% of cases remain undiagnosed (smear-negative). Mortality rates among such subjects were observed to be higher compared to smear-positive patients.[1,3] The probable reason behind such high mortality rates has been hypothesized to be the lack of microbiological confirmation, leading to a delay in treatment initiation. As far as the gold standard is concerned, *Mycobacterium* culture has high sensitivity as well as specificity. But due to the high turnaround time for culture [turnaround time (TAT) of 2–8 weeks], it is an unpragmatic investigation for clinical use.[1] To overcome these obstacles, GeneXpert MTB/RIF assay, also known as cartridge-based nucleic acid amplification test (CBNAAT), has been developed and employed for clinical use. Being a cartridge-based test, TAT for CBNAAT is 2–4 hours and has a sensitivity of 73–85% (comparable to that of culture).[4] Following these attributes, in 2017, the government of India decentralized the services of CBNAAT under the flagship program of NTEP (National Tuberculosis Elimination Program).[5]

However, notwithstanding the extraordinary impact of GeneXpert in diagnosing smear-negative TB cases in trial settings, 43% of cases of PTB continue to remain undiagnosed (in the field), leading to significant delays in treatment initiation.[6] In usual practice, a proportion of these subjects are started on ATT without microbiological confirmation, whereas others are referred to higher centers for bronchoscopy or other invasive investigations.

Probable reasons behind the failure of CBNAAT in real-world settings among a cohort of subjects have been that around one-third of TB cases either do not provide an adequate biological sample or have a very low concentration of TB bacilli in the collected specimen. Therefore, alternative methods of obtaining representative samples have been tested and studied, such as sputum induction (SI) with 3% hypertonic saline, bronchial washings (BWs), and bronchoalveolar lavage (BAL).[7] The reviewed study by Gopathi et al. showed that, even though SI is a simple and relatively safe procedure, there is significant heterogeneity in the technique of the procedure, and a large number of patients are unable to produce an adequate sample

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or remain GeneXpert negative after SI.[8] The diagnosis in such cases remains a challenge for the physician, and they commonly proceed with empiric treatment or subject patients to flexible optic bronchoscopy (FOB). In a recent meta-analysis, which included 90 studies, SI was found to have a diagnostic yield of 35–95% with significant heterogeneity among studies.[9]

Though SI might seem to be a beneficial and benign addition to the standard of care, it might still be associated with treatment delays and potential dissemination of MTB due to its aerosol-generating attributes. Also, it remains unknown if the sequential technique of sample collection (SI followed by FOB) offers an increase in diagnostic yield after negative induced sputum results. Therefore, the true impact of SI and flexible bronchoscopy-guided sampling needs to be evaluated in real-world settings. The present study was designed to examine the real-world role of SI and sequentially performing BAL, in a prospective fashion, among patients with clinical suspicion of PTB, who were either smear-negative or unable to produce sputum.

Materials and Methods

Study Design and Setting

It was a single-center, prospective, single-arm observational study, conducted in the Department of Respiratory Medicine, and Pulmonary and Critical Care Medicine, along with the Department of Microbiology at a tertiary care university teaching hospital in Northern India from January 2018 to 2020 after obtaining approval from the Institutional Ethics Committee (vide letter number BREC/17/536 dated 29th November 2017). Sputum-scarce and smear-negative cases with clinical suspicion of PTB were enrolled in the study. After written informed consent, patients above 18 years of age, belonging to either sex, sputum-scarce or smear-negative, sputum GeneXpert-negative, with radiological and clinical findings consistent with active PTB, were included in the study. Patients with a history of ATT use, refractory hypoxia, unstable hemodynamics, human immunodeficiency virus (HIV)-positive status, chronic kidney disease, chronic heart failure, chronic liver failure, known cases of any chronic lung disease (interstitial lung disease, chronic obstructive pulmonary disease, or bronchial asthma), and those who were unwilling to comply with study procedures were excluded from the study.

Study Procedure

Sputum induction was done according to the technique described previously.[10] In brief, 10 mL of 3% hypertonic saline was delivered through an ultrasonic noiseless nebulizer (Dr Odin® PN-100 nebulizer) for 20 minutes in a well-ventilated room after 15 minutes of two puffs (100 µg puff) of albuterol inhalation (using a metered-dose inhaler). Patients were encouraged to cough every 5 minutes with occasional gentle chest percussion. The sample was collected in a Falcon tube. The procedure was done in a well-ventilated room with only one of the investigators inside for chest percussion.

Flexible optic bronchoscopy was performed after the patient had fasted overnight, under local anesthesia and conscious procedural sedation.[11] During the procedure, a stepwise airway examination was done. BAL was obtained as per the standard protocol described previously[5] from the diseased segment of the lobe (as localized by computed tomography of the thorax) and sent in a Falcon tube for further investigations such as AFB smear, GeneXpert, MTB culture, and cytology. Other routine investigations, as indicated clinically/radiologically, like pyogenic culture and sensitivity, fungal culture and sensitivity, and endobronchial biopsy were also done. GeneXpert MTB/RIF assay was done as per the technical guidelines of the World Health Organization (WHO).

Final Diagnosis

The final diagnosis of PTB was based on the composite reference standard (CRS), which consists of two criteria: bacteriologically confirmed PTB and clinically diagnosed PTB.[12] "Bacteriologically confirmed PTB" were the cases in whom MTB was positive on GeneXpert or culture in induced sputum or BAL samples, whereas "clinically diagnosed PTB" were the cases in which GeneXpert and culture in induced sputum and/or BAL samples were negative for MTB but had no possible alternate diagnosis and were started on empirical ATT with complete or partial but objective resolution of clinical and radiological features of PTB during follow-up in the intensive phase of treatment.

Statistical Analysis

Demographic, clinical, and procedural data were collected on paper CRF (case record forms). Data were later entered into Microsoft Excel® where it was cleaned, curated, and coded. Subsequently, data were analyzed using International Business Machines (IBM)® Statistical Package for the Social Sciences (SPSS) version 26. Descriptive and inferential statistical analysis was carried out. Results of continuous measurements were reported as mean ± SD (among normally distributed) and median (with IQR, among skewed data), whereas results of categorical measurements were presented in numbers (%). Normalcy of the data was tested using the Shapiro–Wilk test. Diagnostic yield, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy (DA), and *p*-value were calculated and reported for the GeneXpert, MTB culture, and AFB smear in induced sputum and BAL samples. The Chi-squared test was used to determine the significance of study parameters on a categorical scale between two tests. A *p*-value of <0.05 was considered significant. The manuscript was written and findings were reported using STROBE guidelines.

Results

Over a period of 2 years, 220 patients with signs, symptoms, and computed tomography of thorax findings suggestive of PTB were screened, of which 156 were enrolled (Fig. 1). The mean age of the study population, comprising 94 males, was 40.95 ± 16.9 years. Demographic details, clinical features, and radiological features of patients are depicted in Table 1.

The most common clinical symptom was cough (70.5%), followed by fever (58.3%), and the most frequent radiological abnormality was consolidation (24.07%). The chest radiograph did not show any abnormality in 20.5% of cases. Computed tomography of thorax frequently reported bronchiectasis changes, centrilobular nodules, miliary mottling, and ground-glassing. The tuberculin skin test (TST) was positive in 90% of patients, with a mean induration of 16.4 ± 3.6 mm (Table 1).

All patients were subjected to SI, of which 80 (51.28%) patients were able to expectorate after induction. They were included in group A (successful SI). In 43 (61.42%) cases of group A, MTB was positive by GeneXpert in induced-sputum samples. Seventy-six patients who could not expectorate even after induction (group B) and 37 cases who were negative for MTB using GeneXpert in induced sputum (from group A) were subjected to FOB. Out of these 113 cases who underwent FOB, a bacteriologically confirmed diagnosis of TB was reached in 86 cases, using either GeneXpert, MTB culture, or AFB smear [85 (75.22%), 54 (47.78%), and 28 (24.77%) cases, respectively], performed on BAL samples. One patient was GeneXpert negative but culture positive for MTB. An alternate diagnosis was made after FOB in 24 patients [bacterial pneumonia 11 (7.05%), bronchogenic carcinoma 7 (4.49%), fungal pneumonia 3 (1.92%), and non-tubercular mycobacteria (NTM) 3 (1.92%)]. Finally, of the

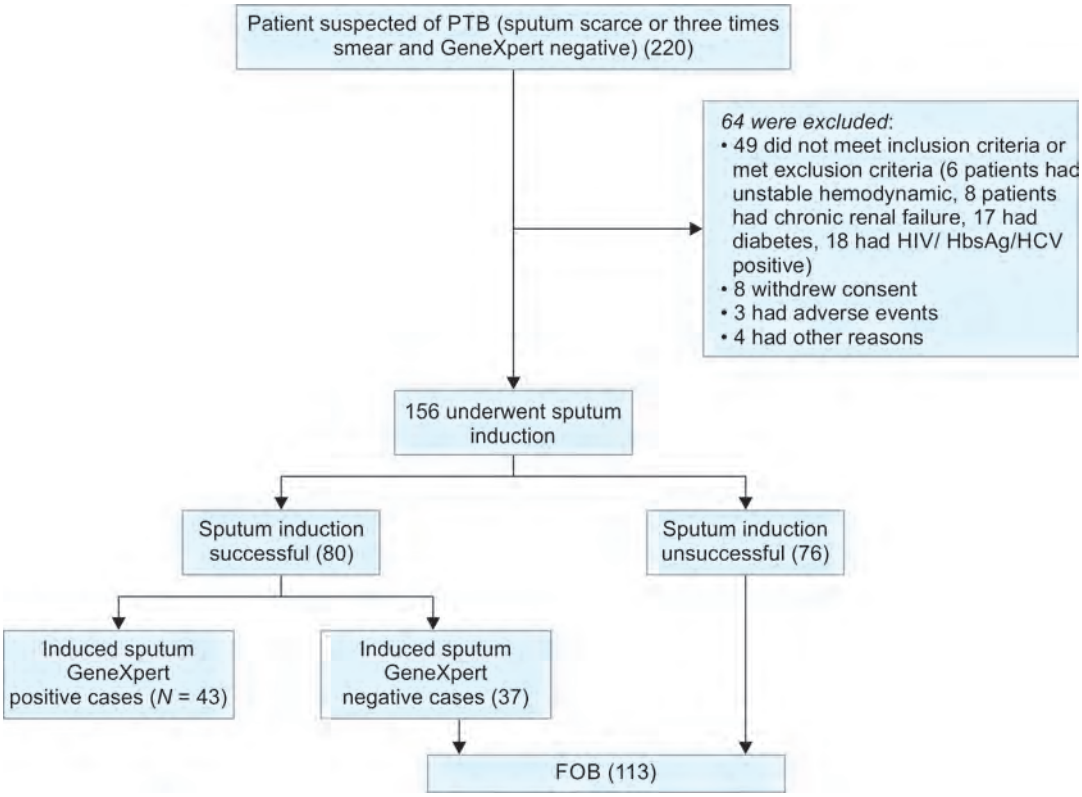

Fig. 1: Flow diagram of the patients included in study; FOB, fiberoptic bronchoscopy; Neg, negative; Pos, positive; PTB, pulmonary tuberculosis

156 patients, 132 (82.61%) had a diagnosis of PTB based on the CRS, of which 129 (97.72%) patients were bacteriologically confirmed PTB, and 3 (2.27%) (who were negative for TB or an alternate diagnosis even after FOB) patients were clinically diagnosed PTB (Table 2). GeneXpert in BAL samples resulted in the diagnosis of 85 patients, who had failed the SI process either due to failed induction or negative GeneXpert results. The percentage positivity of GeneXpert in BAL samples (75.22%) was higher than in induced sputum samples (53.75%).

GeneXpert had a higher sensitivity and specificity (95.51 and 100%, respectively) compared to AFB smear (31.46 and 87.5%, respectively, p-value < 0.001) and a higher sensitivity and similar specificity compared to culture (60.67 and 100%, respectively, p-value < 0.001) using the CRS as the reference standard (Table 3). The sequential technique had a higher sensitivity (97.73%) compared to both SI (61.42%) and FOB (96.62%) (Table 3).

M. tuberculosis was sensitive to rifampicin in 121 cases and resistant to rifampicin in eight cases, who were subsequently started on multidrug resistant (MDR) treatment. All were BAL samples. All procedures were well tolerated. The most common reported adverse events during SI were bronchospasm (3%) and cough (0.5%). Whereas sore throat (0.7%), bleeding (0.2%), and transient hypoxia (1.5%) were the most common adverse events reported during FOB. All adverse events were either grades 1 or 2 as per CTCAE 5.0.

Discussion

The results of the present study have demonstrated a gain in diagnosis in 129 cases by the sequential technique of SI followed by FOB using GeneXpert as the method of evaluation. Also, sequential BAL was able to diagnose eight cases of (primary) MDR TB in patients who had negative GeneXpert results in induced sputum or were unable to produce sputum even after SI. Using SI, 43 study subjects (27.6%) were able to defer bronchoscopy for the diagnosis of pulmonary TB. BAL samples offered an additional advantage in the diagnosis of diseases mimicking TB, such as non-resolving pneumonia, persistent atelectasis, ILD, cancer, etc.

Sputum induction and BAL techniques have been sparingly used for respiratory sample collection and remain underutilized for the diagnosis of PTB, especially in resource-limited settings.[13] The present study describes the role of the sequential technique in sputum-scarce/sputum-smear-negative TB and in eliminating the gap in bacteriological confirmation by the rational use of these techniques. Unlike previous studies, we did sequential SI followed by, if needed, BAL and showed that it offers an advantage over SI alone and prevents unnecessary exposure to invasive procedures like FOB and BAL. While SI was unable to diagnose PTB in approximately two-thirds of cases, one-quarter of cases were able to avoid the invasive procedure of bronchoscopy with the help of SI. The sequential technique had a higher sensitivity (97.73%) compared to SI (61.42%) and FOB (96.62%). To our knowledge, this is the first prospective study to evaluate the real-world objective role of SI followed by FOB (sequential approach) in the diagnosis of clinically suspected sputum-negative or sputum-scarce PTB subjects.

By using a sequential approach, we were able to reduce as well as rationalize the number of bronchoscopies required. In our study, BAL was able to diagnose 27 cases who were negative on SI and showed the advantage of doing BAL in induced sputum-negative cases, as it results in a high-quality biological sample being taken from the specific active diseased site. Also, BAL is less likely to be contaminated by oral flora, whereas induced sputum has a high chance of contamination with oral flora.[8]

Bronchospasm has been commonly considered to be an adverse event related to SI, but only three such reactions were noted in our study, all of which were grades 2 or 1. These findings corroborate with the observation of a study conducted by Geldenhuys et al., which evaluated the safety and tolerability of SI

Table 1: Clinicoepidemiological profile of smear negative PTB patients

Character	*Subset*	*Total patients*	
		Number	*Percentage (%)*
Gender	Male	94	60.25
	Female	62	39.74
Age (years)	≤30	57	36.53
	31–60	76	48.71
	>60	23	14.74
Symptoms	Cough	110	70.51
	Fever	91	58.33
	Hemoptysis	28	17.95
	Shortness of breath	43	27.56
	Chest pain	38	24.35
	Appetite and weight loss/weakness, malaise	87	55.77
Duration of symptoms	≤2 weeks	19	12.17
	2–6 weeks	35	22.43
	>6 weeks	102	65.38
BMI (kg/m^2)	≤20	89	57.05
	21–25	50	32.05
	>25	17	10.89
Residence	Rural	117	75
	Urban	39	25
Addiction	Smoking	80	51.28
	Alcohol	26	16.67
Radiology	Cavitation	8	5.12
	Consolidation	46	29.49
	Nodular opacities	5	3.20
	Pulmonary infiltrates	28	17.94
	Fibrobronchiectatic changes	20	12.82
	Ground glassing	5	3.20
	Miliary shadows	3	1.92
	Normal finding	32	20.51
	Others	7	4.49

Table 2: Disease distribution of the total cases ($n = 156$); BAL, bronchoalveolar lavage; CRS, composite reference standard; NTM, non-tubercular mycobacteria; PTB, pulmonary tuberculosis

Disease		*Number of cases (N) (%)*	
1.	PTB (CRS)	132	(84.61%)
	A. Bacteriological confirmed PTB	129	(82.68%)
	Induced sputum GeneXpert	43	(27.56%)
	BAL (GeneXpert/culture)	86	(55.13%)
	B. Clinical diagnosed PTB	3	(1.92%)
2	Non-PTB	24	(15.38%)
	A. Malignancy	7	(4.49%)
	B. Bacterial pneumonia	11	(7.05%)
	C. Fungal infections	3	(1.92%)
	D. NTM	3	(1.92%)
Total		156	(100%)

in adolescents and adults with suspected PTB.[14] One of the reasons behind such a low incidence of bronchospasm could have been the uniform use of salbutamol inhalation prior to SI.

Another topic for debate has been the ideal concentration of saline for SI. One school of thought, as proposed by Butov et al., suggested that higher concentrations of nebulized saline could lead to a greater osmotic impact on airway secretions, resulting in increased induced sputum volume and, therefore, higher diagnostic efficacy.[15] However, others have positioned that higher saline concentrations might carry a higher risk of airway reactivity and increased rates of adverse events during the procedure. A meta-analysis, after accounting for confounding factors, found that higher saline concentrations did not necessarily result in improved diagnostic yield for SI.[16,17] Consequently, our study employed a 3% normal saline concentration, which is easily available and cheaper compared to a 7% saline formulation.

Evaluating multiple attempts of SI before proceeding to FOB, it has been shown that repeated use of the same modality might add to the delay in time to treatment initiation without adding much to the diagnostic ability. The same has been demonstrated in the study by Schoch et al., where FOB had a significantly higher diagnostic yield when compared to multiple induced-sputum samples.[18]

Sputum induction samples have a high risk of contamination with secretion from the oral cavity or upper airway (salivary

Table 3: Performance values of various diagnostic techniques (*N* = 156) and diagnostic tests (*N* = 113); AFB, acid fast bacilli; BAL, bronchoalveolar lavage; CRS, composite reference standard; FOB, fibreoptic bronchoscopy; MTB, Mycobacterium tuberculosis; PTB, pulmonary tuberculosis; SI, sputum induction

		Sensitivity	*Specificity*	*p-value*
A. Diagnostic technique				
	SI	61.42%	100%	0.001
	FOB	96.62%	100%	0.01
	Sequential approach (SI + BAL)	97.73%	100%	0.001
B. Diagnostic tests				
Results compared to MTB culture	GeneXpert	98.15%	45.76%	0.001
	AFB	51.85%	94.92%	0.001
Results compared to CRS	GeneXpert	95.51%	100%	0.001
	AFB	31.46%	87.5%	0.01
	MTB culture	60.67%	100%	0.01

contamination), which reduces their sensitivity. Other studies have also shown that induced sputum may be unsuitable for GeneXpert testing because of the high chance of obtaining a salivary sample from the oral cavity rather than the lower respiratory tract. In up to 48.72% of the cases, induced sputum fails to provide an adequate sample for further testing. In previous studies, patients underwent SI for 3 days, as compared to one day, which only marginally adds to the diagnostic yield.[6,19,20] In a high-burden country like India, 3 days of SI adds to the cost, risk of dissemination of infection, and unnecessary visits to the hospital/hospitalization. Hence, we stuck to one attempt of SI alone, that too in a controlled and supervised setting, to mimic the most real-world scenario. However, we had a very low drop-out rate and high diagnostic yield rates for FOB, which could have been due to our center being a high-volume center for FOB with high expertise among the operators.

A previous meta-analysis demonstrated that for the diagnosis of sputum smear-negative PTB, the diagnostic yield of SI and bronchoscopy was similar.[7] However, our study contradicts these findings due to several reasons. Firstly, the previous studies did not include GeneXpert, and secondly, the sample size was too small. Additionally, the population was heterogeneous, and the culture techniques used in the different studies varied. In the index study, the yield of SI and BAL was higher compared to other previous studies.[8,14,15,17,21] This could be because we uniformly used GeneXpert as a diagnostic tool instead of conventional microscopy and culture, unlike what was performed in earlier studies. This is in line with the national program for TB, which encourages the replacement of conventional microscopy with nucleic acid testing for TB diagnosis.[5]

At present, costs for the GeneXpert system are similar to those required to set up an automated liquid culture system for TB, but as this test is offered only at WHO centers for TB control, it is available free of cost to the patient.[5]

Despite its novelty and pros, our study had a few limitations, such as being a single-center observational study and the inherent possibility of referral bias, as our center is the apex center in the state. Being single-centered reflects upon the homogeneity of the practices, but the data lacks representation from other parts of the country. The single-center nature of the study also limits the generalizability of the research. In addition to these factors, evaluating the cost-effectiveness of the three techniques could have added value to the study. Finally, we did not evaluate the delay in treatment due to our approach of going sequentially. However, we can assume that if the treatment had been started empirically in such cases, a significant number of cases would have been mistreated as TB.

Conclusion

The present study highlighted the pros of SI and sequential BAL with their role in uplifting detection and reducing the gap in clinically diagnosed but sputum-negative PTB cases. It can be recommended that induced sputum for GeneXpert be used as a point-of-care diagnostic test at peripheral centers, and BAL be kept as a referral test in the diagnostic algorithm of smear-negative PTB management. Encouraging the employment of SI and BAL for microbiological diagnosis of TB can help in achieving the goals of the End TB strategy.

Author Contributions

Conceptualization, DC and KBG; methodology, KK and KBG; software, PKS and GA; validation, AA and GA; formal analysis, PKS, GA, and AC; investigation, KK and PKS; resources, AC and DC; data curation, KK, PKS, and GA; writing—original draft preparation, KK and AC; writing—review and editing, DC and AA; visualization, KBG and GA; supervision, AC; project administration, AC and KBG.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of Pt BD Sharma Post Graduate Institute of Medical Sciences, Rohtak vide letter number BREC/17/536 dated 29 November 2017.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The anonymized individual patient data can be shared upon request to the corresponding author and permission by the IEC.

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REVIEW ARTICLE

Implementation Strategies to Improve Survival Outcomes after Out-of-Hospital Cardiac Arrest: Global Challenges and Disparities

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Abstract

Out-of-hospital cardiac arrest (OHCA) is a major global public health problem, contributing to high mortality and morbidity. There is significant variability in OHCA incidence and survival rates across different countries and communities and in various geographical locations, even within the same country. Cardiopulmonary resuscitation (CPR) knowledge and skills are critical to achieving better survival outcomes during OHCA. Community CPR training rates vary widely from country to country. Most low-middle-income countries (LMICs) lack an organized prehospital care system and are relatively far from the acceptable standards recommended for better outcomes by international organizations. Several factors contribute to disparities in outcomes during the management of OHCA in a given community in any country. The key challenges are lack of OHCA awareness, community CPR training, well-trained medical personnel, first responders, essential emergency equipment, high-quality emergency medical services (EMS) and funding, as well as access to and provision of timely, evidence-based emergency cardiac care. It is important to understand the structure of a given geographical community before planning and implementing a sustainable program to enhance outcomes during OHCA globally. There is a need for ground-level research and surveillance to improve outcomes from OHCA. Addressing these challenges and disparities is critical in improving survival outcomes after OHCA.

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Introduction

Out-of-hospital cardiac arrest (OHCA) is a major public health threat worldwide. There is significant variation in OHCA incidence and rates of survival across different regions and countries.[1] Prevalence of bystander cardiopulmonary resuscitation (CPR) and access to emergency medical services (EMS) significantly influence survival after OHCA. Disparities in OHCA survival are due to disparities in bystander CPR, accessibility to automated external defibrillators (AEDs), EMS arrival, and postcardiac arrest care.[2] There is a need for a global effort to address the disparities in the chain of survival and barriers to implementing strategies to improve survival outcomes from OHCA.

Global Data on Out-Of-Hospital Cardiac Arrest

OHCA affects 3.8 million people annually.[3] Globally, OHCA survival with good neurological function is around 10% (ranging from 6 to 22%).[4] The incidence of OHCA among adults is 55 OHCAs per 1,00,000 person-years.[5] The number of OHCA cases attended by EMS ranges from 30 to 97 per 1,00,000 population, with a global average of 82.1.[6] Survival rates after OHCA (surviving to hospital discharge or 30 days after the event) range from 3.1 to 20.4%.[6] In instances of bystander-witnessed shockable OHCA, survival rates to hospital discharge or 30 days can be much higher, ranging from 11.7 to 47.4%.[6] Favorable neurological outcomes are known in 9.9–33.3% of these cases.[6] There are marked differences in CPR training rates among populations worldwide. CPR training is prevalent in 40% of the global population. Resuscitation training in high-income countries is twice as high as in upper-middle-income countries (50 vs 23%).[7] Many countries lack sufficient data on resuscitation training. Standardized reporting of resuscitation training warrants the implementation of internationally accepted Utstein guidelines worldwide.

Factors Influencing the Survival of Out-Of-Hospital Cardiac Arrest Subjects

The "chain of survival" concept outlines a series of critical steps that significantly influence patient outcomes. This includes early recognition of OHCA, early activation of EMS, early high-quality hands-only CPR, rapid defibrillation, advanced resuscitation by EMSs, and evidence-based postresuscitation care and recovery. After resuscitation, rehabilitation and psychological support are essential for complete recovery. By strengthening each link in the chain of survival, we can significantly improve the chances of survival for those experiencing OHCA.[8] This involves coordination between laypeople, emergency dispatchers, first responders, EMS, and hospital providers.

OHCA is a time-critical emergency where the likelihood of survival decreases with every minute treatment is delayed. The Utstein data elements serve as the cornerstone of clinical research in resuscitation. These standardized elements allow researchers to accurately track and analyze factors that influence survival after OHCA. They include factors involving dispatch, patients, events, processes, and outcomes.[9] Studies show a significant increase in survival rates at discharge, 1 month, and even 1 year for OHCA patients who had their cardiac arrest witnessed by EMS or a bystander and who received CPR from the bystander.[10,11] This underscores the life-saving potential of bystander CPR training and the importance of bystander intervention in the chain of survival. Apart from person-specific factors like age, gender, race, health condition, and community participation, the organizational structure of EMS and the quality of healthcare systems impact the chances of survival of OHCA subjects in various countries.

Following an OHCA event, the chance of attaining return of spontaneous circulation

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(ROSC) varies greatly, with success rates between 0 and 62%. Studies show that a well-functioning chain of survival can lead to ROSC in nearly half of OHCA cases (49%) and a 27% survival rate 1 year later.[12] Prehospital efforts like early recognition of cardiac arrest, high-quality CPR performance, and AED use impact early ROSC. Subsequently, rapid transport to a specialized cardiac care center, comprehensive postcardiac care, and adherence to evidence-based protocols for managing postcardiac arrest syndrome impact the survival of the OHCA subject.

Evidence of Improvement of Outcomes via Hands-Only Cardiopulmonary Resuscitation and Automated External Defibrillator

Bystander CPR is a key step in improving survival after OHCA. The global rate of bystander CPR is low, ranging from 35 to 40%.[13] Significant variability in OHCA survival is noted due to differences in bystander response. Ample evidence shows that combined CPR and AED use lead to better outcomes after cardiac arrest. Initiation of CPR and defibrillation within 5 minutes of OHCA increases the chances of survival (50–70%). Every minute of delay in CPR reduces survival by 10%.[14] Studies have shown that 30-day survival is increased twofold with bystander CPR at 5 minutes and threefold at 10 minutes. However, the positive impact of bystander CPR diminishes over time, becoming less significant after 13 minutes.[15] A study involving 2,32,703 patients concluded that, in comparison to no CPR, bystander intervention can nearly double a person's chance of survival after OHCA.[16] Bystander CPR prevents the degeneration of a shockable rhythm into a nonshockable rhythm.[17] Studies show a positive association between bystander CPR and 30-day survival rates, even with varying ambulance response times. Thirty-day survival rates decreased overall with longer ambulance response times, regardless of the application of bystander CPR.[15] This finding highlights the importance of implementing initiatives such as optimizing ambulance deployment, organizing first responders, and increasing the availability of AEDs in communities.

Bystander Cardiopulmonary Resuscitation

Bystander CPR is CPR performed by someone who witnesses a cardiac arrest and is not part of a formal emergency response team (such as firefighters, paramedics, or EMTs). Even medical professionals like doctors or nurses, when not part of the emergency response team, can be considered bystanders in situations of OHCA. Bystander CPR may be compressions-only or compressions with ventilations.[9] It is important to differentiate between lay responders, who are not formally trained, and emergency medical responders (EMRs), who are trained. Lay responders can play a crucial role in the chain of survival by performing key actions such as calling EMSs, retrieving an AED if available, and performing CPR. Lay responders include the general public or off-duty healthcare personnel. They may or may not have previous CPR training.

Bystander CPR (BCPR) is a key modifiable factor that has a major impact on a person's chance of surviving an OHCA. BCPR increases the survival of OHCA patients and helps those whose initial rhythm is shockable. Variability in OHCA survival and neurological outcomes is due to disparities in bystander CPR rates. BCPR complements short emergency department response times. Evidence-based best practices are crucial to increasing bystander CPR rates. Across various studies, bystander CPR use varied between 19.1 and 79%, while AED use ranged from 2.0 to 37.4%.[6]

The time taken to initiate CPR significantly impacts survival. The critical moments following a cardiac arrest often rely heavily on the actions of the community. By initiating CPR and maintaining the victim's viability until emergency services arrive, bystanders can significantly impact survival rates. The Utstein survival specifically focuses on a group with the highest chance of recovery: patients whose cardiac arrest was witnessed by a bystander and whose initial heart rhythm was ventricular fibrillation or pulseless ventricular tachycardia.[18] These rhythms are particularly responsive to CPR and defibrillation, making early intervention crucial.

High-Quality Cardiopulmonary Resuscitation

The quality of CPR varies between systems and locations and contributes to disparities in survival from OHCA. The quality of CPR during a cardiac arrest has a major impact on a person's chance of survival. The wide variations in survival rates observed across different healthcare systems can often be attributed to disparities in CPR quality. Studies have shown that performing high-quality CPR, with a chest compression fraction (CCF) of >80%, improves survival by 200–300%. Data also reveal a clear link between lower chest compression fraction—the percentage of time spent on high-quality compressions—and decreased chances of attaining ROSC and surviving hospital discharge.[19] In simpler terms, the more time spent performing effective chest compressions during CPR, the greater the likelihood of a successful outcome.

Bystander Effect

A study by Johnston et al. (2003) demonstrated that people were more likely to perform CPR on a victim if they believed they were the only witness and less likely to perform CPR in the presence of others. This is considered the **Bystander effect**, which occurs when multiple individuals are present during an emergency.[20]

Barriers to layperson response[21]:

- Inadequate CPR knowledge and training.
- Fear of hurting the victim.
- Fear of infection (especially during the COVID-19 pandemic).
- Fear of litigation.
- Lack of familiarity with Good Samaritan laws.
- Postevent stress.
- Lack of debriefing.

Debriefing OHCA bystanders by emergency medical dispatchers boosts the confidence of the lay responder in providing CPR in the future.[22]

Barriers to the Provision of Bystander Cardiopulmonary Resuscitation and Automated External Defibrillator Use

Widespread public education and training programs that reduce barriers to bystander CPR and defibrillation are crucial public health initiatives for every country.[8] There is a need to implement programs to improve lay bystanders' ability to locate and use public AEDs, which may encourage early retrieval of AEDs and thereby improve OHCA outcomes. Gender, race, and socioeconomic differences, besides fear of legal problems, are also contributing factors to lower rates of bystander CPR.

Strategies to Increase Bystander Response to Out-Of-Hospital Cardiac Arrest

Strategies like telecommunicator CPR or dispatch-assisted CPR to reduce ambulance response time and ensure the dispatch of

nearby trained lay or first responders for early intervention with CPR and defibrillation are likely to increase survival after OHCA.[23]

Use of Mobile Phone Technology to Improve Citizen's Response

Mobile phone systems can alert citizens in the vicinity of a cardiac arrest, effectively turning them into potential first responders.[24] In a study involving 1,42,740 patients, 53% of events were witnessed by a bystander, but only 32% received bystander CPR.[25] By optimizing bystander CPR and AED use within communities, we can significantly improve survival rates for OHCA victims. The isolated reports of bystander CPR rates in countries such as India (1.3–9.8%) are similar to those reported by two international registries, the DA-CPR study (2021) and the PAROS registry (2022).[26–28]

Willingness of Individuals to Perform Cardiopulmonary Resuscitation

Even though rapid initiation of bystander CPR is effective in OHCA, <50% of subjects receive bystander CPR. A crucial factor in improving survival rates after OHCA is increasing the willingness of bystanders to intervene. In real-life settings, several factors influence whether or not lay rescuers (people with no formal medical training) perform CPR. Consideration of these factors is crucial in designing CPR training programs aimed at improving CPR performance by lay rescuers in real-life situations.[29] Bystanders may hesitate to perform CPR due to feelings of panic, lack of confidence, fear of injuring the victim, or language limitations. Communication issues, including telephone difficulties, physical frailty, disagreeable physical characteristics, female gender, race, low socioeconomic status, and community education level, affect willingness to perform CPR. Lack of adequate CPR knowledge and skills is the most frequently recognized barrier to initiating CPR.

Factors Increasing Bystander Willingness to Perform Cardiopulmonary Resuscitation

Higher education levels, previous CPR training, and wider community awareness of CPR, as well as the presence of multiple bystanders, positively impact increasing bystander CPR rates. Studies show a concerning gender disparity, with men more likely to receive bystander CPR than women in public places [45 vs 39%; OR (1.27), 95% CI (1.05–1.53), $p = 0.01$]. This translates to a 29% higher chance of survival for men compared to women.[30] To address health disparities and promote equity in CPR knowledge and skills, policymakers, emergency call centers, and CPR training organizations need to work together.[31]

Several promising strategies, such as dispatcher-assisted CPR, innovative training methods utilizing video-based training, smartphone apps, virtual reality simulations, and CPR training for middle and high school students, can help increase bystander CPR rates.[32] Variations in the Utstein elements template, including system factors, dispatch procedures, patient characteristics, and resuscitation processes, all contribute to the diverse outcomes observed in bystander-witnessed shockable out-of-hospital cardiac arrests (OHCA). Several factors in real-life OHCA settings encourage or discourage lay rescuers' CPR performance.

A comprehensive review of research over the past 40 years sheds light on the global picture among people who received CPR worldwide: return of spontaneous circulation (ROSC), 29.7%; survival to hospital admission, 22.0%; survival to hospital discharge, 8.8%; survival at 1 month, 10.7%; and survival at 1 year, 7.7%.[11] However, the study also revealed a concerning trend in survival rates, which are significantly lower in developing countries compared to developed countries. The disparity can be attributed to several factors, including differences in initial heart rhythm, witnessed cardiac arrest, Utstein survival, quality of bystander CPR, and early defibrillation.

Community Cardiopulmonary Resuscitation Training

A global gap exists in CPR training for laypeople.[7] High-income nations have double the training rates compared to upper-middle-income countries. Standardized reporting of CPR training utilizing internationally recognized Utstein guidelines is required to address this disparity. Insufficient CPR knowledge and skills are primary barriers preventing laypeople from attempting resuscitation. Bystander CPR rates increase when communities have access to well-structured CPR training programs.

A review of existing practices of CPR education helps in planning community CPR training. To design impactful community CPR training programs, we must gather data on training prevalence, public perceptions, and barriers through public surveys. The proportion of laypeople trained in CPR ranges from 3 to 79% (median 40%)—18–73% based on national studies and 3–79% per subnational studies. This significant variation in CPR training rates is attributed to various factors such as differences in community CPR training implementation worldwide and variations in study design and research reporting.

Most studies on CPR training come from developed countries where CPR training programs are extensively conducted. Research suggests that only 34% of people have received recent CPR training (within a year), highlighting the need for refresher courses. The success of a community CPR training program can be assessed by how many people in the community have recently received CPR training. Younger individuals and those with higher educational qualifications are more likely to have CPR training. Age, gender, educational status, nature of employment, and occupation are potential determinants of previous resuscitation training. There is a need to increase public awareness of resuscitation.

The recommended approach for designing future CPR training programs emphasizes competency-based learning, where the focus is on measurable skills acquired by participants rather than course participation alone. For instance, a well-designed 30-minute CPR and AED training session can effectively equip laypeople with CPR knowledge and ensure skill retention for up to 6 months, demonstrating its effectiveness compared to traditional, longer courses.[33]

Disparities in Layperson Resuscitation Education

Several barriers and enablers impact the ability of laypeople to participate in resuscitation training. While CPR training is crucial for improving survival rates after cardiac arrest, several factors can prevent people from participating. Some common personal barriers include advanced age, lower socioeconomic and educational background, language barriers, and belonging to a marginalized racial or ethnic group. Several factors can motivate people to overcome these obstacles and get trained in CPR, such as previous instances of witnessing a cardiac arrest, knowledge of the availability of AEDs in public places, working in certain professions (e.g., healthcare, education), or legal requirements for CPR training. A thorough understanding of participation barriers and enablers is key to implementing effective CPR training programs that reach

those less likely to participate in resuscitation training programs.[34]

Utstein Formula to Improve Survival

The Utstein formula stresses the importance of combining medical science with effective education and local adaptation for successful community implementation.[35] This is exemplified by the effective use of complementary bystander CPR programs to achieve best practices in CPR.

Improving Early Detection of Cardiac Arrest

Unwitnessed cardiac arrests significantly reduce the chances of survival. However, innovative technology applications like wearable devices (e.g., smartwatches, fitness trackers), smart speakers, and machine learning hold promise for minimizing these occurrences. The latest wearable technology often includes built-in arrhythmia detection capabilities.[36,37] These combined functionalities could significantly improve response times and increase the chances of survival for cardiac arrest victims, even if they are alone.

Automated External Defibrillator Use

Research indicates that if an AED is utilized within 3 minutes, survivability can increase to greater than 74%. On the other hand, for every minute that passes without treatment, a person's survival chance drops by 7–10%. While AEDs are a critical tool for improving survival rates after OHCA, their actual use remains disappointingly low. Several factors, such as limited availability, accessibility, and knowledge gaps among bystanders in the use of an AED, contribute to this issue.

Promising strategies like optimizing AED deployment, innovative delivery methods such as utilizing drones for AED delivery, and AED locator apps improve AED use. In addition to these technological advancements, comprehensive public education campaigns to raise awareness of OHCA, promote BLS training, and encourage AED use equip bystanders with the knowledge and confidence to intervene effectively. Strategic placement of AEDs in high-traffic areas like airports, train stations, aircraft, shopping malls, and casinos, along with counseling EMS staff and training the public in AED usage, is essential.[38]

The guidelines also emphasize the importance of AED registries that link AED locations to emergency dispatch centers. This allows dispatchers to direct callers to the nearest AED during a cardiac arrest event. Dispatchers are also expected to guide bystanders through the process of using an AED, empowering them to take lifesaving action.

Public-Access Defibrillation

Public-access defibrillation (PAD) facilitates bystanders in using AEDs early during a cardiac arrest. With each passing minute after a cardiac arrest, the chance of survival dramatically decreases. Even in well-developed urban areas with robust EMS, response times typically exceed 6 minutes.

Innovative Approaches to Public-Access Defibrillation

- Early detection of cardiac arrest through technology utilizing predictive algorithms and wearable devices or sensors that can detect cardiac arrest and automatically trigger emergency calls and dispatcher alerts for rapid defibrillation.[39]
- Boosting public awareness and creating a culture of action through effective public messaging.
- Training children in AED use.
- Addressing psychological barriers.
- Addressing legal concerns.
- Optimizing AED availability.

Community Initiatives

Community participation is relevant in the first step of the chain of survival in recognizing cardiac arrest, performing high-quality CPR, and using an AED to improve the early return of spontaneous circulation (ROSC). A statewide program, part of the Heart Rescue Project in North Carolina, trained bystanders and family members to recognize sudden cardiac arrest, alert EMS quickly, and perform CPR and use AEDs. This is the first study that analyzed the impact of interventions on cardiac arrests in public locations and private residences. Statewide initiatives promoting bystander CPR and first-responder defibrillation may be associated with enhanced survival and reduced brain injury in people with out-of-hospital cardiac arrest.[40]

The AHA's endorsement of lay rescuer CPR training in 1973 led to CPR training programs worldwide. Following a study of 21,266 patients who experienced OHCA, it is known that better bystander CPR and survival rates were associated with implementing community initiatives. Community initiatives or interventions focusing on improving bystander CPR are known to increase survival following OHCA. Interventions that include community and health service components result in improved bystander CPR rates greater than community-only interventions.

Community-based programs, with and without health system interventions, are associated with increased rates of bystander CPR, more frequent use of AEDs by bystanders, improved overall survival rates, and higher chances of survival with good neurological function.[41]

Challenges like fading of knowledge over time, panic, hesitation, and lack of motivation prevent the lay public from performing bystander CPR. Only about a third of trained laypeople perform CPR during a cardiac arrest event. Studies show that after a single CPR training session, adequate skills are retained only for 2–6 months.

Various community initiatives, such as the Take Heart America program, Heart Rescue Project, TAKE10 program, LifeSavers campaign in England, and World Restart a Heart initiative, focus on improving bystander CPR rates. Targeted CPR training for family members of high-risk cardiac patients significantly increases the likelihood of CPR being performed during a cardiac arrest event and has the potential to substantially improve survival rates after OHCA. Each country needs to implement community programs of a long-term, sustainable nature, which are likely to result in optimized provision of CPR and AED use.

Emergency Medical Services

About 10% of OHCAs were EMS-witnessed worldwide. Various registries have pointed out that different EMS systems account for the variation in OHCA survival rates. Studies show that EMS-witnessed cardiac arrests have a much higher chance of survival compared to those that are unwitnessed or witnessed only by bystanders.[42]

Certain factors within EMS agencies, such as response times, are linked to better survival rates for patients who reach the hospital after a cardiac arrest.[1] This suggests that improving EMS response efficiency could significantly impact survival outcomes. In communities with high-performing EMS systems, the survival rate for cardiac arrest can reach around 20%. Notably, in about half of these cases, the initial heart rhythm is ventricular fibrillation, a condition that responds well to defibrillation.

Only one-third of African countries have functional EMS. Despite optimized EMS systems in urban areas, the median response time for ambulances still exceeds 6 minutes. In

general, EMS in urban areas is superior to that in rural areas, as patients in the former have a lower transport time, which is associated with better outcomes and a favorable prognosis.

Out-Of-Hospital Cardiac Arrest across the World and Out-Of-Hospital Cardiac Arrest Registries

Epidemiological data on OHCA is compiled as registries based on standard international (Utstein) guidelines.[9] Ongoing quality improvement in the management of OHCA involves the mantras of "measure" and "improve" through clinical research with high-quality data collection utilizing an OHCA registry.[43] The registry features data elements in the Utstein format that predict survival outcomes.

A well-maintained OHCA registry serves as a powerful tool for continuous improvement. By providing valuable data and insights, it helps identify and address critical gaps in the chain of survival, ultimately leading to better outcomes for cardiac arrest victims. Benchmarking against international registries and implementing best practices in EMS is possible through a registry.

The International Liaison Committee on Resuscitation (ILCOR) strongly encourages organizations responsible for emergency care in resource-limited settings to establish local registries for data collection and outcome tracking. These registries should follow the Utstein-style reporting format to ensure consistency and allow for global comparisons.

Numerous existing registries around the world, such as the Cardiac Arrest Registry to Improve Survival (CARES) registry, Resuscitation Outcomes Consortium from the USA, the European Registry of Cardiac Arrest (EURECA), the Pan-Asian Resuscitation Outcomes Study (PAROS) network of Asia-Pacific, the Australia New Zealand registries, the Cardiac Arrest Registry to Improve Outcomes (UKCAO), and registries from other developed countries, have played a crucial role in providing data on OHCA as per internationally accepted Utstein guidelines.[44]

Out-Of-Hospital Cardiac Arrest in Low-Resource Settings

Many low- and middle-income countries (LMICs) fail to meet international standards for prehospital care systems, which are crucial for improving survival rates after emergencies like cardiac arrest. These countries face several significant challenges, such as a shortage of well-trained medical professionals and first responders, inadequate infrastructure, a lack of communication systems and basic resources, a lack of essential life-saving equipment, and inadequate transportation. These challenges all contribute to a lower survival rate with full neurologic recovery for subjects of OHCA in low-resource settings.

The apparent scarcity of resources and diminished workforce meant for resuscitation care systems further weaken healthcare systems and contribute to poor outcomes. Most LMICs lack studies on OHCA with data to measure and monitor community CPR training. This is possible through collaborative research based on standard Utstein guidelines. There is a dire need for continued support from respective governments and healthcare agencies for regional and national cardiac arrest registries.

Providing uniform and timely high-quality emergency cardiac care services in various geographical locations (and even within the same country) is a significant challenge that affects OHCA outcomes in both developing and developed countries. There is a need to develop a framework of resuscitation care with minimum resuscitation standards for low-resource settings while balancing other health priorities.[45]

Out-Of-Hospital Cardiac Arrest in India

There is no national registry on cardiac arrest in India. Previous research in India finds low bystander CPR rates (1.3–9.8%), except for the WACAR study (27.8%). The reported bystander CPR rate in India thus falls considerably short of the target goal of 62% established by the American Heart Association's Emergency Cardiovascular Care program (AHA-ECC).

The WACAR, the most extensive prospective observational study of OHCA and the first OHCA registry from India, highlighted various aspects of OHCA per the modified Utstein template. Key problems identified in the study included delayed initiation of CPR by bystanders, infrequent use of ambulance services for transport, and slow arrival times for EMS personnel.[46] A nationwide program implementing consistent CPR promotion initiatives is crucial to effectively promote bystander CPR in India.

Poor prearrival care, an under-resourced EMS system with prolonged wait times, including a lack of ambulance availability, and an understaffed healthcare system with poor-quality training in basic life support (BLS) and advanced cardiovascular life support (ACLS) contribute to the dismal outcomes of OHCA in India.[26] The WACAR study offers valuable lessons to improve data collection and ensure accurate reporting of OHCA data.

The need of the hour is to implement a nationwide registry involving all regions, with data collection based on Utstein guidelines. OHCA events must also be reportable throughout the nation. Raising awareness of cardiac arrest, enhancing bystander CPR training, and improving EMS infrastructure will help improve outcomes from OHCA in India.

Coronavirus Disease 2019 and Out-Of-Hospital Cardiac Arrest

The COVID-19 pandemic has been associated with a global rise in OHCA cases, decreased success rates for resuscitation efforts, and higher overall mortality. The pandemic significantly worsened patient outcomes from OHCA due to several factors, including increased disease severity in patients, reduced access to emergency care, longer ambulance response times, and disruptions to both emergency medical response and hospital systems.[47,48]

Fear of contracting COVID-19 further discouraged bystanders from performing CPR, and healthcare workers faced ethical dilemmas in implementing resuscitation guidelines due to limited resources.

Interventions for Better Outcomes in Out-Of-Hospital Cardiac Arrest

It is essential to assess the barriers and limitations specific to a given geographical community in any country to implement evidence-based protocols to improve OHCA outcomes. Adequate knowledge of the community in question is needed, including the existing healthcare infrastructure, response time and quality of the local EMS, access to tertiary cardiac care centers, community awareness and literacy, public access to AEDs, governmental Good Samaritan laws, and financial resources.

A pilot project based on the geographical area's information and resources will be helpful in building and guiding any sustainable healthcare initiative. A regional and national cardiac arrest registry is mandatory for designing the project and tracking outcome progress.

News media play a significant role in raising community awareness and motivating CPR training. Police officers, who may be the first responders, must undergo formal CPR training, especially in low- and middle-income

countries. Additionally, CPR training in high schools needs to be mandated to promote early preparedness.

Summary of Strategies to Improve Survival from Out-Of-Hospital Cardiac Arrest

- Establishing a National Cardiac Arrest Registry: Develop a registry based on standard Utstein guidelines to provide data on OHCA, identify areas for improvement, and monitor progress.
- Enhancing EMS performance: Implement dispatcher-assisted CPR and ensure high-quality CPR delivery.
- Improving hospital care: Develop strategies to enhance in-hospital systems for postcardiac arrest care.
- Advancements in resuscitation research: Promote research across basic science, clinical trials, and healthcare delivery, incorporating innovative technologies and treatments.
- Public education: Train the public on activating EMSs and performing CPR with AEDs.
- National collaboration: Establish a National Cardiac Arrest Collaborative to unify goals and improve patient survival rates.

Future of Out-Of-Hospital Cardiac Arrest

By strengthening every link in the Chain of Survival, we can achieve significant improvements in OHCA survival rates. An optimized Chain of Survival can lead to a return of spontaneous circulation (ROSC) in up to 49% of cases.[12] With a robust Chain of Survival, the 1-year survival rate after cardiac arrest can reach 27%.[12] Comprehensive cardiac resuscitation systems of care connect various stakeholders—community organizations, EMS, and hospitals—to improve the process of OHCA care and outcomes. There is a need to establish a clear national policy for implementing evidence-based resuscitation guidelines across all levels of care.[49]

Summary of Evidence-Based Global Recommendations Affecting the Outcomes in Out-Of-Hospital Cardiac Arrest

The recommendations, planning, and implementation of projects to improve cardiac arrest survival outcomes in any country, geographical area, or community need to be based on existing OHCA-focused local infrastructure, resources, and healthcare priorities.

- Community-specific: Increase awareness, education, and training in CPR and AED use, including high school CPR programs and the deployment of public-access AEDs.
- Technology-specific: Utilize smartphone apps and drone-delivered AEDs in remote areas to improve response times.
- EMS-specific: Standardize ambulances with state-of-the-art Advanced Cardiovascular Life Support (ACLS) equipment and ensure adequate training and periodic re-training of EMS personnel.
- Physician training: Enhance physician training and improve access to tertiary cardiac care centers capable of providing timely, evidence-based emergency interventions.
- Government-specific: Secure funding, establish regional and national cardiac arrest registries, mandate death certificates, implement friendlier Good Samaritan laws to encourage bystander CPR participation, and promote international collaborations in resuscitation research based on Utstein-style consensus guidelines.

In conclusion, implementing a well-designed program tailored to a particular community's needs, along with ongoing assessment of the results, could lead to significant global improvements in out-of-hospital cardiac arrest outcomes. Support from governments and nongovernmental organizations in implementing evidence-based guidelines advocated by international organizations such as the International Liaison Committee on Resuscitation (ILCOR) and the American Heart Association (AHA) is crucial.

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REVIEW ARTICLE

Prehyperuricemia Deserves More Attention in this Era of Metabolic Explosion: A Review

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Abstract

The global population is experiencing a metabolic explosion, with the prevalence of hyperuricemia (HU) as a metabolic disorder and a causal factor for noncommunicable diseases (NCD) increasing rapidly worldwide over the last 2 decades. This rise is attributed to diets high in purine, alcohol, red meat, high-fructose foods, and lifestyle changes. The connection between HU and various NCDs is now stronger than ever. As HU progresses, systemic inflammation arises, leading to endothelial dysfunction and end-organ damage—molecular changes that were previously unrecognized. HU is increasingly seen as a metabolic disorder, particularly a vascular disorder rather than just a crystallization disease. Asymptomatic HU is no longer considered benign, and it should not be equated with gout. It is crucial to diagnose HU early, at a high normal level, and manage it to prevent the development and complications of related extra-articular diseases. For broader recognition and significance, this high normal level of serum uric acid (UA) should be termed prehyperuricemia (PHU). Like prediabetes and prehypertension, PHU should be identified early, regardless of age and sex, with preventive actions implemented to maintain UA at a safer level.

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Introduction

Uric acid (UA) is a weak organic acid and the final product of purine metabolism in humans. The global prevalence of hyperuricemia (HU) has doubled or even tripled during the last 2 decades. Recent epidemiological studies have shown that HU exhibits a linear correlation with noncommunicable diseases (NCDs) and many other conditions. The pathophysiology of HU involves oxidative stress, endothelial dysfunction, and end-organ damage. The underlying molecular changes induced by HU begin even before the present cutoff value of 7 mg/dL. However, the period and the UA level at which these changes begin and become a causal factor for NCDs remain unclear. NCDs are the leading causes of morbidity and mortality globally. Numerous clinical studies have shown that a reduction in serum UA (SUA) levels can prevent the development of many NCDs and their complications. Therefore, it is essential to perform early screening for HU to prevent metabolic disorders. A new metabolic terminology, prehyperuricemia (PHU), has been introduced. Complications of HU require many years to develop. By increasing awareness among healthcare providers regarding abnormal UA levels and screening for HU, the development of symptomatic or asymptomatic HU with many NCDs can be prevented. Furthermore, PHU can be managed using nonpharmacological measures, such as lifestyle modifications and enhanced quality of life.

Search Strategy

We searched for relevant articles on Google Search and PubMed published from 1965 to 2024 using the following keywords: uric acid, hyperuricemia, high normal value of serum uric acid, metabolic disorder, noncommunicable disorder, molecular mechanism, and preventive measures. This article emphasizes the substantial increase in the occurrence of HU, its molecular connections with NCDs and various other conditions, the critical need for early detection of HU, and strategies for its management.

Definition of Hyperuricemia

An SUA level that is defined as HU signifies a level greater than 7 mg/dL in men and greater than 6 mg/dL in women. Although gout was the most common complication of HU until a few decades ago, it is slowly changing to a metabolic disorder. The incidence of gout in the HU population is <9%. Patients with HU are not always symptomatic. Asymptomatic HU is more dangerous because it silently leads to endothelial dysfunction, oxidative stress, insulin resistance, and macrovascular and microvascular complications, indicating a classical iceberg phenomenon. High UA levels adversely affect almost all systems.

Why do not all HU patients develop gout? HU is a metabolic disorder where systemic inflammation is the primary pathology. This systemic inflammation progresses and may affect joints, leading to gout by UA deposition. However, this phenomenon occurs only in the presence of a favorable physiological environment and the level of lubricin in joints. Research indicates that the threshold for increased total mortality is 4.7 mg/dL for UA levels and 5.6 mg/dL for increased cardiovascular mortality risk, both of which are significantly below the clinical diagnostic threshold of 7 mg/dL for HU. Given the metabolic implications, there is a recommendation to lower the cutoff value to below 7 mg/dL in men and below 6 mg/dL in women or to place greater emphasis on SUA levels that are high yet within the normal range, reflecting the shift in focus from joint crystallization to metabolic disturbance in the context of HU.

Definition of Prehyperuricemia

Prehyperuricemia is defined as a metabolic condition where the SUA value is at a high normal level, between 6 and 7 mg/dL in men and 5 and 6 mg/dL in women. This value is presently considered normal or high normal. Even at or below these levels, UA-induced systemic inflammation can develop (Flowchart 1).

Epidemiology

Humans lost the ability to degrade UA due to a mutation in the uricase enzyme over 15 million years ago.[1] Gout is one of the oldest diseases and was named in 1200 AD. Although UA was identified 2 centuries ago, the exact pathophysiology of HU remains

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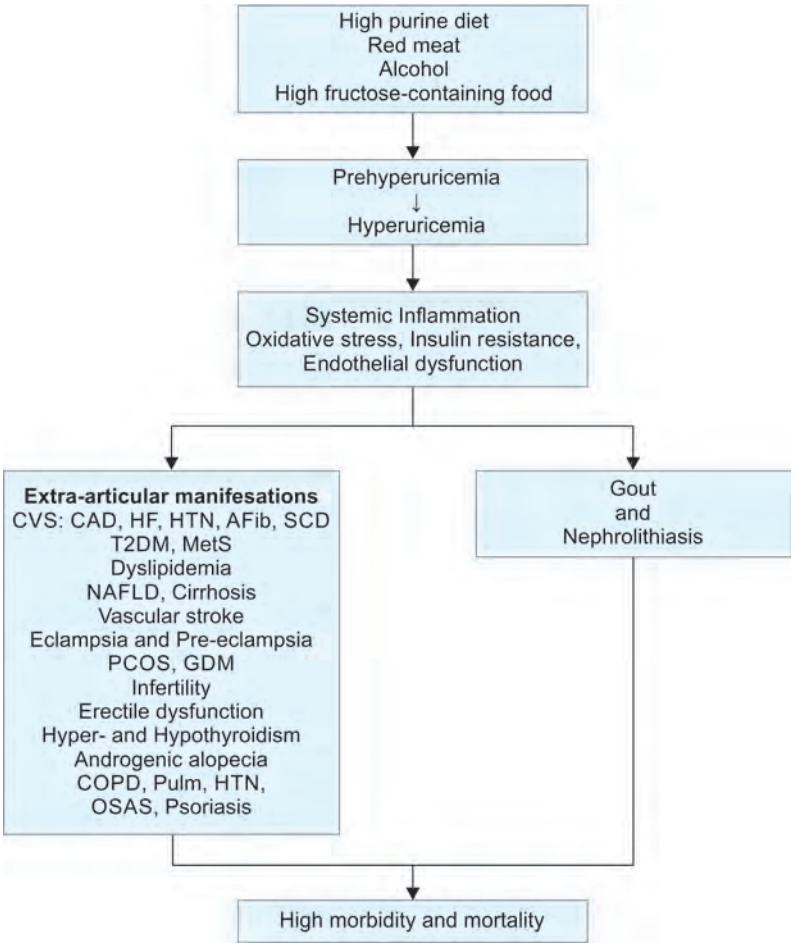
Flowchart 1: Detrimental effect of hyperuricemia; AFib, atrial fibrillation; COPD, chronic obstructive pulmonary disease; GDM, gestational DM; HF, heart failure; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; OSAS, obstructive sleep apnea syndrome; PCOS, polycystic ovarian syndrome; SCD, sudden cardiac death



unclear. Currently, the mean SUA level is slowly increasing. A US study reported that the mean SUA levels rose from <3.5 mg/dL to 4.2 mg/dL between the 1920s and 1940s. However, from the 1950s to the 1980s, the SUA levels increased more, from 5.0 to >6.0 mg/dL.[2]

Over the last 2 decades, the perception of HU has swiftly shifted from being solely associated with crystallization diseases, such as gout and nephrolithiasis, to being recognized as a significant risk factor and biomarker for various metabolic and hemodynamic abnormalities. HU, once considered benign, is now acknowledged as a potential silent killer.

Currently, HU is the second most common metabolic disorder after diabetes mellitus.[3] Modern lifestyle changes, characterized by the consumption of high-purine diets, red meat, alcohol, and high-fructose foods, have elevated the prevalence of HU to the fourth most common NCD, following hypertension, diabetes mellitus, and dyslipidemia.[4] As a result of modernization, HU prevalence has increased two- or threefold over the past 2 decades.

In certain populations, its prevalence has escalated to 85%, indicating a continuing upward trend.[5] In 2019, the prevalence of HU was reported to be 170 million in China and 32.5 million in the United States.[6,7]

Uric Acid-induced Molecular Mechanism

UA is the most abundant and potent antioxidant in humans. However, at higher concentrations, UA exerts a pro-oxidant effect.[8] UA acts as a double-edged sword: it can be an antioxidant in the extracellular environment (primarily in plasma) or a pro-oxidant at the intracellular level (primarily within cells). UA acts as an antioxidant up to a level of 4.7 mg/dL. When UA is transported into cells by specific organic anion transporters, it induces an oxidative cascade in vascular smooth muscle cells, endothelial cells, adipocytes, islet cells, renal tubular cells, and hepatocytes. HU leads to the development of NCDs by regulating molecular signals, such as inflammatory responses, oxidative stress, insulin resistance, endothelial dysfunction, and endoplasmic reticulum stress, even before reaching pre-HU levels.[9–13]

In addition, when UA enters vascular cells and adipocytes, it exerts a pro-oxidative effect by activating the NADPH oxidase system and stimulating mitochondrial oxidative stress.[14] Markers of systemic inflammation, such as leukocyte count, C-reactive protein, and inflammatory cytokines (e.g., interleukin (IL)-6, IL-1RA, IL-18, and tumor necrosis factor-α), may increase in HU and PHU.[15] Researchers have reported an association of HU and PHU with systemic inflammation.[16] Jesse's article posits that the relationship between UA and insulin resistance is unidirectional, with HU occurring first, followed by insulin resistance, which then leads to hypertension.[17]

The global mean UA level is slowly increasing to 6–6.5 mg/dL, suggesting that molecular and inflammatory processes detrimental to health may commence even before UA levels reach what is considered high normal, potentially leading to NCDs and organ damage. A reduction in SUA levels can improve systemic inflammation markers, NCDs, and their complications.[18–20] HU and high normal UA levels suggest the presence of low-grade systemic inflammation even without gout.[15] This UA-induced systemic inflammation could be a key mechanism by which UA contributes to the development of NCDs, regardless of the presence of gout.[21]

Hyperuricemia-associated Extra-articular Diseases

Uric Acid and Cardiovascular Disease

UA is a modifiable and independent risk factor for CVD, especially in patients with comorbidities. High SUA levels have been associated with sudden cardiac death and cardiovascular mortality[22,23] (Fig. 1).

Hypertension

A study published in 1966 reported that 47% of hypertensive patients were hyperuricemic.[24] Currently, UA is a biomarker of HTN. An increase of 1 mg/dL in SUA levels leads to a 13% increase in the occurrence of HTN.[25] Approximately, 25–40% of patients with untreated HTN and >80% of patients with malignant HTN have high SUA levels.[26] SUA has emerged as the strongest and independent risk factor for prehypertension, which later progresses to hypertension.[27] This progression from prehypertension to hypertension has increased by >20% over 5 years in hyperuricemic people compared with normouricemic individuals, indicating the effect of UA on prehypertension.[28] Moreover,

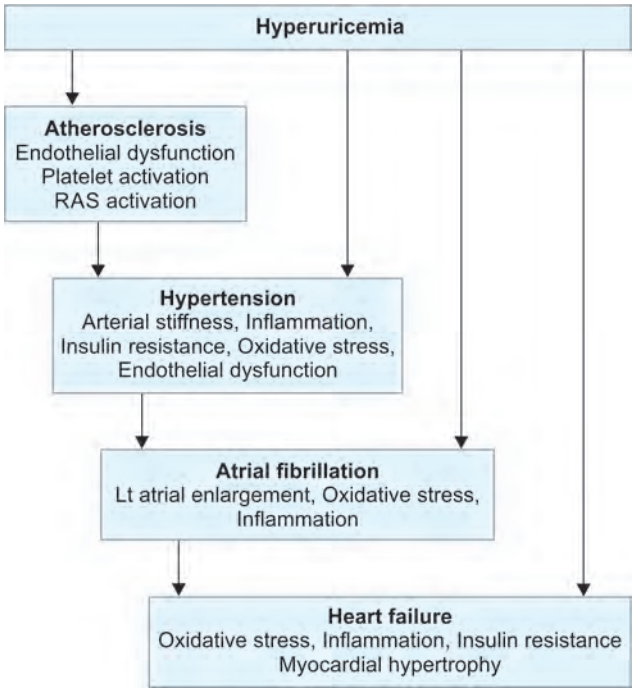


Fig. 1: Effect of hyperuricemia on the cardiovascular system

the study highlighted the importance of managing HU at the prehypertensive stage. SUA is strongly and independently associated even with nocturnal nondipping of HTN.[29] Recent findings suggest that urate-lowering therapy can reduce blood pressure in adolescents.[30]

Atherosclerosis

UA is a contributing factor to the development of atherosclerosis. HU produces atherosclerosis in both macrovascular beds and the microvessels of major organs. In young individuals, HU is associated with coronary artery calcification, indicating that even a high normal UA level is a risk factor for subclinical atherosclerosis. SUA levels starting from 6.2 mg/dL may increase pulse wave velocity, contribute to arterial stiffness, and accelerate vascular aging.[31]

CAD

UA is a marker and risk factor for acute coronary events. Every 1 mg/dL increase in SUA is linked to a 15% higher risk of coronary artery disease (CAD) mortality.[32] Xiao et al. highlighted the relationship between SUA levels and CAD in individuals under 45, suggesting that UA may contribute to increased aortic pressure and stiffness.[33]

Arial Fibrillation

HU is a novel marker for atrial fibrillation (AFib), both in its chronic and paroxysmal forms. UA levels are independently associated with AFib with or without comorbidities, and higher serum levels are correlated with a greater likelihood of the condition.[34]

Heart Failure

The risk of heart failure increases by 20% with every 1 mg/dL increase in SUA.[35] In heart failure, HU may be linked to an upregulation of xanthine oxidase activity, which in turn increases the risk of heart failure by 65%.

Uric Acid and Metabolic Syndrome

A quarter of the adult global population is affected by metabolic syndrome (MetS). Choi et al. reported that up to 60% of individuals with MetS were hyperuricemic.[36] The third National Health and Nutrition Examination Survey highlighted the prevalence of MetS at various SUA levels, indicating that MetS can begin even at SUA levels below 6 mg/dL. The survey demonstrated a linear increase in MetS incidence with rising SUA levels and suggested including HU as a MetS criterion and addressing it early to prevent complications.[36] Currently, HU is recognized as a marker for the early diagnosis and prevention of MetS.[37] Maintaining lower SUA levels could help reduce the burden of MetS.[20]

Diabetes Mellitus

A population-based study identified UA as a strong and independent risk factor for T2DM.[38] The diabetogenic potential of SUA was reported in 1950.[39] The risk of T2DM increases by 15–20% for every 1 mg/dL increase in SUA, regardless of comorbidities.[40] The future risk of T2DM is directly proportional to the SUA level, irrespective of age. Another study reported that high normal SUA levels (5–6 mg/dL) significantly increase the risk of diabetes in women, whereas for men, the risk elevation is noted at SUA levels of 6–6.8 mg/dL.[41] Researchers have now recognized that HU is equivalent to T2DM in terms of cause, pathophysiology, and management.

Uric Acid and Lipid

Serum total cholesterol, LDL cholesterol, and triglyceride levels are directly associated with SUA levels, but HDL cholesterol is inversely related to SUA levels.[42]

Uric Acid and Kidney

SUA is a marker for chronic kidney disease (CKD) and acute-onset renal disease. A high SUA level is associated with a longitudinal decline in GFR and worsening renal function. Furthermore, a high SUA is associated with a reduction in nephron numbers, renal tubular atrophy, and thus low GFR.[43,44] Reducing SUA levels can lead to decreased albumin excretion and a slower decline in eGFR, particularly in those with T2DM.[45] In T2DM, a high normal SUA level might predict CKD development even in those with preserved renal function. Urate-lowering therapy reduces inflammation and slows down renal disease progression even in patients with moderate CKD.[19] Kanbay reported that UA lowering might slow down the progression of renal disease in hyperuricemic populations, and they noted improvements in renal function following the treatment of asymptomatic HU.[18] Moreover, Siu noted that the treatment of asymptomatic HU delays the progression of renal disease.[46] SUA is an independent risk factor for CKD, even in the absence of T2DM.[47] Renal dysfunction in T2DM may begin at an SUA level of 6.3 mg/dL (high normal value), associated with a poor prognosis[48] (Fig. 2).

Uric Acid and Liver

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver function abnormality, affecting >20% of people globally.[49] The relationship between SUA and NAFLD was first described in a small Italian study in 2002.[50] Every 1-mg/dL increase in the SUA level led to a 21% increase in NAFLD risk.[51] Urate-lowering therapy may prevent NAFLD.[52]

Uric Acid and Brain

Stroke

The pro-oxidant neurotoxic effect of UA may lead to acute stroke. A higher SUA level is associated with an increased stroke rate and mortality.[53]

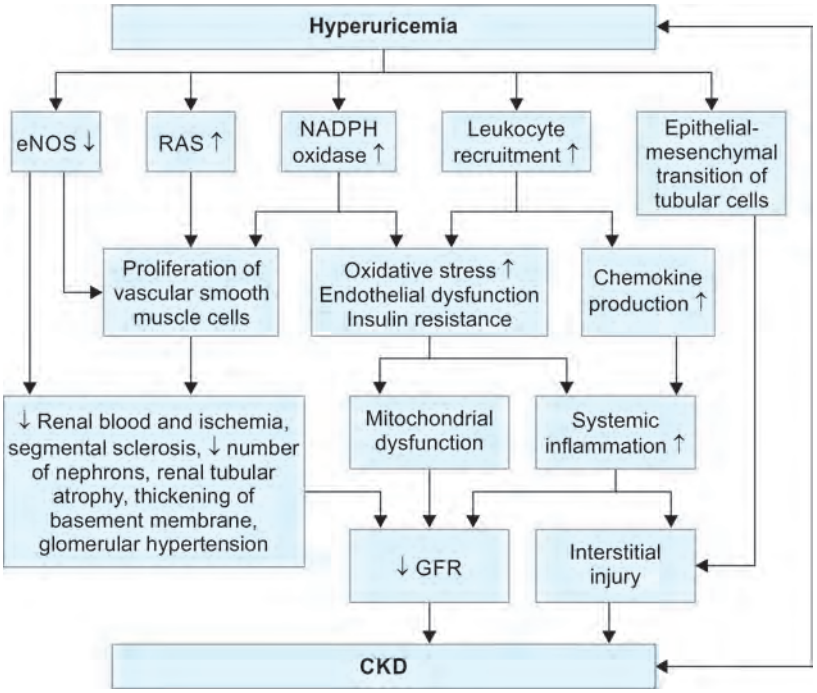


Fig. 2: Effect of hyperuricemia on the kidney; CKD, chronic kidney disease; eNOS, endothelial nitric oxide synthase; NADPH, nicotinamide adenine dinucleotide phosphate; RAS, renin-angiotensin system

Dementia

High UA levels are noted in patients with vascular or mixed dementia.[54] However, UA, as an antioxidant, exerts a neuroprotective role in Alzheimer's disease and Parkinson's disease. (However, this concept is changing now; young HU individuals develop Alzheimer's disease earlier.) Thus, UA should not be reduced to a hypouricemia level (<2.5 mg/dL) in these patients.

Other Associated Disorders

SUA levels may be high in patients with COPD, with higher levels being correlated with increased mortality.[55] In acute respiratory distress syndrome, elevated SUA levels are observed and have a prognostic role. In hyperthyroidism, HU is caused by higher BMR and elevated urate production. However, in hypothyroidism, HU results from decreased renal blood circulation. High SUA levels were detected in patients with psoriasis and chronic dermatitis. Younger males with high SUA levels exhibited androgenic alopecia.[56] SUA levels were higher in women with polycystic ovarian syndrome.

In 1917, Slemons and Bogert first observed high UA levels in patients with preeclampsia/eclampsia, and elevated UA is now recognized as a stable biomarker of these conditions.[57] An increased SUA level in pregnancy increases the risk of gestational DM (GDM) by 4%. HU may be a marker of an increased risk of erectile dysfunction (ED) and male infertility. Each 1-mg/dL increase in SUA level was associated with a twofold increased risk of ED.[58]

Ocular abnormalities, such as retinopathy, dry eye syndrome, red eye, uveitis, glaucoma, and cataracts, are associated with high UA levels.[59] High salivary UA was associated with periodontitis and recurrent aphthous ulcers.

Lifespan

According to a new study by researchers at the University of Limerick's School of Medicine, high SUA levels can reduce lifespan by up to 11 years for men and 6 years for women.[60]

Discussion

NCDs have become the leading cause of morbidity and mortality, responsible for 41 million deaths annually, which represents 71% of all global deaths, signifying an epidemic. Moreover, there is an exponential increase in the prevalence of HU globally. HU is associated with not only cardio-reno-metabolic disorders but also a broader range of conditions. HU is not synonymous with gout. The association between NCDs and HU has become more pronounced in recent years. HU can be symptomatic or asymptomatic, a debate that was prominent 2 decades ago. Currently, HU is increasingly regarded as a metabolic disorder rather than merely a crystallization disease. UA has recently regained clinical interest and popularity based on emerging data suggesting the causative role of HU in NCDs and many other conditions. The term "asymptomatic HU" may need re-evaluation because it can be a precursor to more severe conditions. The adverse effects of HU begin even before SUA levels reach 7 mg/dL. The complex relationship between UA and diabetes is gaining clarity, with recent studies showing that lowering SUA can reduce inflammatory markers, confirming UA's role in the development of NCDs through systemic inflammation.

In gout and even tophi, UA levels may be normal. Not all cases of HU are symptomatic, and not all gout patients have HU. However, systemic inflammation can be present in both these groups of people. HU is not equivalent to gout or vice versa and is a metabolic disorder. Gout is just one of the many clinical manifestations of HU, and it is characterized by pain, unlike other forms of HU, which are painless and often labeled as asymptomatic. This asymptomatic HU is a causal factor for many NCDs, leading researchers to suggest its inclusion in the metabolic syndrome criteria.

Some diabetes patients may be asymptomatic, similar to most hypertensive and dyslipidemia patients. These conditions are not referred to as asymptomatic diabetes, hypertension, or dyslipidemia but are treated based on target values. Acute myocardial infarction may also occur without pain. Thus, pain should not be the sole criterion for diagnosis and treatment in metabolic disorders. Like prediabetes and pre-HTN, PHU should be screened, diagnosed early, and managed to prevent the onset of many NCDs and their complications. Like prediabetes, PHU is also reversible with lifestyle modifications. HU and diabetes mellitus are now considered akin; they should be managed with similar strategies. In the modern era, HU is becoming recognized as equivalent to diabetes in its potential health impact. During progression from PHU to HU, the endothelium undergoes inflammatory changes that could lead to various NCDs and organ damage. Prevention is superior to cure, emphasizing the need for greater focus on PHU to curb the rising tide of metabolic disorders.

Management of Prehyperuricemia

Pharmacological: The current urate-lowering drugs are associated with many adverse effects and drug interactions. Present evidence does not support recommending pharmacological therapy for PHU. Instead, managing comorbidities with medications that incidentally reduce UA, such as losartan, fenofibrate, and SGLT2 inhibitors, is advised.

Nonpharmacological: The mouth is the primary gateway for numerous disorders, particularly metabolism-related. Controlling dietary intake can prevent PHU and various metabolic disorders. Lifestyle modifications in PHU are cost-effective and simple, with studies showing they can reduce SUA by 1 mg/dL.[61–63] Recommendations include following a low-purine diet, limiting intake of red meat, alcohol, and high-fructose foods, consuming low-fat dairy products, ensuring adequate hydration, engaging in regular physical activity, and maintaining an ideal body weight. SUA levels should be maintained below 6 mg/dL in men and 5 mg/dL in women to avert systemic inflammation.

Conclusion

The epidemiology of HU has shifted globally over the past 2 decades due to significant lifestyle changes, leading to its increasing prevalence. The link between HU and NCDs is becoming more evident and established, with UA-induced systemic inflammation and endothelial dysfunction as key underlying mechanisms. These processes begin even before reaching the current HU threshold, as demonstrated by the reduction in inflammatory markers and reversal of UA-related conditions when UA levels are lowered. UA is poised to become one of the most significant risk factors for various NCDs.

To gain wider acceptance for early diagnosis, treatment, and prevention of UA-related diseases and complications, the term PHU could be used to denote high normal SUA values. Due to the lack of safe urate-lowering drugs, lifestyle modification is the preferred approach at this stage. Identifying and addressing the disease at a preclinical stage is a smart strategy to prevent numerous cardio-reno-metabolic conditions. Keeping SUA at a safe level is emphasized. The authors of the article suggest, perhaps with some exaggeration, that by controlling SUA below the PHU level, we could potentially eradicate gout and prevent various diseases associated with HU.

Declaration

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REVIEW ARTICLE

Consensus to Reduce Withdrawal and Improve Adherence with SGLT2i: Consensus TWO SGLT2i Adherence Group

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Abstract

Background: Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are a class of medications that have shown significant efficacy in regulating blood glucose levels and providing additional benefits, such as cardiorenal protection. This study aims to analyze the factors leading to nonadherence and discontinuation of SGLT2i treatment and to identify strategies that can enhance patient compliance and reduce withdrawal rates.

Materials and methods: This consensus involved an expert committee comprising 14 leading opinion leaders, chosen for their profound expertise and experience in type 2 diabetes mellitus (T2D) and SGLT2i therapy. Prior to the meeting, a comprehensive document—developed through an extensive literature review on current challenges, best practices, and potential strategies for improving adherence and reducing withdrawal of SGLT2i—was distributed to the committee members. This allowed ample time for thorough review and preparation. The expert committee convened virtually multiple times to engage in in-depth discussions on various aspects of SGLT2i adherence and compliance. The finalized manuscript encapsulates the consensus achieved by the experts, presenting actionable recommendations aimed at enhancing adherence and reducing withdrawal rates in SGLT2i therapy.

Results: Based on the literature, several factors contribute to the nonadherence of SGLT2i, including being of Black race, older age (>65 years), high unemployment rate, lower income levels, extended duration of diabetes, a greater number of baseline comorbidities, genital infections, and limited access to healthcare facilities. To maintain good adherence, appropriate patient selection and education are essential. Healthcare practitioners should be well-informed about the drug's indications, interactions, and side effects.

Conclusion: Regular monitoring, lifestyle adjustments, and open communication between healthcare practitioners and patients are crucial. Developing personalized care plans, educating patients, promptly addressing their concerns, and cultivating a collaborative healthcare relationship are critical in maintaining adherence.

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Introduction

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) represent a class of drugs demonstrating significant efficacy in regulating blood sugar levels and mitigating cardiovascular risks. By directly inhibiting SGLT2, a protein located in the proximal tubules of the kidneys, these inhibitors hinder glucose reabsorption in the renal system. This action results in increased glucose excretion in the urine.[1] Glucosuria diminishes as blood glucose levels normalize, and the impact of inhibiting the SGLT2 receptor on blood glucose becomes less pronounced as the estimated glomerular filtration rate (eGFR) decreases.[2] Apart from their primary mechanism, SGLT2i offer a range of additional benefits, such as lowering blood pressure (BP), reducing serum urate levels, and promoting weight loss.[3] In 2023, a consensus statement from the American Association of Clinical Endocrinologists (AACE) suggested SGLT2i as the first-line therapy for individuals with type 2 diabetes (T2D) who either have or are at a high risk of atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and/or chronic kidney disease (CKD).[4,5]

According to an expert consensus statement, all patients with T2D and established cardiovascular disease (CVD) and/or CKD should be started on an SGLT2i. Initiating SGLT2i for the first time is not advised for individuals with an eGFR below 20 mL/minute/1.73 m^2 (the specific threshold may vary depending on the individual agent). However, for patients already on this medication, it may be continued.[6] SGLT2i demonstrate effectiveness across the entire spectrum of HF conditions, including heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range (mildly reduced, that is, borderline) ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF), and acute heart failure (AHF), irrespective of ejection fraction (EF) and being diabetic. These inhibitors offer substantial benefits in terms of both mortality and morbidity, encompassing cardiovascular mortality, all-cause mortality, sudden cardiac

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death, reduced hospitalization for heart failure (HHF), alleviation of HF severity, and prevention of HF worsening. In India, these drugs are approved for use in individuals with HF, regardless of their diabetes status, irrespective of the presence of hypertension, atrial fibrillation (AF), congestion, or stroke.[7] SGLT2i is often recommended not only as an add-on therapy to metformin but also as a first-line antihyperglycemic medication (or in patients intolerant to metformin).[8]

SGLT2i have emerged as a significant advancement in diabetes management within the Indian context. Beyond their role in glycemic control, these agents offer multifaceted benefits, encompassing cardiorenal protection, BP reduction, and favorable impacts on lipid profiles. Moreover, their cost-effectiveness further underscores their value as a therapeutic option. Despite the potential benefits, the efficacy of SGLT2i therapies is frequently hindered by challenges related to patient adherence and withdrawal. This paper aims to scrutinize the factors contributing to nonadherence and discontinuation and identify strategies to enhance compliance and mitigate withdrawal rates.

Materials and Methods

This consensus engaged a group of healthcare professionals (HCPs) to establish a consensus on improving adherence to SGLT2i among patients with T2D. This paper was designed to gather and consolidate expert opinions to develop strategies for reducing withdrawal rates and enhancing adherence to SGLT2i therapy. The expert committee was composed of 14 key opinion leaders, selected for their extensive expertise and experience in the field of T2D and SGLT2i therapy. These experts were chosen based on their contributions to the domain through research, clinical practice, and participation in related professional organizations.

A comprehensive literature search was conducted using Google Scholar and PubMed databases. The search focused on articles published from 2015 onwards to ensure the inclusion of the most recent and relevant findings. Keywords used in the search included "T2DM," "type 2 diabetes mellitus," "SGLT2i," "sodium-glucose co-transporter-2 inhibitors," "adherence," "compliance," and "withdrawal." The search aimed to gather information on current challenges, best practices, and potential strategies for improving adherence and reducing withdrawal in patients using SGLT2i.

A detailed literature review document was prepared based on the findings from the literature search. This document provided a comprehensive overview of existing knowledge and identified gaps that needed to be addressed. The document was shared with the expert committee members well before the meeting to allow thorough review and preparation. The expert committee assembled virtually multiple times to discuss the document. The meeting facilitated an in-depth deliberation on various aspects of SGLT2i adherence, including factors contributing to nonadherence, strategies to enhance compliance, and methods to reduce withdrawal. Each expert contributed their insights and practical experiences to the discussion, aiming to reach a consensus on best practices.

Following the virtual meeting, feedback and responses from the experts were systematically compiled into a draft manuscript. This draft was shared with the expert committee members for review, ensuring that all opinions were accurately represented and any additional comments were incorporated. The finalized manuscript summarized the consensus reached by the experts, providing actionable recommendations for HCPs to improve adherence and reduce withdrawal rates in SGLT2i therapy.

The consensus reached by the expert committee offers valuable insights and practical guidelines for HCPs to enhance adherence and minimize withdrawal in patients using SGLT2i. This article serves as a useful tool for clinicians, researchers, and policymakers aiming to optimize treatment outcomes for patients with T2D.

Discussion

In addition to diminishing the effectiveness of the treatment, poor adherence can contribute to deteriorating patient health outcomes. Medication discontinuation can be attributed to diverse reasons, encompassing adverse effects, perceived ineffectiveness, or psychological factors like patient motivation and belief in the treatment, besides the cost. Due to their distinctive mechanism of action, SGLT2i can give rise to adverse events (AEs), including genital and urinary tract infections,[9,10] and uncommon AEs such as diabetic ketoacidosis (DKA),[11] fractures, dehydration, hypovolemia, amputations, and Fournier's gangrene.[12,13] When evaluating the risks and benefits of SGLT2i, it becomes evident that the benefits outweigh the potential risks associated with their use. The barriers to adherence and withdrawal vary, spanning from the side effects linked to the medication to the intricacies of handling a chronic condition like diabetes.

Factors for Nonadherence

The adherence of patients to medications, as observed in observational studies or real-world populations, may deviate from that noted in an experimental clinical trial setting. In clinical trials, study participants are typically supplied with medications and undergo regular follow-ups with study personnel.[14] This controlled environment can influence adherence rates and may not fully replicate the complexities and challenges faced by individuals managing their medications in the real-world setting. Factors such as lifestyle, access to healthcare, socioeconomic status, and individual motivation can significantly impact medication adherence in everyday life, introducing variations that may not be as prominent in the controlled environment of clinical trials.

A systematic review and meta-analysis (22 studies, $n = 1,23,854$) assessed adherence using the proportion of days covered (PDC). The study found that the pooled mean PDC at six months and one year was 0.77 and 0.72, respectively. The proportion of adherent individuals (PDC ≥ 0.80) declined from 59.5% at 6 months to 49% at 1 year. Additionally, the pooled proportions of people showing persistence (defined as the absence of a gap of ≥90 days) also decreased from 81.5% at 6 months to 58.9% at 1 year and further to 34.7% at 2 years.[15] Another study demonstrated that patients with T2D who initiated therapy with an SGLT2i exhibited good adherence, with a PDC reaching 77% throughout the first year of treatment.[16]

In a study by Packer et al.,[17] the withdrawal of empagliflozin was associated with several notable changes. These changes included elevated fasting glucose, body weight, systolic blood pressure, estimated glomerular filtration rate (eGFR), N-terminal prohormone B-type natriuretic peptide (BNP), uric acid, and serum bicarbonate levels. Additionally, there were reductions in hemoglobin and hematocrit levels, along with an elevated annualized risk of cardiovascular death or HHF. Canagliflozin demonstrated better adherence and persistence when compared to other oral antidiabetic drugs.[18,19]

As indicated by the KAMOGAWA-A study,[20] the primary reasons for discontinuing SGLT2i included older age, frequent urination, genital infection, improved glycemic control, and renal dysfunction. In a retrospective cohort study, Yang et al.[21] found that regions characterized by a higher unemployment rate, lower income level, lower high school education rate, poorer nutrition environment, fewer healthcare facilities, and higher Area Deprivation Index (ADI) scores were associated

with lower adherence to SGLT2i in patients with T2D.

According to a study conducted by Luo et al.,[22] factors such as black race, male gender, older age (above 65 years), greater baseline comorbidities, and receiving a prescription from a primary care provider as opposed to an endocrinologist were identified as associated with higher odds of primary nonadherence. As per the DARWIN-T2D study,[23] individuals who chose to discontinue dapagliflozin were frequently characterized by being female, having elevated baseline fasting plasma glucose (FPG), higher levels of HbA1c, and a lower prevalence of metformin use. Additional factors associated with discontinuation included older age, longer duration of diabetes, elevated albumin excretion, and a higher frequency of insulin use (Table 1).

Patient Selection for Sodium-glucose Co-transporter-2 Inhibitors

Patient eligibility for SGLT2i should be determined by considering a range of factors, such as their clinical profile, individual characteristics, and specific treatment objectives. When choosing SGLT2i, it is crucial to consider the patient's preferences and lifestyle. Dosing frequency, tolerability, and potential weight loss effects can significantly impact treatment choices. Tailoring the selection to align with these individual considerations enhances the likelihood of treatment adherence and success.[24] Prescribing SGLT2i for T2D should align with the guidelines provided by the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD),[25] and the Indian consensus.[26] These guidelines are formulated based on the most up-to-date evidence available (Table 2).

Table 1: Summary of factors for nonadherence of SGLT2 inhibitors

Patient characteristics

- Demographics—Black race, older age (>65 years)
- Socioeconomic status: High unemployment rate, lower income level, lower high school education rate, poor nutrition, higher ADI scores
- Individual motivation
- Higher insulin use
- Frequent urination
- High baseline glycemic parameters

Comorbidities

- Extended duration of diabetes
- Greater baseline comorbidities
- Genital infections
- Renal dysfunction

Others

- Less access to healthcare facilities
- Improved glycemic control
- A prescription from a primary care provider and not an endocrinologist

Healthcare Providers and Patient Perspectives on Adverse Effects

Healthcare providers should comprehensively review a patient's medical history and conduct a thorough physical examination before recommending SGLT2i. Identifying any preexisting conditions or factors that might elevate the risk of adverse effects is imperative. The appropriate SGLT2i and dosage should be tailored to each patient based on their unique medical history and circumstances. HCPs must ensure that patients are well-informed about the medication, its intended purpose, and potential side effects. Additionally, patients should receive education emphasizing the importance of adhering to prescribed dosages and schedules. Ensure that regular follow-up appointments are scheduled to evaluate the patient's response to treatment, monitor for potential side effects, and make any necessary adjustments to the treatment plan. Regular follow-up visits are essential for ongoing assessment and effective patient health management in response to the prescribed treatment.

Incorporating patient education guidance within the prescription for SGLT2i ensures the prompt provision of essential information as patients initiate their medication regimen. Clear and concise instructions aid in understanding the medication's purpose, correct administration procedures, and possible side effects. Furthermore, including advice on nutrition, hygiene, and hydration positively impacts patients, encouraging them to embrace and maintain healthier lifestyle habits.[33]

Patients should comprehend the purpose of the medication and be aware of potential side effects. They should seek clarification from their HCP if any concerns or questions arise. It is crucial to adhere strictly to the prescribed medication regimen, and any decisions to discontinue or alter dosages should be made in consultation with the HCP. Patients should promptly inform their HCP of any new or persistent symptoms, changes in health status, or plans for significant lifestyle modifications, such as alterations in diet or increased physical activity. Additionally, the HCP should be informed about all medications being taken, including over-the-counter drugs and supplements, to prevent potential interactions. This proactive communication with the healthcare team ensures a comprehensive and safe approach to medication management. Resolving these challenges necessitates a comprehensive

Table 2: Patient selection for SGLT2i[27,28]

SGLT2i can be prescribed	*SGLT2i prescribed with caution*	*SGLT2i should be avoided*
• First line/metformin contraindicated or intolerant • Second or third line to other antidiabetic drugs • Established CVD, history of HF, prior stroke • Overweight or obesity • Vulnerable to the effects of hypoglycemia • CKD/diabetic kidney disease (DKD) (eGFR: 20 mL/minute/1.73m^2)/renal impairment	• Frail/elderly/cognitive impairment (may interfere with the adequate understanding to take action to prevent and identify DKA) • History of PAD, foot ulceration & limb amputation • Existing diabetic foot ulcers • Ketogenic/low calorie/low carbohydrate diet • Recurrent urinary tract infections (UTI) and genital/mycotic infections • Receiving systemic steroid therapy	• Age <10 years, acute illness/volume depletion • DKA/ any previous episode • Excessive alcohol intake • Catabolic state and sepsis • Diabetes due to other causes, including type 1 diabetes • Severe insulin deficiency state • Predisposing risks for Fournier's gangrene* • During major surgery (duration)** • Pregnancy/breast-feeding/planning for pregnancy • eGFR lower than allowed (based on the medication being considered) or patient on dialysis***

*Predisposing risks for Fournier's gangrene: Uncontrolled T2DM with poor genital hygiene due to morbid obesity, older age, immunosuppression, and local trauma[29]; **According to the ADA and Food and Drug Administration (FDA) guidelines, SGLT2i should be discontinued 3 days before scheduled surgeries. The medication can be resumed once the patient's oral intake has returned to baseline levels[30]; ***Patient on dialysis: Though SGLT2i are not recommended for patients on dialysis, some studies show encouraging results in this population. However, there are potential risks associated with SGLT2i in peritoneal dialysis, emphasizing the need for a cautious and thorough investigation of dosing, long-term safety considerations, and patient-specific factors through comprehensive clinical trials[31,32]

approach involving patient education, implementing effective communication strategies between HCPs and patients, and establishing a therapeutic alliance that promotes trust and mutual understanding.

Diabetic Ketoacidosis

Euglycemic diabetic ketoacidosis (eDKA) is an uncommon yet potentially life-threatening complication associated with the use of SGLT2i. In contrast to classic diabetic ketoacidosis (DKA), eDKA often manifests with near-normal or only mildly elevated glucose levels.[34] According to the ADA, eDKA is defined as the presence of high anion gap metabolic acidosis and increased plasma ketones in conjunction with blood glucose levels below 250 mg/dL (13.9 mmol/L).[35] The osmotic diuretic effect triggered by SGLT2i results in decreased insulin production and increased glucagon secretion (promotes a shift from glucose to fat metabolism), increased urination, and potential dehydration, thereby exacerbating the risk of developing ketoacidosis.[36,37]

In a systematic review and quantitative analysis (160 reports, $n = 77$), findings revealed that DKA was more prevalent in middle-aged female patients with T2DM who were taking SGLT2i in combination with metformin. The study also identified surgery as a precipitating factor for DKA in this patient group.[11] Similar findings were seen in a meta-summary of case reports (108), in which common symptoms were gastrointestinal (nausea, vomiting, abdominal pain) and respiratory (breathlessness), and the precipitating factor was an acute severe infection (Table 3).[36]

Genitourinary Infections

The elevated urinary glucose levels attributed to the administration of SGLT2i lead to glycosuria. Consequently, this heightened glycosuria amplifies the risk of genitourinary tract infections (such as balanitis, balanoposthitis, urethritis, genital warts, and epididymo-orchitis in men, and vulvovaginitis, genital warts, and pelvic inflammatory disease in women) and, to a relatively lesser extent, urinary tract infections (UTIs).[9,26] The glycosuric effect of SGLT2i can potentially increase the susceptibility of patients to genitourinary infections. Clinical trials have reported an overall incidence of genital infections ranging from 4 to 6% with the use of SGLT2i. Notably, these events were more prevalent among women, with rates of approximately 7 to 11% compared to men.[12] The consensus statement from the South Asian Federation of Endocrine Societies (SAFES) recommends maintaining perineal hygiene as a preventive measure against genital tract infections (GTIs). Additionally, the statement suggests that after 3 months of being free from GTIs, patients with T2DM can be prescribed SGLT2i and prophylactic antifungal coverage.[41] Typically, genital infections can be resolved with standard antifungal therapy, and there is usually no need to discontinue the diabetes medication regimen.

A study conducted by Shrikrishna and Archana revealed that 16.6% of patients had GTI and UTI, with a higher incidence among females.[42] In a study conducted by Prasanna et al.,[43] the prevalence of genital mycotic infection was found to be 3.4% with canagliflozin 100 mg and 4.5% with canagliflozin 300 mg. Another study by Gill et al.[12] reported that genitourinary tract infection was the most common adverse effect, occurring in 20.6% of cases, followed by generalized weakness, reported in 10.5% of participants. A meta-analysis by Fadini et al.[44] (five studies) reported that combination therapy with a dipeptidyl peptidase-4 (DPP-4) inhibitor appears to reduce the frequency of UTIs and GTIs associated with SGLT2i when compared to those on SGLT2i alone {pooled risk ratio 0.51 [95% confidence interval (CI) 0.28–0.92]}. According to Singh et al., the incidence of UTIs decreases with the prolonged use of SGLT2i.[45]

Fournier's gangrene is a rare yet potentially life-threatening necrotizing fasciitis affecting the genitalia and perineum, predominantly in men. Individuals using SGLT2i should be cautioned to promptly seek medical attention if they encounter severe pain, tenderness, erythema, or swelling in the genital or perineal area, accompanied by fever or malaise. In cases where Fournier's gangrene is suspected, immediate discontinuation of the SGLT2i is advised, and urgent treatment should commence, including antibiotics and, if necessary, surgical debridement (Table 4).[29,40,46]

Volume Depletion

The glycosuria induced by SGLT2i leads to volume depletion by expelling more bodily fluid through osmotic diuresis.[41,48] Adverse events linked to volume depletion include reductions in blood pressure, dehydration, postural dizziness, orthostatic hypotension, orthostatic intolerance, syncope, and a decrease in urine output. A *post hoc* analysis reported an elevated incidence of volume depletion–related adverse events associated with SGLT2i in an Indian population (Table 5).[43]

Hypoglycemia

The risk of hypoglycemia is rare but increases when SGLT2i are concurrently administered with insulin secretagogues such as sulfonylureas or insulin (Table 6).[26]

Other Adverse Events

Bone fractures, osteoporosis, and amputations are very rare, and long-term studies have shown a reduced incidence. SGLT2i, through

Table 3: HCP and patient perspective in preventing DKA[28,38–40]

HCP's perspective
• Patients should be thoroughly assessed before initiating SGLT2i therapy
• Patients with a history of DKA, pancreatitis, severe dehydration, or other risk factors may not be suitable candidates
• HCPs should be vigilant about recognizing precipitating factors that may lead to ketoacidosis (e.g., insulin cessation, prednisone administration, dehydration, hyperglycemia, low carbohydrate intake/low food intake, excessive alcohol use)
• It is crucial to educate patients about the signs and symptoms of DKA, including nausea, vomiting, abdominal pain, and altered mental status. This information empowers patients to recognize potential issues promptly and seek immediate medical attention if necessary
Patient's perspective
• Avoid a very low carbohydrate diet
• In case of illness involving diarrhea, vomiting, fever, or unusual drowsiness, discontinue SGLT2i and refrain from restarting until feeling better and able to eat and drink fluids normally
• Hydration is crucial; drinking plenty of water for up to 24 hours helps prevent dehydration
• If you are particularly unwell due to an infection or illness, seek medical advice. Ketone levels can be elevated even with normal glucose levels
• Symptoms such as nausea, vomiting, abdominal pain, stupor, fatigue, and difficulty breathing should raise suspicion of DKA—immediate medical advice should be sought. If ketones exceed 1.5 mmol/L, additional blood tests may be necessary to confirm or exclude DKA
• SGLT2i should be discontinued 48 hours before elective surgery. Periodic ketone checks may be required if the admission is for emergency surgery. SGLT2i can be resumed 24 hours after returning to normal oral intake
• Reduce alcohol intake

Table 4: HCP and patient perspective in preventing genitourinary infections[39,40,47]

HCP perspective
• Before initiating SGLT2i, gather a patient's history regarding urinary tract infections, yeast infections, and genital infections
• Evaluate the benefits and risks carefully before starting an SGLT2i, particularly in individuals with a history of multiple UTIs and GTIs
• Exercise caution and refrain from prescribing an SGLT2i to individuals with a history of recurrent UTIs or those currently experiencing an active UTI
• Educate patients on the importance of maintaining daily fluid hydration while on SGLT2i
• Educate patients on symptoms to monitor for, such as genital itching, burning, discomfort, pain, or discharge
• Educate patients about the mechanism of SGLT2i, emphasizing increased glucose excretion in urine, which can elevate the risk of yeast infections
• Consider prescribing antifungal medication (oral or topical) in case of itching or rash, ensuring proactive management of potential side effects
Patient perspective
• Maintain proper hydration
• Inform the doctor of symptoms of itching, pain, and redness
• Obtain a urinalysis when symptoms are present
• Wash the genital organs after urination or defecation
• Consider the use of routine hygienic wipes or sprays
• Advise women to wash from front to back
• For uncircumcised males, retract the prepuce before washing
• Use clean water for washing and opt for mild soap if necessary
• Avoid using alcohol-based disinfectants for washing

Table 5: HCP and patient perspective in preventing volume depletion[39,49]

HCP perspective
• Before initiating treatment with SGLT2i, assess patients' volume status and correct it as necessary. Patients should be closely monitored throughout therapy for signs and symptoms of hypotension, and appropriate treatment measures should be implemented as needed
• Inform individuals about the mechanism of SGLT2i, which involves increased glucose excretion through urine. This could potentially lead to hypovolemia and a subsequent decrease in blood pressure
• Emphasize the importance of maintaining daily fluid hydration
• Use caution when prescribing SGLT2i in individuals concurrently taking loop diuretics. Consider adjusting the diuretic dose as necessary
• Educate patients on the importance of daily blood pressure monitoring
Patient perspective
• Check your blood pressure regularly
• Notify your HCP if weight decreases by >3 pounds in 24 hours, 5 or more pounds in a week, or if you experience symptomatic hypotension

Table 6: HCP and patient perspective in preventing hypoglycemia

HCP perspective
• Reduce the dose of the insulin secretagogue or insulin when prescribing SGLT2i in combination
• Educate the patient to monitor glucose levels regularly
Patient perspective
• Regularly monitor glucose levels
• Inform your HCP if you experience regular episodes of hypoglycemia
• Keep candies, jellybeans, or gumdrops readily available in case of hypoglycemia

their osmotic diuretic effect, contribute to volume depletion, disrupting electrolyte concentrations in the body, particularly serum calcium and phosphate, which may harm bone health.[26,27] The CANVAS trial reported an increased risk of amputation with canagliflozin, with proposed risk factors including previous amputation, peripheral vascular disease, and neuropathy.[50] Amputations predominantly involve the tarsal and metatarsal regions.[3,42] The CANVAS trial observed a slight increase in fracture risk and alterations in bone mineral density (BMD).[43] However, recent studies have shown no significant association between SGLT2i and fractures (Table 7).[51–53]

Importance of Follow-ups and Regular Monitoring to Reduce Withdrawals and Improve Adherence

Monitoring and follow-up play crucial roles in ensuring the safety and effectiveness of SGLT2i therapy. Consistent follow-up enables HCPs to recognize and manage any adverse events or side effects of SGLT2i. Timely intervention can alleviate discomfort or concerns, reducing the likelihood of patients discontinuing the medication. Regular follow-up appointments serve as a forum for open communication, addressing patients' concerns or questions about their medication. These follow-up visits also present opportunities to discuss and reinforce lifestyle modifications that complement SGLT2i therapy. They offer a platform for setting realistic expectations regarding treatment outcomes. By examining potential challenges and highlighting the gradual benefits of the medication, HCPs can effectively manage patient expectations, ultimately enhancing long-term adherence.

During follow-up visits, monitoring blood pressure and assessing hydration status are important. Additionally, when appropriate, renal function and serum electrolytes should be checked. Consistent monitoring, including glycemic control through HbA1c and self-monitoring of blood glucose (SMBG), is necessary for optimal treatment outcomes. Adjust therapy as needed to achieve personalized glycemic targets.[38] Additionally, addressing genitourinary infections and providing guidance on their prevention is vital. Comprehensive patient education about the benefits, risks, and potential side effects of SGLT2i is essential. Empowering patients to engage actively in their diabetes management is a key aspect of successful treatment. Furthermore, collaboration with primary care providers, cardiologists, endocrinologists, and allied health professionals can enhance communication and optimize therapeutic efforts.[49] This interdisciplinary approach contributes to a more holistic and effective management of patients receiving SGLT2i therapy.

Conclusion

In summary, the endeavor to develop strategies that mitigate withdrawal and bolster adherence to SGLT2i emerges as a crucial objective in diabetes management. The cornerstones of this pursuit encompass regular monitoring, fostering open communication between HCPs and patients, and crafting personalized care plans. Patient education—elucidating the benefits, risks, and potential side effects of SGLT2i—coupled with the prompt addressing of concerns and cultivating a collaborative healthcare relationship, plays a pivotal role in sustaining adherence. By integrating lifestyle adjustments, establishing pragmatic expectations, and adopting a proactive stance toward adverse events, HCPs

empower patients to participate actively in their treatment journey. The unwavering dedication to comprehensive, patient-centric care not only diminishes withdrawal rates but also amplifies the therapeutic effectiveness of SGLT2i, ultimately elevating overall health outcomes for individuals managing T2D. The myths and facts related to SGLT2i are discussed in Table 8.

Table 7: HCP and patient perspective in preventing other adverse effects[39,47]

HCP perspective
• Before prescribing SGLT2i, consider fall risk and hypotension, as they may lead to fractures
• Before initiating treatment with SGLT2i, assess a history of osteoporosis, osteopenia, or medication-induced bone loss
• Obtain a bone mineral density study (DEXA) if required
• Exercise caution when initiating SGLT2i in individuals with active foot ulceration or a history of lower limb amputation
• Measure foot examination and ankle-brachial index score in people with a history of foot ulceration
• Provide education on proper foot care measures, including inspecting each foot daily
• Educate individuals on achieving and maintaining good glycemic control for overall health
• In cases of foot ulceration, osteomyelitis, or gangrene, consider discontinuing SGLT2i
Patient perspective
• Regularly monitor glucose levels
• Regularly check your feet and maintain hygiene
• Promptly report any signs of foot infection or ulceration to your HCP
• Inform your HCP about any prior episodes of hypotension, instances of amputation, or a history of osteoporosis. Additionally, provide comprehensive information about your current medication regimen

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Table 8: Myths and facts regarding SGLT2i therapy

Myths	*Facts*
SGLT2i is only an antihyperglycemic medication	SGLT2i offer additional benefits besides glycemic control, such as lowering blood pressure, reducing serum urate levels, and promoting weight loss. They are also recommended as first-line therapy for individuals with type 2 diabetes (T2D) who have or are at high risk for atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and/or chronic kidney disease (CKD)[54]
SGLT2i are not given to individuals below 18 years	The Food and Drug Administration (FDA) has approved the use of SGLT2i as an adjunct to diet and exercise to improve blood sugar control in children aged 10 and older with T2D[55–57]
SGLT2i cause weight loss and should be avoided in individuals with low body mass index (BMI)	SGLT2i are associated with a modest reduction in body weight. However, they should not be viewed as a primary weight loss treatment for patients with high or very high BMI, as the weight loss achieved is typically <5%.[58] Notably, the degree of weight loss tends to increase with higher BMI. The benefits of SGLT2i remain consistent across all BMI categories[59]
SGLT2i and HbA1c	Patients with T2D can benefit from SGLT2i regardless of their glycemic control status, as these medications do not increase the risk of adverse effects in those with higher HbA1c levels.[60] SGLT2i may help mitigate the long-term damage caused by poor glycemic control in the early years following a diabetes diagnosis. Early introduction of SGLT2i has been associated with better renal outcomes, regardless of the HbA1c levels[61,62]
SGLT2i increase the risk of fractures	Recent meta-analyses have shown no significant association between SGLT2i and fractures[51,52]
SGLT2i increases the risk of acute kidney injury (AKI)	SGLT2i cause a modest but acute reduction in eGFR by about 3–5 mL/minute/1.73 m^2, which might be mistaken for AKI in clinical and trial settings. Propensity score–matched analyses have shown a reduced risk of AKI among SGLT2i users.[63] A meta-analysis, which included data from the EMPA-REG OUTCOME, CANVAS, DECLARE TIMI 58, and CREDENCE trials, found that AKI risk decreased by 25%.[64] Additionally, a real-world analysis comparing SGLT2i to DPP4 inhibitors indicated a 53% reduction in AKI risk for users of SGLT2i[65]
SGLT2i cannot be prescribed for the elderly	SGLT2i are well-tolerated and safe in the elderly.[66,67] Caution may be required in very old frail patients[68]
SGLT2i increases the risk of amputation	SGLT2i are not associated with an increased risk of amputations.[69,70] Patients with peripheral artery disease (PAD) may benefit from SGLT2i due to the associated reduction in heart failure hospitalization rates[71]

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CASE REPORT

An Elusive Diagnosis Hiding in Plain Sight

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Abstract

This case report highlights the diagnostic and therapeutic challenges faced in the management of a middle-aged female patient presenting with persistent left gluteal pain and a history of remote pulmonary tuberculosis. Despite multiple hospital admissions and diagnostic procedures, the cause of her debilitating symptoms remained elusive. The diagnosis was clinched when a repeat investigation, including bone biopsy and bone marrow aspirate, revealed the growth of *Salmonella* Typhi (S. Typhi). The patient's symptoms markedly improved following treatment with appropriate antibiotics, underscoring the importance of considering atypical clinical presentations of common organisms.

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Introduction

Salmonella Typhi (S. Typhi), the causative organism of typhoid fever, commonly presents with systemic and gastrointestinal symptoms. However, atypical presentations can perplex clinicians. We report the case of a 42-year-old female without comorbidities, who presented with severe, persistent left gluteal pain, with a distant history of treated pulmonary tuberculosis. Despite numerous diagnostic efforts, the cause remained elusive until a culture from computed tomography (CT)-guided bone biopsy and bone marrow aspirate revealed S. Typhi infection. This case highlights S. Typhi's ability to affect musculoskeletal structures, emphasizing the need for a comprehensive approach to diagnose and manage atypical infectious disease presentations.

Case Description

A 42-year-old female, with no existing comorbidities, presented to the outpatient department with left gluteal pain for the past 3 weeks. The pain was acute in onset, severe; to an extent where the patient was unable to walk, radiating to the medial aspect of the lower limb. She had a history of pulmonary tuberculosis, 20–25 years ago, for which she had taken a complete course of antitubercular therapy.

She was previously admitted at another hospital for the same complaints, where she had several fever spikes. Blood cultures were taken and intravenous amoxicillin–clavulanate was started, to which she developed an allergic reaction. She was shifted onto cefoperazone–sulbactam, which was continued for 5 days. Cultures were sterile. On magnetic resonance imaging (MRI) of the hip, hyperintense signal abnormalities were visualized in the left iliacus and adjacent paraspinal muscles, likely due to infective or inflammatory etiology. As her fever subsided, she was discharged on oral cefuroxime for 5 more days.

However, her hip-ache persisted; hence, she sought evaluation at a tertiary care hospital. Laboratory investigations showed no leukocytosis (7,290 per cu. mm) and C-reactive protein levels of 45 mg/L. Pelvic/gluteal collections were ruled out via ultrasonography. MRI was repeated, which showed marrow edema within the subarticular regions of the left sacroiliac joint (SIJ). Mild edema and fluid were noted in surrounding soft tissues (Fig. 1). The joint was biopsied under CT-guidance, and the obtained sample was sent for culture and Gene-Xpert, both of which were negative. Histopathological examination was suggestive of nontubercular bacterial infection. She was discharged, but her pain remained unresolved; hence, she finally consulted our hospital.

On initial evaluation at our hospital, the history suggested that the left hip-ache had not improved over the previous 3 weeks despite two hospitalizations. Left sacroiliac and gluteal region was tender with straight leg raise test positive after 30° of leg raise. However, no significant neurological deficit was apparent. Relevant laboratory investigations were done (Table 1), and she was initially started on injection ciprofloxacin and teicoplanin.

In view of persistent symptoms, repeat CT-guided bone biopsy from left SIJ was obtained along with bone marrow aspirate (Fig. 2). Bone biopsy was sterile on culture, and simultaneous Gene-Xpert test was negative. However, bone marrow aspirate grew quinolone-resistant S. Typhi (Table 2).

Cotrimoxazole was started as per culture sensitivity and favorable bone penetration[1] and continued for a total of 3 months. The patient responded to the given line of treatment and there was significant symptomatic improvement. On subsequent follow-ups, the patient reported a marked reduction in joint pain, improved joint mobility, and was free from any further fever spikes.

Discussion

Salmonella infections encompass a spectrum of conditions, such as acute gastroenteritis, bacteremia, enteric fever, and localized infections. Less than 1% present as localized bone and joint infections, typically occurring in individuals with underlying conditions such as human immunodeficiency virus (HIV) infection, systemic lupus erythematosus (SLE), sickle cell anemia, or immunosuppressive therapy.[2,3] Our patient did not have HIV or any other immunosuppressive state. Also, she was evaluated for SLE, which was negative. She was not evaluated for sickle cell disease as her clinical situation did not warrant such an evaluation.

Unilateral sacroiliitis primarily stems from infections, early ankylosing spondylitis, juxta-articular neoplastic lesions, or traumatic osteoarthritis. Bilateral involvement is associated with collagen/autoimmune disorders. In India, patients with unilateral sacroiliitis are initially suspected of tuberculosis until proven otherwise.[4]

Salmonella Typhi infection can manifest as either reactive or septic arthritis. S. Typhi reactive arthritis typically emerges 1–4 weeks after infection, presenting as asymmetrical oligoarthritis, with a preference for lower extremity joints, alongside cervicitis,

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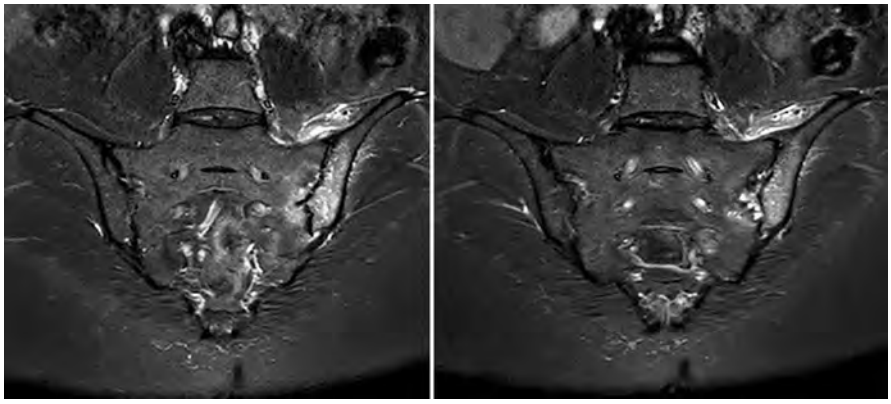

Fig. 1: Magnetic resonance imaging short tau inversion recovery (STIR) sequence–coronal section showing subarticular marrow edema with mild effusion, changes likely suggestive of left sided sacroiliitis

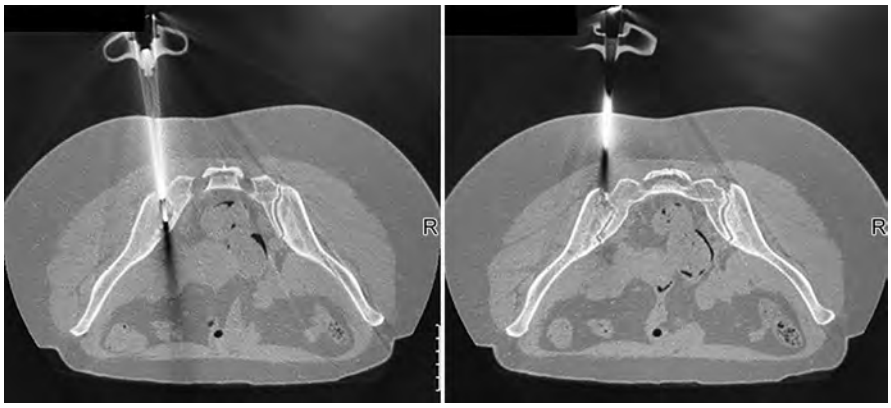

Fig. 2: Still images depicting CT-guided biopsy obtained from the left SIJ

Table 1: Results of initial evaluation at our center

Hb/TLC/Plt	8.7 g/dL 7,470 per cu. mm 2,87,000 per cu. mm
HLA–B27	Negative
Widal test	O Antigen—1:240 H Antigen—1:480
Brucella IgM/IgG	Negative
TPHA	Negative
Cryptococcal Antigen	Negative
CRP	3.70 mg/L

Hb, hemoglobin; TLC, total leukocyte count; Plt, platelet count, CRP, C-reactive protein

conjunctivitis, and uveitis. Most patients who develop S. Typhi reactive arthritis are HLA-B27 positive (50–70%).[5] S. Typhi septic sacroiliitis is less common, primarily affecting adolescents and young adults, with a predilection for the left SIJ.[4] During the initial 2 weeks, radiographs tend to appear normal, while MRI often reveals abnormalities. Retrospective comparison of MRI, CT, and nuclear medicine revealed greater sensitivity of MRI.[6]

Table 2: Bone marrow aspirate antibiotic sensitivity report

Antibiotic	*Interpretation*
Amoxicillin–clavulanic acid	Sensitive
Cefotaxime	Sensitive
Ceftriaxone	Sensitive
Ciprofloxacin	Intermediate
Aztreonam	Sensitive
Cefixime	Sensitive
Ampicillin	Sensitive
Chloramphenicol	Sensitive
Tetracycline	Sensitive
Cotrimoxazole	Sensitive
Azithromycin	Sensitive

All reported cases of S. Typhi sacroiliitis are characterized by a high titer Widal test, positive cultures for S. Typhi (blood and/or joint aspirate), and elevated erythrocyte sedimentation rate (ESR).[5] In our patient, blood culture was negative, which could be because of receipt of prior antibiotics.

In all available case reports, including our own, unilateral sacroiliitis involving the left SIJ was observed. It is unclear why the left-sided SIJ is more involved compared to the right. The treatment protocol for typhoid fever complicated by sacroiliitis is yet to be established. Antibiotic treatment should be tailored based on sensitivity patterns and local resistance. Most patients receive treatment with intravenous quinolones (such as ciprofloxacin) or third-generation cephalosporins.[3] However, cotrimoxazole is a good option for the treatment of bone and joint infection,[7] given its adequate bone diffusion. For bone and joint infections, a 3-month therapy is needed.[1]

Learning/Take Home Points

- Salmonella infections can present as rare localized bone and joint infections.
- Unilateral sacroiliitis is commonly related to infections, ankylosing spondylitis, neoplastic lesions, or traumatic osteoarthritis.
- S. Typhi can lead to reactive or septic arthritis.
- S. Typhi septic sacroiliitis is more common in adolescents and young adults and often affects the left SIJ.
- Imaging, especially MRI, is crucial for early diagnosis in sacroiliitis. Antibiotic treatment administered for a minimum of 14 days. Cotrimoxazole is a good option given its adequate bone diffusion. Usually, a 3-month therapy is needed.

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CASE REPORT

Quadrivalvular Heart Disease Complicated by Fatal Infective Endocarditis of Pulmonary Valve: A Case Report

Shankar Yallappa Machigar[1*], Akash Shah[2], Satyavan Sharma[3]

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Abstract

A middle-aged sick male with rheumatic heart disease and prior mitral and aortic prosthesis was admitted for tricuspid valve replacement. Preoperative assessment revealed a hitherto undiagnosed pulmonic condition.

This unusual case is reported not only to highlight the quadrivalvular disease with possible coexisting rheumatic and congenital etiology but also the fulminant endocarditis of pulmonary valve.

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Case Description

A 45-year-old male was admitted to a tertiary care facility in February 2023 for a surgical tricuspid valve replacement (TVR).

The chronology of the long medical history began with hospitalization for acute rheumatic fever (ARF) at the age of 8 years, mitral valve replacement (MVR) for mitral stenosis and regurgitation using Starr–Edwards ball and cage prosthesis at 11 years of age (1989), aortic valve replacement (AVR) for severe aortic regurgitation (AR) using Medtronic Hall valve at 15 years of age (1993), fully recovered right hemiplegia (1995), and subdural hematoma requiring burr hole surgery in 2016 without any residual neurological deficit. Over the years, the patient has been on regular injection benzathine penicillin prophylaxis every 3 weeks and adequate anticoagulation using warfarin with international normalized ratio (INR) maintained between 2.5 and 3. Diabetes mellitus (DM) was diagnosed 3 years back and is well controlled on oral medication.

The patient was aware of tricuspid regurgitation (TR) being diagnosed at a young age. For the last 5 years, he has been in congestive cardiac failure (CCF) responsive to diuretics and needed hospitalization in years 2020 and 2022 for intravenous (IV) medication. CCF was worsening despite increasing doses of diuretics (daily furosemide 100 mg, spironolactone 50 mg, metolazone 10 mg) during the last 10 months. Due to worsening status, the patient was evaluated for TVR.

Physical examination revealed atrial fibrillation, normal peripheral arterial pulses, elevated jugular venous pressure up to the angle of the mandible with prominent V wave and Y descent, bilateral edema of the feet, and blood pressure of 100/70 mm Hg. There were parasternal pulsations, varying intensity S1, loud P2 and right ventricular third heart sound, grade 4/6 pansystolic murmur in the tricuspid area, and a grade 3/6 ejection systolic murmur along the left sternal border, pulsatile hepatomegaly, and clear lung field. Skiagram chest PA and lateral views revealed marked cardiomegaly (cardiothoracic ratio of 0.7) with prominent superior vena cava (SVC), right ventricle (RV), right atrium (RA), and main pulmonary artery (MPA) segment. Both mitral and aortic metallic prostheses were visualized. Electrocardiogram revealed atrial fibrillation, ventricular rate 100/minute, QRS axis +90°, rsR pattern in V1, and generalized ST-T changes. Transthoracic 2D echocardiography (TTE) in apical four-chamber view revealed thickened tricuspid valve (TV) leaflets with failure to coapt and severe TR and normal mobility of mitral Starr–Edward prosthesis (Fig. 1A). Parasternal long axis view demonstrates normal mobility of aortic prosthesis (Fig. 1B). The transmitral peak and mean gradients were 23 and 9 mm Hg with no paravalvular regurgitation. Transaortic peak and mean gradients measured 28 and 13 mm Hg, with no paravalvular regurgitation. TV annulus measured 58 mm, tricuspid annular plane systolic excursion (TAPSE) was 17 mm with estimated pulmonary artery (PA) systolic pressure of 67 mm Hg and inferior vena cava of 17 mm. Transesophageal echocardiography (TEE) did not show any paravalvular leak, pannus or vegetations over both the metallic prostheses. Findings of TV morphology and dilated left atrium (LA) and RA were confirmed.

Biochemical investigations, including renal and liver function tests, were within normal limits. Coronary vessels were normal on angiography with right dominance. Hemodynamics studies revealed aortic pressure 120/60, MPA 40/20, RV 70/18, transpulmonary valve pull back gradient 30, and RA pressure with V wave of 32, and mean of 20 mm Hg. Right ventriculography in lateral view revealed doming, thickening, and restricted mobility of pulmonary valve (PV) with poststenotic dilatation of main PA segment (Fig. 2A). Review of TTE images revealed thickening of PV and a 20 mm Hg systolic gradient.

Four days after TEE, the patient developed chills, fever, and loose motions with rapid progression to acute kidney injury and multiorgan failure. Repeated bactec and fungal blood cultures were negative. Chest X-ray PA view showed multiple bilateral opacities consistent with septic pulmonary emboli. Bedside TTE revealed a large mobile mass on PV suggesting vegetation (Fig. 2B). Despite higher antibiotics, antifungal agents, ventilatory support, inotropic therapy, and hemodialysis, the patient succumbed to fulminant septicemia.

Discussion

Quadrivalvular involvement is rare and has been reported in young patients during ARF[1] or in chronic rheumatic heart disease (RHD).[2–4] This patient had ARF at the age of 8 years and needed mitral and AVR at a very young age. Tricuspid valve lesion progressed to severe TR in the next two decades and necessitated tricuspid valve surgery. The most intriguing part is the delayed diagnosis of pulmonary valve stenosis (PVS) despite having undergone serial TTE over the years. The diagnosis was obviously missed due to attention on the other valves, the presence of pulmonary hypertension, and mild

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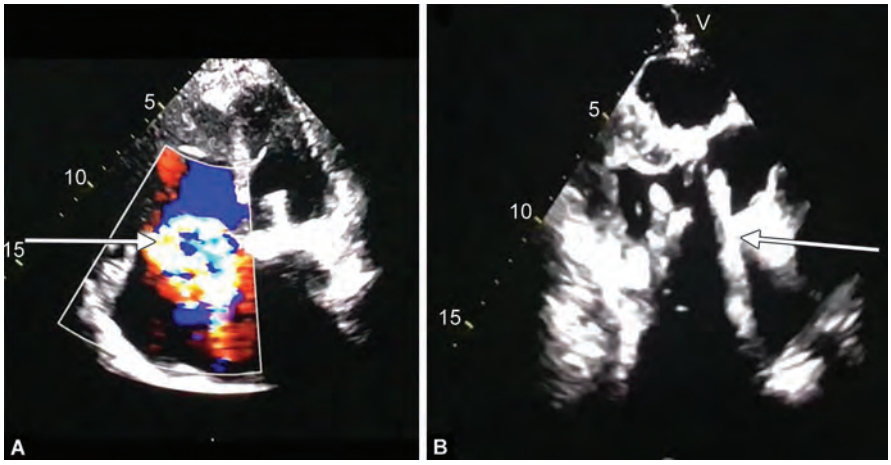
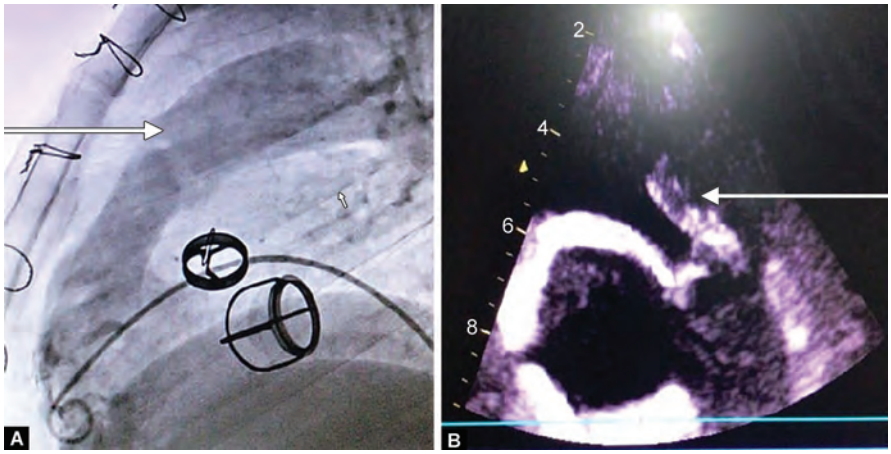


Figs 1A and B: Transthoracic 2D echocardiography and color Doppler findings: (A) Color Doppler interrogation in apical four-chamber view shows severe TR in a thickened valve with failure to coapt. Well-functioning Starr–Edward mitral prosthesis is also visualized; (B) Normally functioning aortic metallic prosthesis



Figs 2A and B: Right ventriculogram and TTE data: (A) RV angiogram in lateral view demonstrating thickened, domed PV with restricted mobility and narrow jet and poststenotic dilatation of MPA (arrow). Aortic and mitral metallic prosthesis are also visualized; (B) Short axis view shows a fleshy, mobile, mass attached to PV (arrow) which protrudes in right ventricular outflow tract

nature of the PVS. The etiology of PVS, whether congenital or rheumatic, needs discussion. There is sparse information on the echocardiographic findings in rheumatic PV involvement and include thickening of leaflets, cuspal fusion, turbulence, systolic gradient across the valve, and varying degree of pulmonary regurgitation.[2–4] There are no reports documenting angiographic findings in rheumatic PVS. The angiographic demonstration in this case of a domed, thickened PV with restricted mobility and poststenotic dilatation strongly favor PVS to be of congenital etiology. Infective endocarditis (IE) affecting PV is extremely rare.[5] PVIE has been reported in a variety of congenital cardiac malformations,[6,7] immunosuppression, and in the background of several hospital-based procedures.[8,9] A combination of chronic illness, healthcare setting with use of IV lines, TEE, and cardiac catheterization precipitated PVIE in this patient with deformed PV. Fulminant septicemia with lethal multiorgan failure as in this case is well documented in PVIE.[9]

This report documents an unusual case where the medical journey began with ARF, led to two valve replacements in juvenile age-group, progressive worsening of heart failure necessitating third valve replacement, and succumbing to the rarest event of the quadrivalvular disease, endocarditis of the native PV.

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API ANNOUNCEMENT

Elections of API, ICP and PRF
(Full details circular No. 1 & 2/2025)

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

Governing Body of API:-

President-Elect – One; Vice President – One; Hon. Treasurer – One; Elected Members – Six and Nine Zonal members (one from each zone)

Faculty Council of ICP:-

Dean-Elect – One; Vice Dean and Elected Members – six posts

Board of PRF

Director Elect – One and Board members – Three

Separate nominations must be submitted for each post.

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

1. **President Elect**: To contest for the post of President Elect the candidate should be a life member of API for at least 12 years and have completed at least three full terms of 3 years each in any elected position in the Governing Body.
2. **Vice President:** To contest for the post of Vice President and the candidate should be a life member of API for at least 9 years and should have completed atleast two continuous full term of 3 years in any elected position in the Governing Body.
3. **Hon. Treasurer, Governing Body and Zonal Member**: To contest for all other elected positions, continuous membership of the Association of at least 3 years is mandatory.

Requirements for eligibility contest of election to Board of PRF

1. Director Elect: A member of API for at least 10 years with research experience and have 10 research publications in peer reviewed indexed journals

2. Board Member: **A** Member of API for at least 10 years with research experience and having 5 research publications in peer reviewed indexed journals.

The members contesting for the PRF election must attach copies of the Research Papers as mentioned above is mandatory.

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

Requirements for eligibility for the contests of election to ICP

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

Vice – Dean
i. A member of API for at least 12 years and
ii. A Founder Fellow or a Fellow of the College of 5 year standing and

iii. Any person who has held the position of Secretary of API or has been a Jt Secretary from HQ for one full term or a member of the Faculty Council for one full term.

Elected Members: A member of API for at least 10 years and a Founder Fellow or a Fellow of the college of 3 year standing.

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

A member shall not contest simultaneously for more than one post (i.e President-Elect, Vice-President, Hon. Treasurer; Member of the Governing Body /Zonal Member) (Dean-Elect; Vice Dean and Elected Members of Faculty Council) and also (Director – elect and Board members of PRF) Post means not only an office-bearer but also member of the Governing Body of API or Faculty Council of ICP or Board of PRF.

Every member is supplied with a nomination form. The nomination form completed in all respects should reach the API Office not later than 31st May 2025. For every post on the Governing Body / Faculty Council / Board of PRF, the nomination must be accompanied by a sum of Rs. 7500/- + 1350/- (GST) = 8850/- (Rupees eight thousand eight hundred only) nonrefundable in the form of Demand Draft payable at Mumbai. The nomination paper NOT accompanied by the Bank Draft of Rs. 8850/- will be deemed invalid.

Important

Canvassing in any form should not be done by the candidate for the election. Instead, they are requested to send a short bio-data NOT MORE THAN 200 words may accompany the nomination paper. Excess of bio-data beyond the first two hundred words shall be deleted. The Biodata will be published online at API Website and shall be available for viewing by members. Canvassing in any form or in favour of the candidate shall not be permitted.

THE CANDIDATE WILL HAVE TO CERTIFY AND SIGN THAT THE INFORMATION PROVIDED IN HIS/HER BIODATA IS CORRECT.

The Candidate shall also give an undertaking that in case of election dispute he/ she will abide by the API Constitution.

The results will be declared at the end of counting of votes and announced in the subsequent issue of JAPI. The report will be placed before the Governing Body for intimation.

DEAD LINES OF ELECTION PROCEDURE

Last date to receive the nomination at API Office	31st May 2025
Last date for withdrawal	10th June 2025
Last date to receive ballot papers at API Office	01st September 2025

Dr. Agam Vora
Hon. General Secretary

CASE REPORT

An Atypical Presentation of Pituitary Neurosarcoidosis as Massive Weight Loss and Failure to Thrive in a Young Female

Paulami Deshmukh[1*], Anushka Deogaonkar[2], Vaishali Deshmukh[3]

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Abstract

Neurological involvement accounts for <5% of patients with sarcoidosis. Manifestations are often those of the concerning site of affection such as hydrocephalus, transverse myelitis, neuropathy, and neuroendocrine dysfunction. We present a case of a 41-year-old female who presented to the endocrine clinic with complaints of fatigue, weight loss, anorexia, and absent menses for 6 years. She had no other comorbidities or chronic diseases. On examination, she was frail and cachectic [body mass index (BMI): 16.8 kg/m^2]. Laboratory assessments revealed anemia, leukocytosis, and eosinophilia. Hormone levels of serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), 8 am cortisol, thyroid-stimulating hormone (TSH), and estradiol were low while erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and angiotensin-converting enzyme (ACE) levels were raised. Antinuclear antibody (ANA) titers were normal along with a negative tuberculin skin test. Magnetic resonance imaging (MRI) of the brain revealed features suggestive of empty sella with a 3 mm pituitary. She was diagnosed provisionally to have panhypopituitarism and failure to thrive secondary to granulomatous changes due to sarcoidosis as a possible etiology. She was treated with oral preparations of corticosteroids (prednisolone), ethinylestradiol, levonorgestrel, and thyroxine. At the subsequent visit, after 6 months, she reported improved general condition, weight gain (18 kg), increased appetite, and resumption of menses. Neurosarcoidosis with selective hypophyseal involvement, although a rare affliction, should be considered while investigating possible endocrinopathies among middle-aged females. Additionally, clinical evidence in the absence of tissue evidence also requires precedence, especially in cases where histopathology and imaging may not suffice to prove the existence of a disease.

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Introduction

Sarcoidosis is a disease of unknown etiology that results in the formation of granulomas in the affected structures. The most common patterns include symmetrical bilateral hilar lymphadenopathy and/or diffuse micronodule formation in intrathoracic organs and lymphatic structures. Among extrapulmonary findings, <10% of patients have skin involvement, uveitis, liver or spleen affliction, or peripheral and abdominal lymphadenopathy.[1] Aseptic meningitis, hydrocephalus, headache, seizures, neuropsychiatric symptoms, neuroendocrine dysfunction, myelopathy, and peripheral neuropathy are a few documented neurological manifestations of sarcoidosis.[2]

The diagnosis of an entity like neurosarcoidosis requires strong clinical evidence supported by symptoms with no other explanation, histopathological studies depicting the characteristic picture of noncaseating granulomas in the affected structure[3] and exclusion of all other plausible causes of granulomatous diseases. Isolated involvement of a neural structure like the pituitary is a rare occurrence. Endocrine diseases often occur as a result of inflammation of the hypothalamic–pituitary system and hormonal deficiencies ensue.

Diagnosis becomes challenging especially when symptoms are not particularly typical and histopathological studies are difficult to perform as in this case, complicated with empty sella syndrome. Through this case report, we wish to present a different spectrum of neuroendocrine manifestations of sarcoidosis which, if detected and corrected in a timely manner, will be instrumental in improving the quality of life of the patient.

Case Description

A 41-year-old woman presented to Deshmukh Clinical and Research Center, Pune, in December 2022, complaining of severe weight loss, loss of appetite, weakness and fatigue, and ceased menstruation for 6 years. She also reported occasional anxiety and irritability. She lost approximately 40 kilos of weight and received many treatments in different hospitals for the last 6 years, but neither did her condition improve nor her weight. The patient did not report any recurrent infections, headache, vision changes, hyper- or hypopigmentation, dizziness, cough, joint pain, rash, other chronic diseases, or sick contacts. There was no family history of endocrine disorders, autoimmune diseases, or malignancy. She complained of extreme tiredness and low energy at the time of examination. Anthropometric measurements were as follows: Current weight: 38 kg; weight 6 years ago: 78 kg, decreased progressively over 6 years; height: 150 cm; body mass index (BMI) = 16.88 kg/m^2. She had a cachectic physique, sunken eyes, and an expressionless face. There was no lymphadenopathy and clinical examination was normal. Blood pressure was 90/64 mm Hg without postural hypotension and pulse rate of 104 beats/minute. Hematological studies showed a hemoglobin level of 11.9 gm/dL, total white blood count of 13,200/mm^3 (leukocytosis), and eosinophilia 1,294/per mm^3.

Antithyroid antibody levels: 8.73 IU/mL (borderline positive). Antinuclear antibody (ANA) stain: Negative, after 1-hour erythrocyte sedimentation rate (ESR) was 61 mm, C-reactive protein (CRP) levels were 21.6 mg/L. Serum follicle-stimulating hormone (FSH) was 1.2 U/L, serum luteinizing hormone (LH) was 0.5 U/L, serum estradiol was <10 pg/mL; serum 8:00 am cortisol was 0.3 mg/mL; serum thyroid-stimulating hormone (TSH) was 0.06 IU/mL, serum Na/K/Cl: 141/4.0/103 mEq/L, serum osmolality was 278 mOsm/L.

Magnetic resonance imaging (MRI) of the brain was performed in view of subnormal levels of pituitary hormones, and it was seen that the height of the pituitary gland was 3 mm (Fig. 1). Another imaging study report in September 2021 showed premature expansion of the sella turcica, which points to an early change in the pathogenesis of empty sella syndrome (Fig. 2).

An X-ray of the chest was normal (no apparent lung involvement such as hilar lymphadenopathy), tuberculin skin test was

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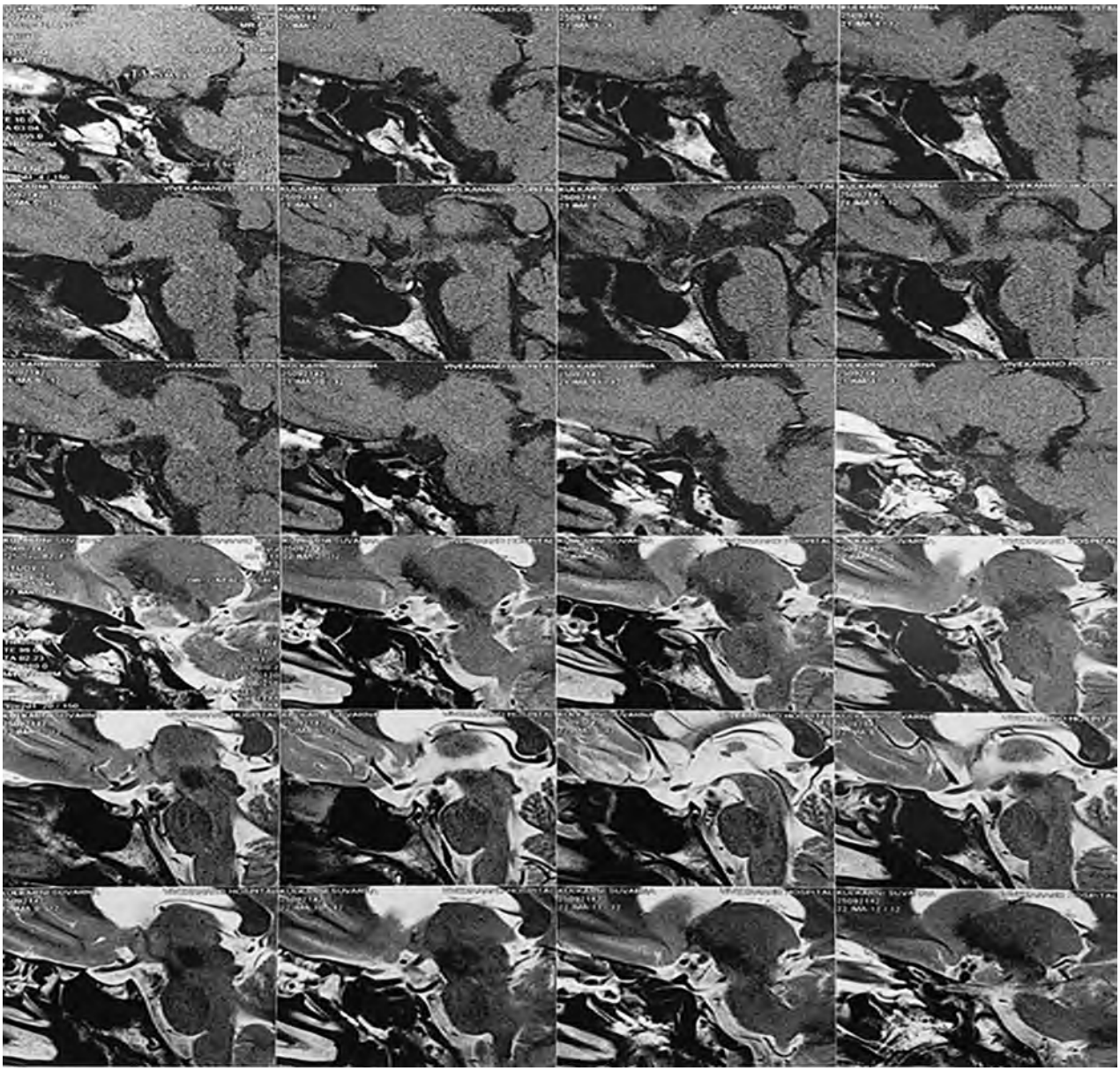

Fig. 1: Magnetic resonance imaging of the patient's brain (sagittal view) showing reduced height of pituitary stalk (around 3 mm) suggestive of hypophysitis secondary to sarcoidosis in this case

negative (induration of <5 mm over 48 hours of purified protein derivative intradermal injection), serum angiotensin-converting enzyme (ACE) level was 96 U/L. Based on the above findings, a diagnosis of panhypopituitarism with secondary hypogonadism, secondary hypocortisolemia, and secondary hypothyroidism was made, possibly due to partial resorption of pituitary as a result of sarcoidosis and empty sella syndrome.

The patient was advised admission to a hospital. Tablet prednisolone 5 mg (1-1/2-1/2), ethinyl estradiol 0.03 mg and levonorgestrel 0.15 mg/L, thyroxine 25 µg daily, and calcium carbonate 500 mg were administered daily to the patient. After 6 months of continued therapy, the patient was asymptomatic, her appetite improved, her menstrual cycle resumed, and her weight increased to 56 kg (up by 18 kg). White cell count reduced to 9,800/mm^3. The neutrophil count decreased from 7,748/mm^3 to 6,321/mm^3, and the lymphocyte count decreased from 4,039/mm^3 to 3,001/mm^3. The eosinophil count decreased to 98 cells/mm^3. ESR decreased to 17 mm/hour and CRP decreased to 0.3 mg/L. After 6 months of treatment, serum ACE levels decreased to 10.56 U/L.

Discussion

The reported prevalence of hypothalamic–pituitary involvement in multisystem sarcoidosis is approximately 5%,[4] with isolated pituitary involvement being relatively unheard of and uncommon. The course of the disease also differs among various patient populations. Peripheral nerve involvement has a better prognosis than central nervous system involvement.[5]

This case resurfaces the atypical picture of this granulomatous disease. This patient had no complaints or clinical findings other than those of failure to thrive. The nonspecific nature of this complaint in addition to the deficiency of objective evidence forced us to consider the utility of treatment as a marker of disease resolution.

Among the documented evidence of neurosarcoidosis presenting with panhypopituitarism-like features, there has been a tissue or imaging study confirming the diagnosis of sarcoidosis or the site of affliction (the pituitary and/or the hypothalamus) has provided the said evidence through the aforementioned tests.[6,7] This case, however,

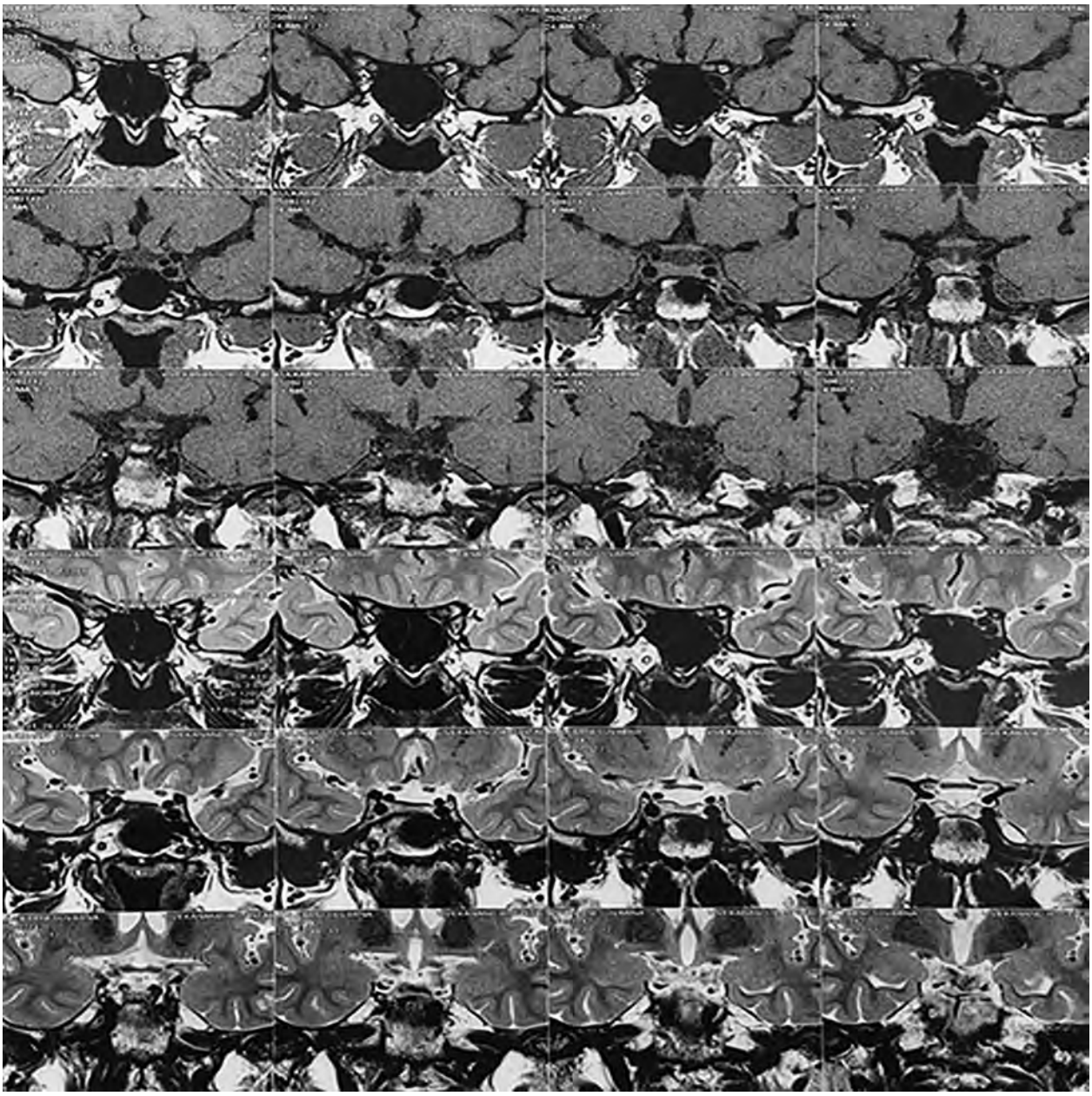

Fig. 2: Magnetic resonance imaging of the patient's brain showing early widening of the sella turcica suggestive of empty sella syndrome

was complicated by empty sella syndrome, creating inconducive conditions for testing.

Neurological involvement of sarcoidosis often results in an aggressive disease. Treatment for granulomatous hypophysitis secondary to sarcoidosis is initially recommended with high dose glucocorticoids and immunomodulatory therapies like methotrexate if a suboptimal response is obtained to the former.[8] This patient had an optimal recovery with an enteral glucocorticoid preparation without any signs of relapse to this day.

Conclusion

Failure to thrive in an adult patient warrants several investigations of bodily systems, including those of the hypothalamo-hypophyseal system. Although established guidelines exist to confirm the presence of a disease entity, one must bear in mind that clinical improvement can also serve as a means to assess disease activity and a state of health, especially when radiographic or histopathological evidence is difficult to obtain, insufficient, or inconclusive.

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CASE REPORT

Intractable Vomiting and Hiccups: An Atypical Presentation of Neuromyelitis Optica Spectrum Disorder

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Received: 13 April 2024; *Accepted:* 11 September 2024

Abstract

A 17-year-old male patient presented with frequent hiccups, nausea, and vomiting. He was initially treated for a hiatus hernia and gastritis with partial relief; however, symptoms recurred and worsened, necessitating a thorough assessment that included upper gastrointestinal endoscopy. Neuroimaging was ordered to look for a central cause of vomiting. The results showed a demyelinating lesion in the area postrema (AP), indicating neuromyelitis optica spectrum disorder (NMOSD). It typically affects the optic nerves and causes inflammatory demyelination of the spinal cord. Anti-aquaporin 4 (AQP4) autoantibodies in cerebrospinal fluid (CSF) were positive and validated the diagnosis. Intravenous methylprednisolone, intravenous immunoglobulin (IVIg), and rituximab were administered, and the patient responded well to the treatment. Regular follow-up and adherence to treatment guidelines are crucial for optimal patient outcomes.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.0911

Introduction

Neuromyelitis optica spectrum disorder (NMOSD), formerly known as Devic's disease or neuromyelitis optica (NMO), is an inflammatory disorder of the central nervous system (CNS), mainly affecting the optic nerves and spinal cord.[1] Various studies have found that the prevalence of NMOSD in adults ranges from 0.37 to 10 per 1,00,000. It typically manifests between the ages of 32 and 41, though cases have also been reported in children and the elderly. Individuals with autoimmune conditions such as systemic lupus erythematosus (SLE), Sjögren syndrome, and myasthenia gravis may have a higher predisposition to developing NMOSD.

Neuromyelitis optica spectrum disorder follows a relapsing course and is marked by acute episodes of bilateral optic neuritis, resulting in severe visual impairment, or transverse myelitis, which leads to weakness in limbs, sensory deficits, and bladder dysfunction. Other associated symptoms include recurrent bouts of nausea, vomiting, hiccups, excessive daytime sleepiness or narcolepsy, and posterior reversible encephalopathy syndrome (PRES). A few patients with NMOSD exhibit brainstem symptoms such as double vision, dizziness, vomiting, difficulty swallowing, and facial numbness or weakness, due to medullary involvement. Around 16–43% of NMOSD patients have area postrema syndrome (APS), which is characterized by nausea, vomiting, or hiccups that can occasionally be intractable and are accompanied by medullary lesions on magnetic resonance imaging (MRI). Acute neurogenic respiratory failure and death are possible consequences of brainstem involvement.

Hereby, we present a case of a 17-year-old boy who presented with recurrent nausea, vomiting, and hiccups, with no other complaints, and was later diagnosed with APS, a variant of NMOSD, which recovered completely with timely diagnosis and management.

Case Description

A 17-year-old boy came to the emergency department with complaints of hiccups for 15 days, nausea, and vomiting for 5 days. The hiccups persisted all day and into the night, to the point that they interfered with sleep. Vomiting was associated with nausea and was projectile in nature. It contained undigested food particles and was non-blood-tinged and non-bilious. The frequency was 15–20 episodes per day. There was no history of fever, abdominal pain, heartburn, reflux/regurgitation, loose stools, or jaundice.

The vitals were within normal limits on presentation. Pulse was 82 beats per minute, blood pressure was 130/80 mm Hg, SpO_2 was 99% on room air, and respiratory rate was 16 per minute. The patient was afebrile, and the general physical examination was also normal. Pallor, icterus, clubbing, cyanosis, lymphadenopathy, and edema were absent. The systemic examination, including the gastrointestinal system, cardiovascular system, respiratory system, and CNS, was normal. All the blood investigations, including complete blood count, renal function tests, serum electrolytes, and liver function tests, were within normal limits.

The patient had experienced similar complaints of nausea, vomiting, and hiccups in the past and had been evaluated at multiple hospitals. An upper gastrointestinal endoscopy was done, which was suggestive of antral gastritis and a small hiatus hernia. He was admitted to an outside hospital and was symptomatically treated with proton pump inhibitors, baclofen, and ondansetron. The patient experienced relief within 4 days of treatment and was discharged. He took the treatment for a total of 10 days after discharge, and upon feeling better, he discontinued the treatment.

The patient's condition on this admission was challenging, as despite being started on proton pump inhibitors, baclofen, ondansetron, and other supportive treatments, there was no significant relief in emesis and hiccups. He exhibited erythema within the oral cavity, accompanied by multiple painful oral ulcers and salivary drooling, likely attributed to the discomfort arising from the oral ulcerations. The patient also experienced dysphagia.

The gastroenterologist advised repeat upper gastrointestinal endoscopy, contrast-enhanced computed tomography (CECT) of the whole abdomen, manometry to assess lower esophageal sphincter (LES) pressure, and a barium swallow. Upper gastrointestinal endoscopy was suggestive of antral gastritis and a hiatus hernia. CECT of the whole abdomen was normal, and manometry to

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assess LES pressure and a barium swallow could not be done, as the patient was experiencing recurrent vomiting and hiccups.

After 4 days of treatment, the patient's oxygen saturation fell to 80% on room air. He was electively intubated and placed on ventilatory support. A chest X-ray was suggestive of aspiration pneumonia, for which broad-spectrum antibiotics were given.

Given the patient's lack of response to medications and treatment, the consideration of central causes for vomiting became imperative in order to address the underlying pathology. An MRI of the brain was conducted to investigate the central causes of vomiting, revealing a demyelinating lesion in the area postrema (AP) of the medulla oblongata. This finding raised the suspicion of NMOSD.

Neurology opinion was taken, a cerebrospinal fluid (CSF) examination was done, and a sample was sent for anti-aquaporin 4 (AQP4) autoantibodies, myelin oligodendrocyte glycoprotein (MOG) antibodies, and oligoclonal bands (OCB) to confirm the diagnosis. AQP4 autoantibodies were positive, and the MOG antibodies and OCB were negative. A diagnosis of NMOSD was made. This case was an isolated presentation of the AP variant of NMOSD. A repeat brain MRI, with whole spine screening, was done to look for optic neuritis and longitudinally extensive transverse myelitis (LETM). As per the NMOSD treatment guidelines, the patient was administered an initial course of intravenous methylprednisolone (1 gm) for 3 days, resulting in partial relief of vomiting and improvement in ventilatory settings. After extensive review of literature, we decided to administer a course of intravenous immunoglobulin (IVIg) at a dose of 2 gm/kg divided into five infusions over 5 days. The patient responded well to this intensive treatment regimen, with no further vomiting, hiccups, or ventilatory support. To prevent further relapses, rituximab was started as per treatment protocol with two 1 gm infusions separated by a 2-week interval. This was followed by a 1 gm rituximab infusion 6 months later along with an MRI scan of the brain, which showed no enhancements. The patient remains in regular follow-up and is currently asymptomatic.

Discussion

An immune-mediated inflammatory disorder of the CNS, NMOSD frequently affects the optic nerves and spinal cord.[2] Recent diagnostic criteria now include the area postrema (AP), diencephalon, brainstem, and cerebral hemispheres as additional potential targets for these autoantibodies after the discovery of its specific serological marker (AQP4) (Table 1).[3–6]

Area postrema syndrome is a rare neurological condition marked by unexplained attacks of intractable nausea, vomiting, or hiccups lasting longer than 1 week.

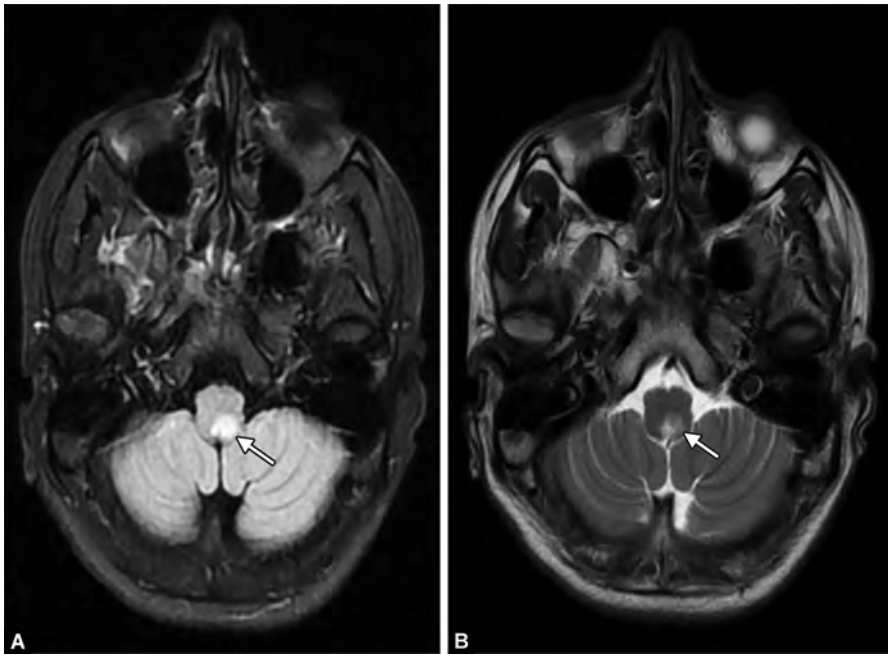
The AP is situated next to the nucleus of the solitary tract (NTS) at the dorsal medulla on the fourth ventricle's floor. It is a region where the blood-brain barrier (BBB) is more permeable and helps with neurochemical communication and precise control of autonomic functions. The AP is a primary target in NMOSD because the leaky BBB serves as an entry point for NMO-IgGs and is enriched with AQP4 channels.[4] In contrast to spinal cord or optic nerve lesions, AP lesions are typically nondestructive, with full remission following resolution of inflammation.

When APS manifests at the onset of NMOSD, particularly in the absence of additional neurological deficits, it is frequently misdiagnosed as a gastrointestinal system disease, delaying the start of treatment and increasing the risk of exacerbating NMOSD.[5,6]

Our patient had a similar presentation initially. He presented to us with recurrent nausea, vomiting, and hiccups. Symptomatic treatment was given, but he did not have any relief in symptoms. A repeat gastrointestinal endoscopy was done, which was suggestive of antral gastritis and hiatus hernia.[8–12] The patient's condition deteriorated further. A central cause of vomiting was considered, and a brain MRI was performed (Figs 1A and B).

Table 1: 2015 Diagnostic Criteria for NMOSD[7]

Criteria for NMOSD with AQP4-IgG		*Criteria for NMOSD without AQP4-IgG or with unknown antibody status*
One or more of the six core clinical characteristics		Two or more of the six core clinical characteristics resulting from one or more clinical attacks
Positive test for AQP4-IgG		Negative test (or tests) for AQP4-IgG
No alternative diagnoses		No alternative diagnoses
Six core clinical characteristics are:		
(1) Optic neuritis	(2) Acute myelitis	
(3) APS	(4) Acute brain-stem syndrome	
(5) Symptomatic narcolepsy or acute diencephalic syndrome characteristic of NMOSD	(6) Symptomatic cerebral syndrome	
In our case, patient was AQP4-IgG positive, and out of the core clinical characteristics, had APS		



Figs 1A and B: Brain MRI, at the level of medulla; (A) Altered signal intensity area appearing hyperintense on FLAIR images is seen involving dorsal aspect of left half of medulla involving AP; (B) Altered signal intensity area appearing hyperintense on T2W images is seen involving dorsal aspect of left half of medulla involving AP

It was suggestive of involvement of AP, pointing toward the possibility of NMOSD. A CSF sample was sent for evaluation, and AQP4 autoantibodies were detected. First-line therapy consists of 3–5 days of high-dose intravenous methylprednisolone at a dose of 1 gm per day.[13]

Limited retrospective and uncontrolled data suggest that patients with severe attacks of NMOSD do better if plasma exchange is started early as an adjunctive therapy with glucocorticoids. As soon as the diagnosis of NMOSD is made, we advise long-term immunotherapy (rituximab) for patients with seropositive NMOSD to lower the risk of relapse (Table 2).

Following the current NMOSD treatment guidelines, the patient was administered an initial course of intravenous methylprednisolone (1 gm) for acute symptoms, resulting in partial relief of vomiting and improvement in ventilatory settings. Subsequently, he received a course of IVIg at a dose of 2 gm/kg divided into five infusions (Fig. 2).

The patient responded well to this intensive treatment regimen, with no further vomiting, hiccups, or ventilatory support. To prevent further relapses, rituximab was started with two 1 gm infusions separated by a 2-week interval. This was followed by a 1 gm rituximab infusion 6 months later, along with an MRI scan of the brain, which showed no enhancements. The patient remains in regular follow-up and is asymptomatic.

Review of Literature

Cases of NMOSD were searched across the literature and summarized according to age, sex, presenting complaints, CNS involvement, radiological findings, autoantibodies, and treatment (Table 3).

Table 2: Treatment protocol[13]

Treatment	*Recommendation*
Glucocorticoid therapy	Initial treatment with high-dose intravenous methylprednisolone (1 gm daily for 3–5 consecutive days), with low threshold for plasma exchange
Adjunctive plasma exchange	For severe symptoms or poorly responsive cases to glucocorticoids, consider plasma exchange. Plasma exchange may be more effective if started early as adjunctive therapy with glucocorticoids
Indication for preventive therapy	Long-term immunotherapy (e.g., eculizumab, inebilizumab, satralizumab, or off-label rituximab) recommended for seropositive NMOSD patients. For seronegative NMOSD, long-term immunotherapy is suggested
Choice of agent	Eculizumab, inebilizumab, or satralizumab preferred for seropositive AQP4-IgG patients, if available. Alternative immunotherapies (rituximab, tocilizumab) can be considered for NMOSD patients meeting diagnostic criteria with or without AQP4-IgG seropositivity
Duration of preventive immunotherapy	Typically continued for at least 5 years for seropositive AQP4-IgG patients due to high risk of relapse. Optimal drug regimen and treatment duration yet to be determined; lifetime treatment may be considered
Prognosis	NMOSD presents a natural history of stepwise deterioration due to recurrent attacks, leading to accumulating deficits in vision, motor, sensory, and bladder functions. Long-term disability and mortality rates are high. Acute and preventive treatment with immunotherapies likely improve long-term outcomes, although unproven

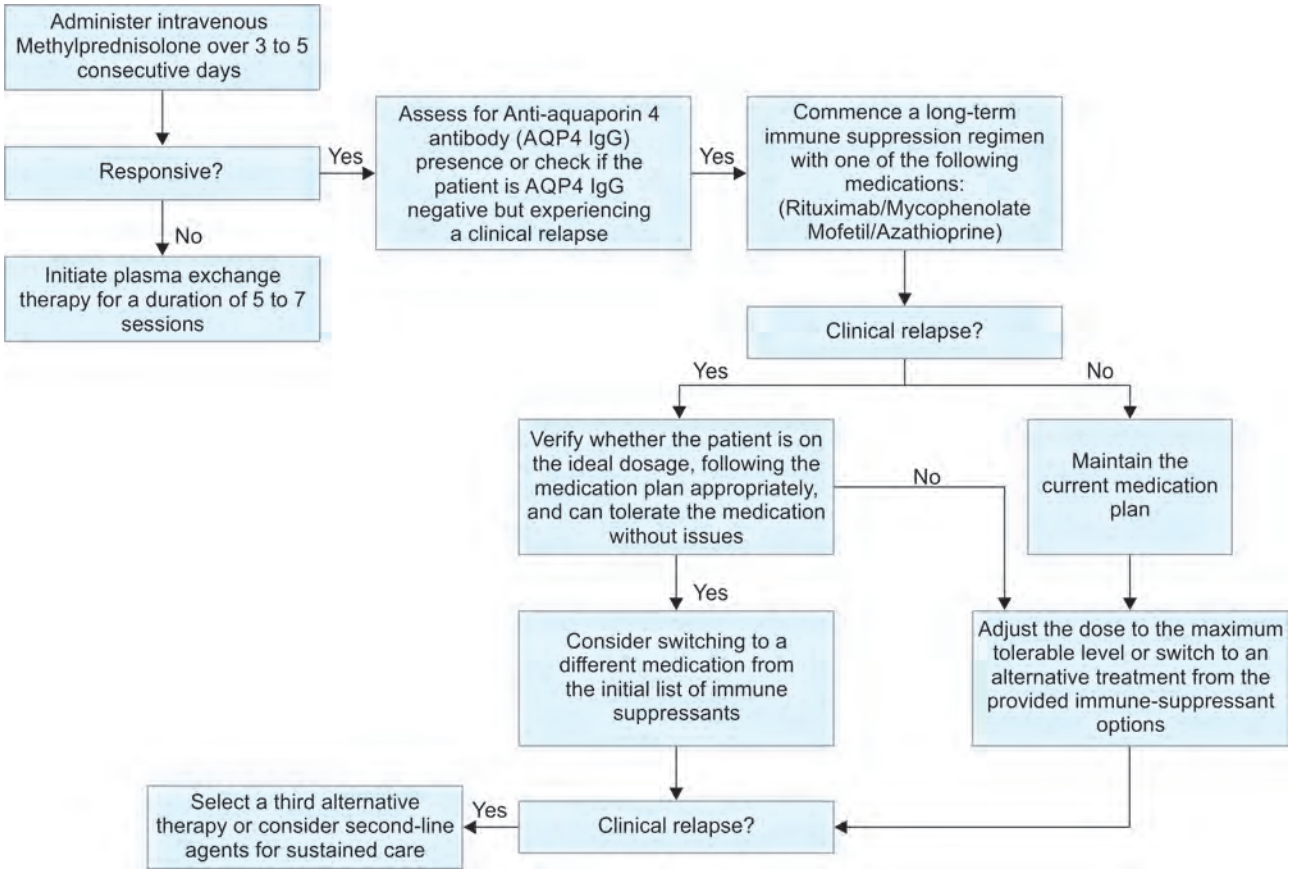


Fig. 2: Treatment algorithm for management of NMOSD[14]

Table 3: Review of literature

Reference number	*Age and sex*	*Presenting complaints*	*CNS involvement*	*Radiological findings*	*Autoantibodies*	*Treatment*
Raj et.al., 2023[9]	25 years old Female	Persistent nausea, vomiting, hiccups for 3 weeks	Absent	Hyperintense lesion in dorsal medial medulla at AP in T2 FLAIR	AqP4-IgG, MOG Negative	Methylprednisolone
Lucas et.al., 2023[15]	38 years old Female	Intractable hiccups, vomiting, headache, back pain, ascending paresthesia	Present	Suggestive of LETM	AQP4-IgG Positive MOG Negative	Methylprednisolone
Shrestha and Kharel, 2022[12]	26 years old Female	Nausea, vomiting, hiccups, slurred speech, headache	Present	Hyperintense lesion in inferior dorsal medial medulla at AP in T2 FLAIR	AQP4-IgG Positive MOG Negative	Methylprednisolone
Zhang et al., 2022[11]	41 years old Male	Intractable hiccups, vomiting, headache, back pain, ascending paresthesia	Present	Longitudinally extensive T2 hyperintensities from C2 to T8 without enhancement	AQP4-IgG Positive	Methylprednisolone plasma exchange IVIg
Khan et al., 2022[1]	33 years old Female	Fever, hypersomnolence, altered mental status, difficulty walking	Present	Bilateral, non-enhancing, patchy fluid-attenuated inversion recovery (FLAIR) hyperintensities in the antero inferomedial thalamus extending to the mammillary bodies	AQP4-IgG Positive	Methylprednisolone plasmapheresis
Chan and Vorobeychik et al., 2020[8]	44 years old Female	Daily intractable nausea, vomiting, hiccups for 1 month	Absent	Enhancement in AP in T2 FLAIR	AQP4-IgG, MOG Negative	Methylprednisolone followed by rituximab maintenance therapy
Apetse et al., 2019[10]	28 years old Female	Persistent vomiting, abdominal pain, hiccups	Present	Hypersignal lesion in the bulbar more lateralized on the left in T2 FLAIR	AQP4-IgG Positive	Methylprednisolone
Wang et al., 2018[6]	43 years old Female	Intractable nausea, vomiting for 2 months, optic neuritis, lower limbs weakness, parasthesia, urinary retention	Present	Hyperintense lesions on T2-weighted images (T2WI) of the medulla and cervical cord	AQP4-IgG Positive	Methylprednisolone

Conclusion

This case emphasizes the importance of considering neurological conditions as a cause of refractory gastrointestinal symptoms. Despite initial treatment for possible gastritis and hiatus hernia, persistent symptoms led to the diagnosis of an unusual presentation of NMOSD, involving the AP. Prompt recognition and timely treatment resulted in symptom resolution. Interdisciplinary collaboration between gastroenterologists and neurologists is crucial for accurate diagnosis and management of complex cases. Long-term follow-up and maintenance therapy are essential to prevent relapse and ensure optimal patient outcomes. This case highlights the necessity for a comprehensive approach in managing atypical presentations of NMOSD, emphasizing the importance of early recognition, intervention, and tailored treatment strategies.

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Primary Hypertrophic Osteoarthropathy—A Rare Cause of Joint Pain

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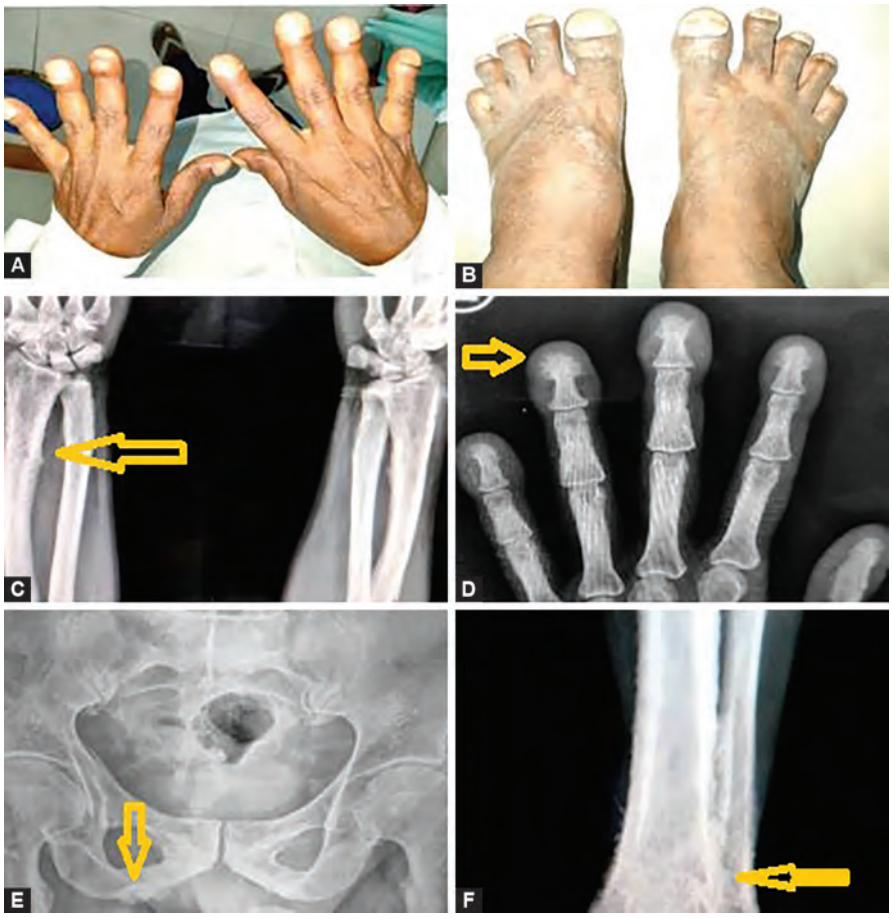
A 48-year-old male displayed pain along with swelling of small joints of the hand and feet, along with low back pain, for the last 7–8 years. The joint pain was not associated with early morning stiffness or constitutional symptoms. On physical examination, all fingers and toes had bulbous enlargement and clubbing (Figs 1A and B). There were no skin changes and no motion restriction of any joint. Other systemic examination was normal. The routine investigations along with inflammatory markers and immunological tests were normal. A radiograph of bones showed periosteal changes in long bones as well as small bones of the hand and feet (Figs 1C to F) suggestive of hypertrophic osteoarthropathy (HOA). The patient was evaluated for secondary causes of HOA, and all his reports were within normal limits. The patient was diagnosed with incomplete primary hypertrophic osteoarthropathy (PHOA) on the basis of clinical and radiological features. The patient was given an infusion of 4 mg of zoledronic acid, along with etoricoxib, once daily. The patient responded to treatment with significant reduction in pain at 4 weeks and etoricoxib was stopped.

Primary hypertrophic osteoarthropathy, which accounts for 3–5% of all HOA, is a condition characterized by digital clubbing, periosteal new bone growth, and arthritis.[1] There are three clinical forms for this autosomal dominant or recessive condition: (1) Complete form, which includes both periostosis and pachydermia; (2) incomplete form, which includes periostosis but lacks pachydermia (as observed in the patient as well); and (3) fruste form, which includes prominent skin changes and minimal periostosis.[2] Few similar cases have been reported in the literature previously.[3] The primary type typically begins quietly in adolescence and progresses gradually. Sixty percent of cases have familial involvement, which was absent in the patient. Mutations in the gene *PGE2* are linked to cause PHOA and cause the periosteal modifications including dimetaphyseal and epiphyseal abnormalities. The patient's life expectancy is normal and prognosis is good, but because of increased soft tissue bulk, they require routine monitoring for ptosis, deafness, kyphosis, osteonecrosis, and carpal tunnel syndrome.[4] Management is symptomatic using nonsteroidal anti-inflammatory drugs (NSAIDs) and bisphosphonates. There is no permanent cure for this condition.



Figs 1A to F: (A, B) Soft tissue bulbous swelling of the fingers of the hands and feet; (C) Forearm shows a bilateral symmetrical smooth periosteal reaction along the diaphysis and distal metaphysis of the radius and ulna bones; (D) The hand demonstrates a thick periosteal reaction surrounding several metacarpal shafts and proximal phalanges, with terminal acro-osteolysis and soft tissue swelling; (E) The hip shows a bilateral symmetrical thick fluffy periosteal reaction along the ischial tuberosity; (F) The leg shows a thick smooth periosteal reaction along the metadiaphyseal tibia and fibula, with periosteal bone thickening

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POINT OF VIEW

Jail Syndrome

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Abstract

"Jail syndrome" is a condition emerging in individuals of high profile and status facing legal repercussions due to involvement in corruption or other illegal activities. This syndrome encompasses a spectrum of symptoms, including anxiety, panic attacks, and psychosomatic symptoms such as chest pain, headache, hysterical attacks, and many more with minimal positive investigations and other evaluations. Its prevalence is notably high among high-profile individuals such as politicians and bureaucrats in contexts marked by corruption, especially in India. The onset of symptoms typically occurs in response to arrest or legal proceedings, complicating clinical diagnosis due to the lack of identifiable organic causes. Distinguishing jail syndrome from genuine medical conditions such as acute coronary syndromes is crucial for effective management. The syndrome reflects a circumstantial diagnosis influenced by the psychological stress of legal consequences, necessitating a careful assessment of both psychological and physiological health. Large-scale studies, research, and data analysis are essential to validate jail syndrome as a recognized clinical diagnosis. Jail syndrome is a self-explanatory clinical diagnosis to convey the onset of symptomatology, etiopathology, and treatment strategy in a person involved in illicit activities with history of charges, imprisonment, or sentencing to jail. Most important is to rule out organic disease because many times organic causes such as acute coronary syndrome, diabetes mellitus (DM), and hypertension (HT) are present. Very important is that large-scale data and their scientific analysis are required to confirm and recognize it as a definite clinical diagnosis of "jail syndrome." No doubt the term jail syndrome is self-explanatory and conveys the message we want to convey.

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Introduction

Jail syndrome is self-explanatory, conveying etiopathology and to some extent a line of treatment. As the name suggests, it is related to the fear of being arrested or when an arrest warrant is issued or when already sentenced to jail (prison) or when a person is already in jail. With this circumstantial history and evidence, there are symptoms ranging from mild anxiety to severe panic attacks or hysterical unconsciousness, or most commonly chest pain of varying degree, and the sole purpose is to get rid of jail or arrest.

This syndrome is prevalent across the globe wherever corruption exists, and rules and regulations have many pitfalls. Jail syndrome has persisted since ages, is very common in India, and the exact incidence is not known, but commonly seen among certain high-profile groups such as bureaucrats, politicians, millionaires, and individuals of high social status arrested or caught red-handed and when an arrest warrant is issued or imprisoned by legal authorities due to involvement in corruption, antisocial, and illicit activities such as money laundering, rape, terrorism, riots, or murders. As the name suggests, jail syndrome starts with the fear of going to jail or after going to jail or in between legal hearings.

Discussion

Definition: "Jail syndrome" is the constellation of a wide variety of symptoms ranging from chest pain, unstable angina, hypoglycemia, altered sensorium or hysterical attacks or nausea, severe headache, and the list is endless with minimal signs and positive investigation in favor of it.

Most common symptoms are chest pain, dyspnea, uneasiness, chest discomfort, headache, unconsciousness, backache, and abdominal pain as these symptoms are subjective in nature and severity and intensity are not measurable. Most of the time biochemical parameters are normal, and tests that are of subjective variation such as endoscopy findings or psychiatric syndromes may be positive or made positive.

Onset of symptomatology is sudden and severe and occurs as soon as they are arrested by legal authorities or exposed to legal repercussions. These symptoms are not easily measurable and does not fit into the frame of any established medical conditions, and most of the medical tests are negative and most common is chest pain labeled as "unstable angina." We know the deleterious consequences of unstable angina sometimes leading to sudden cardiac death; and because of this reason, legal agencies are afraid of health issues, and many times they are prosecuted in the court of law for not taking care of the health of the accused, and victims take advantage of this lacuna and enjoy the benefit of doubt.

Symptomatology varies from time to time depending on the severity of civil or criminal charges and ranges from severe anxiety, panic attacks, paranoia, stress, perspiration, and may exhibit certain behavioral or psychological distress patterns in response to the seriousness of the litigation.

While dealing with jail syndrome, the most important aspect is not to miss any organic disease because most of these persons are living with stress and suffering from lifestyle diseases such as diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), and sometimes are addicted to various agents. It is also a well-known fact that many patients irrespective of class or profile, guilty or innocent, may develop real organic syndromes right from anxiety to panic and acute coronary syndromes as well. So, it is very important to exclude organic syndromes and then and only then label the patient as suffering from jail syndrome.

Jail syndrome is more of a circumstantial diagnosis with varied observed behavior rather than a recognized medical pattern, and history surrounding the occurrence is very important. "Jail syndrome" is a clinical diagnosis, reflecting psychological and behavioral patterns arising in response to the pressure and consequences associated with legal charges. The most important observation is treatment seeking behavior and the dire need of medical assistance, to get transfer from jail to hospital maybe in intensive care units (ICU). To get these paroles, bribe, pressure politics, threat to transfer, or kidnapping of the family member of the jail officials or health care professionals are also used.

"Ganser syndrome" is a rare and similar but controversial entity; first described by Sigbert Ganser in 1898, also known as "prison psychosis" as it was first observed in prisoners. Persons suffering from Ganser syndrome have factitious symptoms of physical or mental

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illness while they are not really sick, and behavior may mimic classical schizophrenia.

We know that factitious disorders are considered mental illnesses as they are associated with emotional problems. Short-term episodes of odd behavior such as other serious mental disorders, confused, absurd statements, hallucinations, and the classic symptom of Ganser syndrome is "*vorbeireden*" which means a person gives nonsense answers to simple questions; "hysterical paralysis" and loss of memory of the events are other common symptoms. Usually, these patients are willing for painful, risky, and costly investigations, procedures, and surgeries to gain sympathy and special attention during the hearings in the court of law.[1]

There are other well-known syndromes known to occur in prison, such as Stockholm syndrome, SHU syndrome, and postincarceration syndrome.

- Stockholm syndrome defined by Cleveland Clinic is a psychological response to captivity, and a prisoner or a victim develops a bond, positive feelings toward their captor such as empathy, love, or sympathy. Otherwise, they may develop negative feelings toward authority, flashbacks, and difficulty in concentrating.[2]
- SHU syndrome coined by Stuart Grassian, a psychiatrist, described the cognitive mechanisms developing in prisoners in isolation and include hyperresponsivity, hallucinations, illusions, panic attacks, and paranoia.[3]
- Postincarceration syndrome is like "post-traumatic stress disorder" (PTSD), which develops after experiencing a shocking, scary, or dangerous event. People who have been incarcerated, even after serving their sentence, the horrible environment damages the mental health in prisons and may develop further negative effects.[4]

The judiciary does not excuse these people from criminal liability involved in corruption or illegal activities, whatever may be the symptoms of "jail syndrome" and does not exempt them from legal actions though consideration for medical and mental health evaluation exists in some jurisdictions.

Most often, treatment consists of shifting to hospital from jail and various tests are performed for an indefinite length of time, till bail. As soon as bail is granted, miracles happen just like glucose infusion in hypoglycemics, and they become alright.

Multiple consultations are taken, and most of the consultants' diagnoses do not match each other, and dilemma and confusion over the diagnosis persist, and benefit of doubt is given to the accused.

Police officials, judiciary, and doctors treating (helping) them are rewarded with promotion, bribes, and appointments of choice while those who are not helping (making correct diagnosis) are punished.

At the back of all these symptoms, the sufferers usually really have HT, dyslipidemia, DM, and high risk for CAD and are under stress.

Conclusion

Jail syndrome is a self-explanatory clinical diagnosis to convey the onset of symptomatology, etiopathology, and treatment strategy in a person involved in illicit activities with history of charges, imprisonment, or sentencing to jail.

Most important is to rule out organic disease because many times organic causes such as acute coronary syndrome, DM, and HT are present.

Very important is that large-scale data and their scientific analysis are required to confirm and recognize it as a definite clinical diagnosis of "jail syndrome."

No doubt the term jail syndrome is self-explanatory and conveys the message we want to convey.

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Henrik Dam and Vitamin K

Jayant Pai-Dhungat

Henrik Dam. Maldives, 19**

15th International Congress on Hemostasis and Thrombosis. Dominican Republic, 1997

Carl Peter Henrik Dam (1895–1976), Danish biochemist, was born in Copenhagen; he obtained his doctorate in 1914 from the University of Copenhagen. During the course of his education, he studied under Pregl in Austria in 1925 and with Paul Karrer in Switzerland (1935).

Working in the faculty of University of Copenhagen from 1923, he attained professional rank in 1929. Dam was studying synthesis of sterols and cholesterol in hens. While he fed hens on a synthetic diet, he noted small hemorrhages under the skin and in the muscles, which looked like hemorrhages that develop in scurvy; hence, he added lemon juice to the diet, which did not make any difference. Dam tried other food additives by adding one or other of the vitamins that were found to be essential at the time. None worked, and he concluded that a vitamin hitherto unknown was involved. Dam showed that an addition of hempseed countered the bleeding and considered that the seed contained the principle. Since it seemed to be necessary for coagulation of blood, he named it vitamin K for *koagulation* (German) in 1934.

Within a few years, American biochemists led by Edward Doisy worked out its formula.

Dam crossed the Atlantic in order to give a series of lectures in the United States and Canada in 1940. While he was there, Nazi armies occupied Denmark. Dam therefore remained in the US during the war, working chiefly at the University of Rochester.

During this period of exile, he and Doisy shared the 1943 Nobel Prize in Medicine or Physiology. He was appointed professor of biochemistry at the Polytechnic Institute in Copenhagen in absentia. In 1946, he returned to liberated Denmark and in 1956 became head of the Danish Research Institute. Henrik Dam died in 1976 at Copenhagen aged 81.

International Conference on Nutrition, Rome, 1992. Stamp—Bangladesh, 1992

Form of vitamin K (vitamin K_1) is synthesized by plants and vitamin K_2 is synthesized by bacteria in the mammalian intestines, which mainly produce vitamin K that the body needs. A synthetic vitamin K precursor menadione (vitamin K_3) is used as a vitamin supplement. Absence of intestinal bacteria, low levels of vitamin K in the mother's milk, may result in bleeding in infants, which can be prevented by the administration of vitamin K shortly after birth.

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Chronic Stable Angina

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Dear Sir,

We read the review article "Stable angina pectoris: a review of pathophysiology, diagnosis, and its management"[1] with interest and appreciate a review on such an important issue. We would like some suggestions to make this review more informative and evidence-based.

First, we suggest that the definition of chronic stable angina should be as mentioned in all textbooks and guidelines as "chest pain or retrosternal discomfort that may radiate to the left arm, neck, or jaw and is precipitated by physical exertion or emotional stress or other stress relieved by rest or with nitroglycerin,"[2] rather than the definition mentioned by the authors, which is a little bit confusing and does not mention rest as a relieving factor and includes pain at rest, which signifies acute coronary syndrome (ACS) rather than chronic stable angina.

Second, the review article mentions that high-sensitivity cardiac troponin concentration is a reliable predictor of obstructive coronary artery disease (CAD) in patients with suspected stable angina, but the existing evidence suggests that high-sensitivity cardiac troponin concentration is a reliable predictor of cardiac necrosis or damage to myocardium in ACS rather than obstructive CAD in patients with suspected stable angina. Evidence suggests doing troponin T or troponin I if there is a clinical suspicion of CAD instability, and if increased, management should follow the guidelines for ACSs management.[3] Once we label the patient as having chronic stable angina, it signifies obstruction in coronaries without any necrosis of myocardium, so high-sensitivity cardiac troponin concentration cannot be an indicator of only obstruction without necrosis or damage to myocardium.

Third, the review article mentions that the use of statins to achieve an optimal low-density lipoprotein cholesterol (LDL-C) level of <70 mg/dL is recommended, but the existing evidence suggests that chronic stable angina is considered at very high cardiovascular (CV) risk, so LDL-C levels of <55 mg/dL (not <70 mg/dL) or a reduction by at least 50% of LDL-C from baseline is the target with high-intensity statin therapy. In many patients, only high-intensity statin therapy is not sufficient to achieve the recommended LDL-C goals or may have side effects and intolerance, so a combination of nonstatin lipid-lowering drug therapy is required in the form of ezetimibe, bempedoic acid, or proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i).[3]

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