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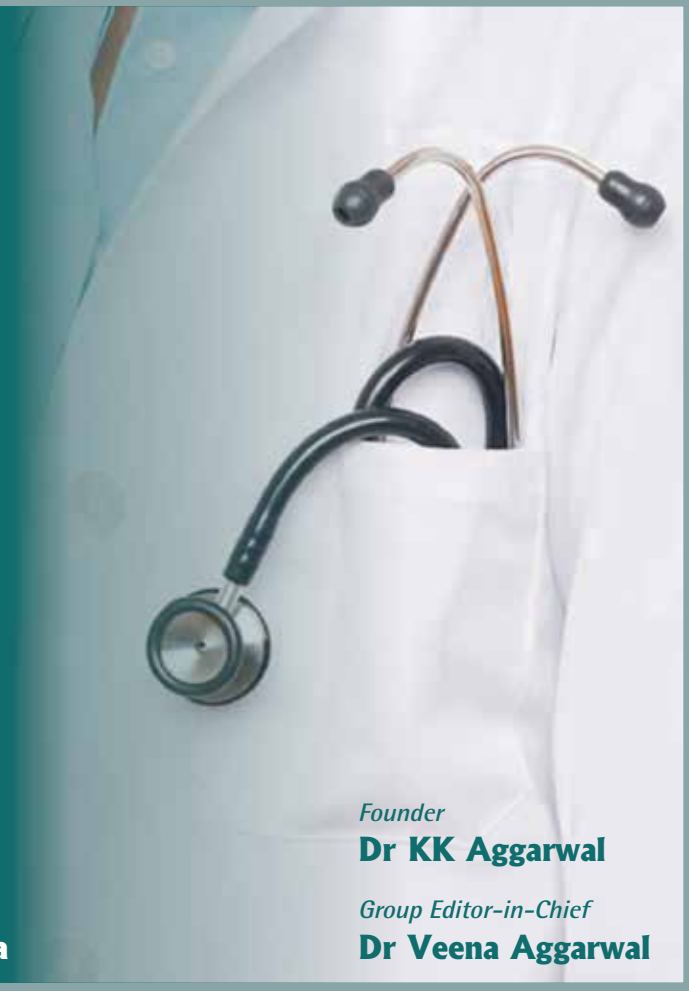

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EDITORIAL

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Gestational Diabetes Pattern and Risk of Incident Diabetes

Women who experience gestational diabetes mellitus (GDM) in the first pregnancy are at a 4.35-fold increased risk of developing new-onset type 2 diabetes compared to women who did not have GDM. This risk increased 7.68-folds if GDM occurred in the second pregnancy only or 15.8-folds in women with a history of GDM in both pregnancies. These findings from a study of nearly half a million women were published May 1, 2024 in *JAMA Network Open*[1].

This retrospective cohort study aimed to compare the odds of incident diabetes among women with GDM in the first pregnancy, second pregnancy, and in both pregnancies in comparison to women without GDM in either pregnancy. The Quebec health administrative and birth, stillbirth, and death registries were used to procure data of women who had two singleton deliveries between April 1990 and December 2012. Data were examined in 2023 between July and December.

The study included 431,980 women who had two singleton deliveries; the mean age at the second delivery was 30.1 years, and the mean time elapsed between deliveries was 2.8 years. None of the participants had a history of diabetes. Of these women, 86.4% (n = 373,415) were European by heritage, and 18.2% (n = 78,770) belonged to the highest quintile of material deprivation. Over a median follow-up duration of 11.5 years, the incidence of GDM was 2.5% in the first pregnancy, 3.7% in the second pregnancy, and 1.9% in both pregnancies.

Women with GDM only in their first pregnancy had nearly 5-folds increased likelihood of developing diabetes with hazard ratio (HR) of 4.35. The risk of future diabetes increased by more than 7.5 times in women with GDM in their second pregnancy only with HR of 7.68. Among those who had GDM in both pregnancies, the risk of diabetes increased almost 16 times with HR of 15.8. Gestational diabetes in the second pregnancy increased the hazard of incident diabetes by 76% compared to GDM in the first pregnancy. The risk was increased 3.63-folds in case of GDM in both pregnancies versus first pregnancy-only GDM.

This study provides evidence of how GDM occurrence in the first, second, or both pregnancies impacts diabetes risk compared to women with no GDM in either pregnancy. It reveals that GDM only in the second pregnancy poses a higher risk of incident diabetes than GDM in the first pregnancy alone. Having GDM in both pregnancies greatly increases the risk of developing diabetes compared to having GDM in only one pregnancy.

The findings underscore the importance of close monitoring and managing GDM, especially in subsequent pregnancies, to mitigate the long-term risks of developing diabetes. Not just the number of times of occurrence of GDM, the specific pregnancy affected must also be considered for comprehensive risk assessment and formulating tailored management strategies for better clinical outcomes.

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Person-Centered Care: Inspiration from the Upanishads

"*If someone among human beings is healthy, prosperous, a lord over others, fully endowed with all human enjoyments, that is the highest joy of human beings.*"

—Brihadaranyaka Upanishad IV. 3:33.

Our aim, as physicians, is to improve the health, and joyfulness, of our citizens. To achieve this, we need to be person-centered.

"*Two companion birds sit together in the shelter of the same pippala tree. One of them is relishing the taste of the tree's berries, while the other refrains from eating and instead watches over His friend.*"

—Śvetāśvatara Upaniṣad 4.6; Mundaka Upanishad III 1:1.

This verse, found twice in the Upanishads[1], underscores the importance of individuality. As physicians, we must understand that each person presenting to us, for care and comfort, has different requirements. Each person responds differently to suggested therapy as well.

The Brihadaranyaka Upanishad relates the story of Prajapati and his descendants, the Gods, human beings, and demons. All three came to him, requesting "Father, teach us". He spoke the same syllable, "da", to all, and asked if they had understood. All three replied in the affirmative. The Gods said, be "self-controlled" (*damyata*), the humans said, "Give" (*daana*), and the demons learnt "Be compassionate" (*dayadhvam*). To all, Prajapati said, "Om, you understood".

The same syllable, this means, has three meanings, all of which are correct, based upon the context of the person hearing it. The Upanishad summarizes this anecdote, advising its readers to "practice this set of three, self-control (*dama*), giving (*daana*), and compassion (*daya*) (V. 2:1-3).

This, in essence, is the noesis of person-centered care. From the Upanishads, we learn the importance of being person-centered[1]. This inspiration, reinforced in the *Charaka Samhita*[2], and the Thirukkural[3], is the foundation of good clinical care. Each person seeking medical care may have a different understanding of what we counsel or explain. We should be accepting of each other's point of view; and be able to relate to our patients in a personalized manner.

These verses serve as an inspiration to respect our patients, and their attitudes, preferences, and values, as we care for them. It is important, at the same time, not to forget our responsibility towards them. Responsible person-centered care calls for taking "on the responsibility of ensuring that the person with diabetes is offered all relevant information, in an understandable manner, so that he or she can take part in a shared decision-making process, which offers the potential for achieving optimal therapeutic outcomes, without ignoring his or her biopsychosocial context"[4].

This is highlighted in the Upanishads as well.

"*The good is one thing and the pleasant another. These two, having different ends, bind a man. It is well with him who chooses the good. He who chooses the pleasant misses the true end.*"

—Katha Upanishad II:1.

We should be able to explain our suggested diagnostic and therapeutic options to our patients, in a simple, easy to understand manner. We also need to work on our trustworthiness and perception management, as

our profession navigates the challenges of working in the modern world. We may take consolation from the fact that such concerns are not new.

"*With juggleries of the non-self-doctrine, with false examples and causes,*

Going astray, the world does not know, the difference between knowledge ignorance."

—Maitri Upanishad VII:8.

"*Abiding in the midst of ignorance, thinking themselves wise and learned, fools go aimlessly hither and thither, like blind led by the blind*."

—Katha Upanishad II:5.

The way forward is also taught by the Upanishads. We need good preceptors, and we need to be good pupils, too.

"*When taught by a man of inferior understanding, this Atman cannot be truly known, even though frequently thought upon. There is no way (to know it) unless it is taught by another (an illumined teacher), for it is subtler than the subtle and beyond argument*."

—Katha Upanishad II:8.

"*Seize as your bow the great weapon of the Upanishad, and set in it an arrow sharpened by contemplation.*

Draw it with a mind that has attained the nature of that. The target is the imperishable: pierce that."

—Mundaka Upanishad II. 2:3.

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■■■■

REVIEW ARTICLE

Systematic Review of the Role of Albuminuria on Kidney Function in Type 2 Diabetes

THAI HAU KOO*, MAFAUZY MOHAMED*, XUE BIN LEONG*

ABSTRACT

Objective: This systematic review explores the impact of albuminuria on renal function in patients with type 2 diabetes (T2D), assessing its role in diagnosing diabetic kidney disease (DKD) and its correlation with reduced glomerular filtration rate (GFR). **Materials and methods:** A systematic review was conducted following PRISMA guidelines. Searches in PubMed, Embase, Cochrane Library, and Medline included studies from 2019 to 2023. Inclusion criteria were adults (≥18 years) with T2D, studies assessing impact of albuminuria on kidney function, including randomized controlled trials, observational studies, or meta-analyses. Primary outcomes included albuminuria progression, renal function decline (estimated GFR [eGFR] or creatinine clearance), and DKD progression. Secondary outcomes evaluated the safety and tolerability of interventions managing albuminuria in T2D patients. Two reviewers independently extracted data and assessed risk of bias. **Results:** From 1,748 records, nine studies involving 9,91,285 patients were included. Studies consistently showed higher albuminuria levels to be significantly associated with reduced eGFR and increased DKD progression risk. **Conclusions:** Our findings underscore albuminuria as a crucial indicator of kidney damage and eGFR as a key marker for DKD severity in T2D patients. This review highlights the need for patient-centered care in managing T2D to reduce renal complications and calls for further research to comprehensively understand DKD outcomes.

Keywords: Albuminuria, kidney function, glomerular filtration rate, type 2 diabetes, kidney disease, outcomes

Concerns about the possible rise in demand for health care services, mainly specialized nephrology treatment, have been expressed due to the greater frequency of chronic kidney disease (CKD) associated with global population aging. Declining estimated glomerular filtration rates (eGFR) frequently complicate type 2 diabetes (T2D). About 35% of adult patients who have been diagnosed with T2D have CKD, and they are more vulnerable to end-stage kidney disease (ESKD) owing to diabetic nephropathy[1]. Various factors have been considered to be reasons for the declining eGFR among patients who have T2D and the eventual progress of the condition to ESKD. However, the courses of treatment for the conditions have been heterogeneous and complex due to the diverse characteristics of patients and the specificity of their conditions[1].

The severity of CKD is commonly evaluated using the eGFR, a measure of kidney function, and the albuminuria level, a sign of kidney damage. To customize CKD care and direct optimal resource allocation, including faster referral of patients at higher risk of CKD progression, both eGFR and albuminuria have proved helpful in developing risk-stratification techniques[2]. The most common method used to identify albuminuria is the urine albumin-to-creatinine ratio (UACR). The typical UACR level in spot urine specimens is <30 mg/g[3]. The urine total protein-to-creatinine ratio or UPCR (mg/g), is often <0.2 in adults[4]. Many situations, such as illness, stress, pregnancy, nutrition, exposure to cold temperatures, and physical activity, can cause a brief increase in urine protein levels. UPCR testing procedure can provide additional information on kidney function. It is highly accurate and can be used to diagnose kidney illness and monitor diseases that damage the kidneys[5,6].

The relationship between albuminuria and proteinuria is well-documented in CKD. Albuminuria often accompanies proteinuria, significantly when 24-hour proteinuria surpasses 500 mg[2]. This relationship is

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crucial for understanding CKD progression. In cases of glomerular damage, there is an increase in glomerular permeability to macromolecules, which raises the amount of plasma proteins excreted in the urine. Albumin, with a molecular weight of about 69 kD, is the most common protein expelled in urine under severe glomerular damage conditions. It often makes up over 50% of the urine proteins. Consequently, albuminuria is the characteristic marker of glomerular proteinuria.

In cases of diabetic glomerulosclerosis, increases in albuminuria indicate disease progression, even when the proteinuria rate is within the normal range (e.g., <200 mg/24 h)[4]. This is a prime example of using albuminuria to monitor the progression of early glomerular injury. Urine albumin at concentrations <1 mg/dL can be detected using immunoassays, which help measure low-level changes in albuminuria. These assays show that the standard 24-hour urine albumin excretion is <30 mg albumin/g creatinine[4]. Albuminuria rates 30 to 300 mg/g creatinine are termed microalbuminuria. Macroalbuminuria is the term used to describe albuminuria rates above this level. When diabetic nephropathy reaches the macroalbuminuria level, albumin takes over as the predominant urinary protein, and proteinuria follows albuminuria. The benefit of evaluating albuminuria over proteinuria usually disappears at that time[3].

A slower decline in the eGFR and an improvement in the renal prognosis are linked to the degree of proteinuria in glomerular disease, which is intimately connected to CKD progression. Renal function in eGFR initially declined in response to improvements in albuminuria and proteinuria[6]. In addition, rises in the level of urinary proteins, which are common in cases of albuminuria, have been related to increased risk of developing coronary heart disease and creating other health problems in patients with CKD and T2D[2]. The link between excessive proteinuria and cardiovascular risks plausibly holds stress on the point of early patient assessment and effective strategy for treating CKD patients[7]. Therefore, monitoring eGFR and albuminuria is essential for CKD risk stratification and developing targeted therapeutic strategies. Early intervention and precise monitoring can help manage CKD progression, mitigate associated cardiovascular risks, and improve patient outcomes.

This study aims to identify the impact of albuminuria on kidney function, specifically its correlation with eGFR, among patients with T2D. By examining existing literature, we seek to clarify the role of albuminuria in predicting DKD progression and highlight the importance of routine albuminuria assessment in clinical practice.

MATERIALS AND METHODS

Subjects

The selection of relevant articles began with screening based on exclusion and inclusion criteria. Participants eligible for inclusion were adults aged 18 or older diagnosed with T2D. The inclusion criteria comprised articles, published in English, that conducted qualitative and quantitative analyses, articles discussing the impact of albuminuria on kidney function in patients with T2D, and studies published between 2019 and 2023. Included studies assessed interventions targeting albuminuria and its effect on kidney function. The exclusion criteria encompassed studies falling outside the specified time interval (before 2019 or after 2023) and studies not directly addressing the association between albuminuria and kidney function in patients with T2D.

Only studies meeting the criteria of quantitative and qualitative analysis, observational studies, randomized controlled trials, and identification of the interaction between proteinuria and albuminuria, and its impact on kidney function were included in this research. The selected studies focused on the relationship between abnormal renal function, decreased eGFR, and enhanced UACR. In the pilot review stage, all retrieved papers were first brought into Endnote 20, and a first de-duplication of the studies was done in it. After retrieving the complete text and any supplementary files, two independent reviewers (THK and XBL) separately assessed the titles and abstracts, per the mentioned eligibility criteria, using the Rayyan Software. Email correspondence was used to inquire about missing data from the corresponding authors of pertinent articles. For the current review, only publications that were available in full text were taken into account.

Study Design

The a priori protocol was created and was listed under PROSPERO CRD42024542353 in the International Prospective Register of Systematic Reviews. For this review, we followed Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) reporting criteria to comprehensively analyze the qualitative and quantitative research examining the relationship between albuminuria and kidney function in patients with T2D. Figure 1 illustrates the search process flow diagram per the PRISMA guidelines.

The search keywords for this research study were initially selected based on database exploration. Electronic databases, including Embase, PubMed, global clinical

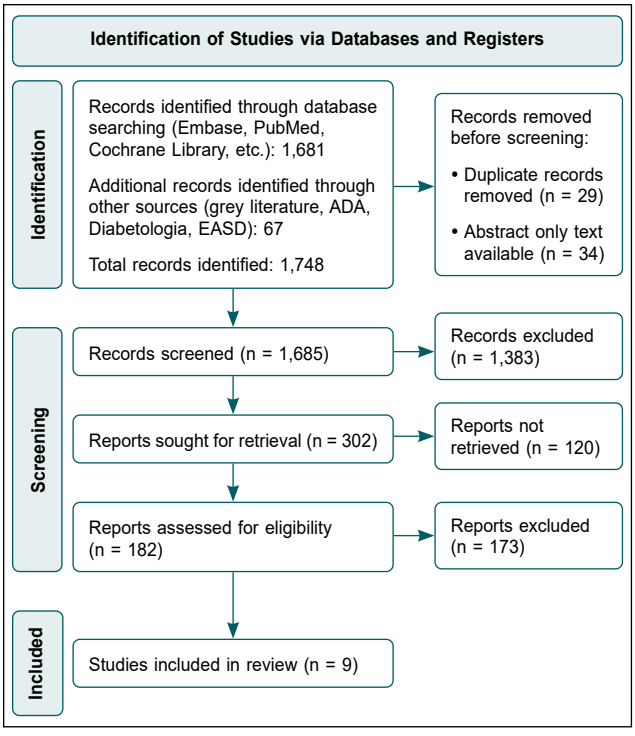

Figure 1. Summary of study search and selection process (PRISMA flow chart).

trials, Cochrane Library (incorporating the CENTRAL - Cochrane Central Register of Controlled Trials), and Medline were utilized. CENTRAL and Medline were targeted explicitly for observational and clinical studies investigating the interaction between albuminuria and kidney function in patients with T2D. We also conducted efforts and attempts to screen the references and citations of published papers for any possible additional studies. Only studies published in the English language were considered for inclusion.

The search strategy was optimized and validated in PubMed and then adapted in other databases using keywords, their synonyms, abbreviations, and MeSH terms for "Urine Protein Creatinine Ratio", "Urine Albumin Creatinine Ratio", "Proteinuria", "Albuminuria", "Glomerular Filtration Rate", "eGFR", "Diabetic Kidney Diseases", "Chronic Kidney Disease", "Outcomes", "Type 2", "Diabetes Mellitus", and "T2DM". Additionally, grey literature was examined using open grey literature databases, and extra databases were identified for grey literature search, including websites and records of ADA (American Diabetes Association), Diabetologia, and EASD (European Association for the Study of Diabetes).

Data Collection

Data extraction and risk of bias assessment were performed by at least two independent reviewers. Before data extraction, a standardized Excel form was created to capture the following information: study identifier, including author and year of publication, study design, and outcomes.

The risk of bias assessment was evaluated using Cochrane's Risk of Bias 2 (RoB2) tool and graded as "low-risk", "some concerns", or "high-risk" of bias. The RoB2 tool assessed for risk of bias in the following components: (i) randomization process, (ii) any deviation from intended interventions, (iii) missing outcome data, (iv) measurement of the outcome, (v) selection of the reported result, and (vi) overall RoB. When there were discrepancies between two reviewers, a third reviewer would perform independent data extraction and risk of bias assessment and arbitrate the dispute.

Statistical Analysis

The primary outcomes in this systematic review will focus on the progression of albuminuria, the decline in renal function measured by eGFR or creatinine clearance, and the development or progression of diabetic kidney disease (DKD). Secondary outcomes involve evaluating the safety and tolerability of these interventions in managing albuminuria and preserving kidney function in patients with T2D. Only data presented using the intention-to-treat (ITT) principle were extracted for the efficacy outcomes. Meanwhile, only data presented using each study's safety analysis set (SAS) were extracted for the safety outcomes.

RESULTS

The initial search (Fig. 1) yielded 1,748 articles. Duplicates (n = 29) and articles that did not have full texts available (n = 34) were removed, leaving 1,685 articles. This was then screened using the study objective and design to remove 1,503 articles further, leaving 182 articles. Eligibility criteria were then applied to remove 174 articles further. This study included nine articles involving 9,91,285 patients with T2D, identifying albuminuria and kidney function as essential outcomes.

Table 1 provides a summary of these studies, highlighting their key findings regarding the association between albuminuria and kidney function outcomes such as eGFR and progression to DKD[1-3,5-10]. The studies consistently demonstrate that higher levels of albuminuria are significantly associated with reduced eGFR and an increased risk of DKD progression.

Kaewput et al[1] conducted a nationwide retrospective cohort study and found a significant correlation between high levels of albuminuria and rapid eGFR

Table 1. Summary of Studies and their Kidney Function Outcomes[1-3,5-10]

Study Title	Authors	Year	Study Design	Location	Sample Size	Purpose	Outcomes
Liver Stiffness, Albuminuria, and Chronic Kidney Disease in Patients with NAFLD: A Systematic Review and Meta-Analysis	Ciardullo et al[2]	2022	Systematic review and meta-analysis	Italy	7,736 participants from 7 studies	To assess the association between liver stiffness, albuminuria, and CKD in patients with NAFLD.	Elevated UACR (≥30 mg/g) in NAFLD patients is associated with higher CKD prevalence and reduced eGFR.
Diabetic Kidney Disease Benefits from Intensive Low-Protein Diet: Updated Systematic Review and Meta-Analysis	Li et al[6]	2021	Systematic review and meta-analysis	China	506 participants from 9 studies	To assess the evidence-based efficacy of a low-protein diet in the management of DKD.	Proper DPI is suggested for adults, but in low amounts, to reduce renal function complications. A DPI ≤0.8 g/kg/day can positively impact renal function, reducing the risk of kidney failure by controlling proteinuria.
Diagnostic Accuracy of Urine Dipstick Testing for Albumin-to-Creatinine Ratio and Albuminuria: A Systematic Review and Meta-Analysis	Mejia et al[3]	2021	Systematic review and meta-analysis	Peru	37,435 patients from 14 studies	To evaluate the diagnostic accuracy of urine dipstick tests for albuminuria.	Urine dipstick tests are helpful for initial screening but have limitations in sensitivity and specificity for detecting elevated albuminuria.
The Level of Serum Albumin is Associated with Renal Prognosis and Renal Function Decline in Patients with Chronic Kidney Disease	Cheng et al[8]	2023	Prospective Cohort	China	754 patients	To investigate the relationship between serum albumin levels and renal prognosis in CKD patients.	Lower serum albumin levels (<3.5 g/dL) are associated with faster renal function decline and poorer renal prognosis.
Lifestyle Interventions, Kidney Disease Progression, and Quality of Life: A Systematic Review and Meta-Analysis	Neale et al[9]	2023	Systematic review and meta-analysis	Australia	15,288 participants from 68 studies	To determine the impact of lifestyle interventions on CKD progression and quality of life.	Lifestyle interventions, including exercise and diet, improved eGFR and reduced albuminuria, slowing CKD progression.
Conversion of Urine Protein-Creatinine Ratio or Urine Dipstick Protein to Urine Albumin-Creatinine Ratio for Use in Chronic Kidney Disease Screening and Prognosis: An Individual Participant-based Meta-Analysis	Sumida et al[10]	2020	Meta-analysis	United States	9,19,383 patients across 33 studies	To evaluate the effectiveness of converting UPCR or urine dipstick protein to UACR for CKD screening and prognosis.	Albumin levels can indicate the status of patients with CKD. Converting UPCR or urine dipstick protein to UACR is effective for CKD screening and prognosis.
Effects of Exercise Training on Proteinuria in Adult Patients with Chronic Kidney Disease: A Systematic Review and Meta-Analysis	Yang et al[5]	2020	Systematic review and meta-analysis	China	623 CKD patients from 11 studies	To assess the effects of exercise training on proteinuria in CKD patients.	Regular exercise training does not aggravate proteinuria in adult CKD patients and also significantly reduces proteinuria levels.

Table 1. Summary of Studies and their Kidney Function Outcomes[1-3,5-10]

Study Title	Authors	Year	Study Design	Location	Sample Size	Purpose	Outcomes
Rate of Kidney Function Decline and Factors Predicting Progression of Kidney Disease in Type 2 Diabetes Mellitus Patients with Reduced Kidney Function: A Nationwide Retrospective Cohort Study	Kaewput et al[1]	2020	Retrospective cohort	Thailand	8,464 T2D patients	To determine the relationship between albuminuria levels and CKD progression in T2D patients.	Higher albuminuria levels (>300 mg/day) significantly correlated with rapid eGFR decline, predicting faster CKD progression.
Prevalence and Risk Factors of Chronic Kidney Disease among Type 2 Diabetes Patients: A Cross-Sectional Study in Primary Care Practice	Jitraknatee et al[7]	2020	Cross-sectional	Thailand	1,096 T2D patients	To identify the prevalence and risk factors of CKD in T2D patients in primary care.	Risk factors for CKD include retinopathy, HbA1c ≥7%, anemia, and albuminuria significantly associated with decreased eGFR.

NAFLD = Nonalcoholic fatty liver disease; CKD = Chronic kidney disease; UACR = Urine albumin-to-creatinine ratio; eGFR = Estimated glomerular filtration rate; DKD = Diabetic kidney disease; DPI = Dietary protein intake; UPCR = Urine protein-to-creatinine ratio; T2D = Type 2 diabetes; HbA1c = Glycated hemoglobin.

decline, indicating that higher albuminuria predicts faster CKD progression. Li et al[6] discovered that a proper dietary protein intake (DPI) of ≤0.8 g/kg/day is suggested for adults to reduce renal function complications, including the risk of kidney failure, by controlling proteinuria. Similarly, Ciardullo et al[2] identified elevated albuminuria levels in patients with CKD characterized by UACR ≥30 mg/g and eGFR <60 mL/min, signifying an increased risk of kidney function deterioration.

Jitraknatee et al[7] conducted a cross-sectional study in primary care practice and identified several predictors of eGFR decrease, including retinopathy, glycated hemoglobin (HbA1c) ≥7%, and anemia, emphasizing the complex risk profile of T2D patients. Mejia et al[3] evaluated the diagnostic accuracy of urine dipstick testing for albumin-to-creatinine ratio and albuminuria, highlighting its limitations in reliably identifying elevated albuminuria.

Cheng et al[8] explored the association between serum albumin levels and renal progression in CKD, demonstrating that lower serum albumin is linked with faster renal function decline. Neale et al[9] investigated lifestyle interventions and found that exercise practices improve creatinine and eGFR, while dietary interventions contribute to improvements in albuminuria.

Sumida et al[10] conducted a meta-analysis on converting UPCR or urine dipstick protein to UACR, showing that albumin levels can effectively indicate the status of patients with CKD. Lastly, Yang et al[5] reviewed the effects of exercise training on proteinuria in CKD patients, confirming that regular exercise has positive effects on reducing proteinuria.

DISCUSSION

Proteinuria predicts future GFR reduction and ESKD onset in population-based studies and controlled trials. When there is overt proteinuria in both diabetic and nondiabetic renal disease, a reduction in proteinuria inevitably results in protection against decreased renal function. A person may have renal disease even if their eGFR is 60 or above if they have albumin in their urine[11]. Various research studies have investigated how dietary interventions help improve the condition of albuminuria[9]. In another study, even when traditional cardiovascular risk factors were considered, there was a nearly 2.6-fold increase in the risk of death for those with a significant decline in eGFR (<45 mL/min/1.73 m^2) in addition to proteinuria[12].

The study by Kaewput et al[1] showed essential data on the severity of CKD in T2D patients and the crucial role of albuminuria in predicting kidney function. The research contained patients with deteriorated kidney function (baseline eGFR between 15 to 59 mL/min/1.73 m^2). These results demonstrate an association between albuminuria and a higher chance of eGFR decline. This indicated that the more albuminuria, the faster CKD will progress to the later stages, such as CKD stage 5 or dialysis.

According to Jitraknatee et al[7], even in primary care, the failure rate of kidneys is relatively standard among T2D patients, and the severity levels may vary from different stages. Regarding risk factors, the study's multivariable logistic regression analysis found several predictors significantly correlated with eGFR decrease, such as retinopathy, HbA1c ≥7%, and anemia. These aspects, inclusive of albuminuria, indicate that patients with T2D tend to have a complex risk profile[7]. It is essential to mention these risk factors because the integrated approach to managing the decline of eGFR in patients with diabetes is not limited to kidney function. It is also taking into account different diabetes-related complications. This comprehensive awareness sets the stage for developing target-oriented therapies and monitoring protocols to prevent higher levels of eGFR reduction. Another study also showed that various risk factors may be related to an ongoing decline in eGFR. Besides albuminuria, other factors such as duration of diabetes, systolic blood pressure, and serum uric acid are associated with an increasing risk of eGFR worsening[13].

This manuscript's qualitative and quantitative studies shed light on the intricate relationship between albuminuria, renal function, and cardiovascular outcomes in T2D patients. The UACR emerges as a critical diagnostic tool, aiding in identifying renal impairment and disease progression. Despite its significance, further research is warranted to enhance the reliability and accuracy of UACR testing in clinical practice.

Additionally, the correlation between albuminuria and rapid eGFR decline underscores the importance of routine check-ups and early diagnosis in postponing CKD progression in T2D patients. Identifying risk factors for eGFR decline, including retinopathy, HbA1c levels, and anemia, enables the formulation of personalized treatment strategies to mitigate CKD progression and improve overall health outcomes.

Moreover, interventions targeting factors associated with slower CKD progression, such as aging and renin-angiotensin-aldosterone system (RAAS) inhibitors, offer promising avenues for disease management. Integrating preventive measures into clinical care, including early diagnosis of albuminuria and awareness of risk factors, can significantly impact long-term outcomes for T2D patients by minimizing CKD progression and improving overall quality of life.

Heterogeneity among the included studies may be considered a severe limitation of the present systematic review on albuminuria and kidney function in T2D patients. Differences in study design, patient populations, and targeted interventions on albuminuria undoubtedly jeopardize generalization. Furthermore, reliance on electronic databases for the search and the restriction of the review to English-language studies probably predispose the selection and may reduce the scope of the review. Another source of variance among the results reported in studies could be the variation in the definition and methods of measurement chosen by the different studies for albuminuria and kidney function. Moreover, publication bias cannot be excluded, as studies with negative or inconclusive results are less likely to be published. Future research is, therefore, needed to overcome these limitations by defining the standard definition, broadening the inclusion criteria, and incorporating the broadest possible range of studies.

A comprehensive approach to managing declining eGFR in T2D patients therefore involves early diagnosis of albuminuria, awareness of risk factors, personalized treatment strategies, and integration of preventive measures into clinical care. Further research is warranted to enhance diagnostic tests' reliability and accuracy and explore additional interventions for mitigating CKD progression and improving long-term outcomes in T2D patients.

CONCLUSIONS

Our findings highlight the importance of investigating albuminuria's impact on eGFR among individuals with T2D. The studies reviewed indicated a strong association between higher albuminuria levels and reduced eGFR, underscoring albuminuria's role as a crucial marker in assessing DKD severity. This review emphasizes the necessity for tailored, patient-centered care in managing T2D to reduce renal complications. Further studies are needed to evaluate DKD outcomes in this context comprehensively, and health care providers should consider albuminuria levels when developing treatment strategies for T2D patients to mitigate the progression of renal disease.

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CLINICAL STUDY

Dyslipidemia – A Risk Factor for Osteoporosis in Women: A Cross-Sectional Study

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ABSTRACT

Background: Osteoporosis has been extensively studied in postmenopausal women but there is a paucity of studies for detection of osteoporosis in premenopausal women. Recent studies point out that dyslipidemia could be a risk factor for osteoporosis in postmenopausal women. It is unclear whether dyslipidemia in premenopausal women is a risk factor for osteoporosis after menopause. This study is an attempt to find whether dyslipidemia in premenopausal and postmenopausal women is associated with decreased bone mineral density (BMD). **Methods:** The study was conducted from November 2013 to March 2014 at Lady Hardinge Medical College, New Delhi. Sixty patients (30 premenopausal and 30 postmenopausal) who were not having any comorbidity and not on any drug affecting lipid or bone metabolism were evaluated for lipid profile and BMD. **Result:** In premenopausal women, there was a negative correlation between very low-density lipoprotein cholesterol (VLDL-C), triglycerides (TGs), and BMD (lumbar vertebra) while a positive correlation was observed between high-density lipoprotein cholesterol (HDL-C) and BMD, which was statistically significant (VLDL-BMD r −0.363, p = 0.049; TRI-BMD r −0.363, p = 0.049; HDL-BMD r 0.359, p = 0.05). Similarly, in postmenopausal women, the negative correlation between VLDL, TG, and BMD was statistically significant (TG-BMD r −0.377, p = 0.04; LDL-BMD r 0.415, p = 0.02), as was the positive correlation between HDL and T-score (HDL-BMD r 0.366, p = 0.04). **Conclusion:** There is statistically significant correlation between BMD and serum lipid levels in both premenopausal and postmenopausal women. Lipid profile variables show a significant association with BMD and can be used as risk factors for osteoporosis.

Keywords: Osteoporosis, lipid profile, premenopausal, postmenopausal, bone mineral density, T-score

Skeleton is a dynamic tissue, getting remodeled constantly throughout life. Compact and cancellous bones are arranged in a fashion to provide tensile strength and density for mobility and protection of the body. Remodeling is achieved by two different cell types: osteoblasts, which synthesize bone matrix, and osteoclasts, which reabsorb it[1]. Osteoporosis in postmenopausal women has been extensively studied and an epidemiological study by Saghafi et al has suggested a correlation between cardiovascular disease and osteoporosis[2]. There is paucity of studies done for detection of osteoporosis in premenopausal women, especially in metropolitan cities. Dyslipidemia is an established risk factor for cardiovascular diseases, but recent studies by Adami et al[3] and Wu et al[4] suggest that it might also be a risk factor for osteoporosis. While much emphasis is given to the morbidity associated with osteoporosis in postmenopausal women after the speculated protective effect of estrogen wanes off, epidemiological data suggest that estrogen deficiency is a risk factor for cardiovascular diseases and osteoporosis. Estrogen receptors have been demonstrated to have effects on osteoblasts and osteoclasts[5]. No study has found a reliable way of detecting these in the premenopausal period itself. While it is true that bone mineral density (BMD) decreases in postmenopausal women[6], it is unclear whether dyslipidemia in premenopausal women is a risk factor for osteoporosis in their postmenopausal period[7,8]. Various studies in mice with controlled age, genetics, and environment have proved to be helpful in identifying the relation between high-density lipoprotein cholesterol (HDL-C) and BMD[9,10]. There is a possible relationship between bone loss and dyslipidemia. Immunological and inflammatory

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factors play an important role in the pathophysiology of both diseases. One of these factors is osteoprotegerin (OPG), a soluble glycoprotein that belongs to the tumor necrosis factor (TNF) receptor super family. It acts as a decoy receptor of the receptor activator of nuclear factor κB ligand (RANKL), which is an important regulator of osteoclastogenesis. OPG is known to inhibit osteoclastogenesis by binding to RANKL, preventing it from binding to the receptor activator of NF-κB on osteoclasts. It has been reported that OPG is highly expressed in the bones, heart, and major arteries. Recently, OPG has been shown not only as an inhibitor of osteoclastogenesis, but also as a preventive mediator of cardiovascular diseases, such as arterial calcification and atherogenesis[11,12]. Both osteoporosis and atherosclerosis are chronic degenerative diseases with high incidence in developed countries. The prevalence of both pathologies increases with advancing age[13,14]. This study aimed to find if dyslipidemia in premenopausal and postmenopausal women was associated with decreased BMD.

MATERIALS AND METHODS

This cross-sectional observational study was conducted from November 2013 to March 2014 in the Institute of Internal Medicine and Department of Radiology, Lady Hardinge Medical College, New Delhi. A total of 60 patients were included. Patients were divided into two groups: premenopausal (30-45 years who had not attained menopause) and postmenopausal (women aged 45 years and older who had attained menopause), with 30 patients in each group. We excluded patients with diabetes mellitus, cancer, hypertension, smoking, bone disease, chronic kidney disease, hypothyroidism, hyperthyroidism, and those receiving antiepileptics, levothyroxine, statins, antithyroid drugs, steroids, estrogen derivatives, bisphosphonates, selective estrogen receptor modulators, or any other drug affecting lipid or bone metabolism.

Each patient was subjected to appropriate history and clinical examinations as per the Proforma and subjected to the following investigations: measurement of height, weight and waist circumference, blood glucose, fasting lipid profile, and dual-energy X-ray absorptiometry (DEXA) scan (lumbar spine). Blood glucose samples were transported in fluoride containers, and samples for lipid profile were transported in plain containers. Both were measured by fully automated analyzer AU480 (BECKMANN) using Randox kits.

DEXA scan was done by Hologic Version 13.0:5, model Discovery Wi (S/N 84571). Statistical analysis was performed by the SPSS program for Windows, version 20.0. Continuous variables were presented as mean ± SD using unpaired *t*-test and Mann-Whitney *U* test. Data was checked for normality before statistical analysis using Shapiro-Wilk test. Pearson correlation was also used to measure the direct correlation between various lipid parameters and DEXA scan reports. For all statistical tests, a p value <0.05 was considered to be statistically significant.

RESULTS

This study included 30 premenopausal women with mean age of 36.10 ± 4.06 years and 30 postmenopausal women with mean age of 59.60 ± 7.29 years. The demographic and anthropometric profile of the patients has been shown in Table 1. The lipid profile and BMD of the patients are shown in Table 2. Pearson's correlation between lipid profile and BMD at lumbar spine is shown in Table 3. The correlation between total cholesterol and BMD in lumbar spine was assessed with the help of the Pearson Product Moment

Table 1. Characteristics of the Anthropometric Parameters of Study Population

Parameters	Premenopausal		Postmenopausal		P value
	Mean	±SD	Mean	±SD	
Height (m)	1.55	0.05	1.51	0.06	0.008
Weight (kg)	54.10	7.05	53.10	7.79	0.302
BMI	22.62	2.78	23.35	3.12	0.173
Waist circumference	68.63	3.96	66.68	3.62	0.040

Table 2. Characteristics of Lipid Profile and DEXA Scan of Study Population

	Premenopausal		Postmenopausal		P value
	Mean	±SD	Mean	±SD	
Total cholesterol	123.83	24.87	163.63	54.65	≤0.001
LDL-C	59.55	24.84	99.87	55.18	≤0.001
VLDL-C	22.65	3.21	24.33	4.62	0.054
HDL-C	41.67	6.27	39.43	7.47	0.107
TG	113.27	16.06	121.67	23.09	0.054
DEXA BMD (L)	0.90	0.10	0.74	0.19	<0.001

Table 3. Correlation Between Lipid Profile and DEXA Scan at Lumbar Vertebra

Lipid profile variables	DEXA BMD (L) Premenopausal		DEXA BMD (L) Postmenopausal	
	Pearson correlation "*r*"	P value	"*r*"	P value
LDL-C	−0.318	0.087	−0.358	0.052
VLDL-C	−0.363	0.049	−0.064	0.738
HDL-C	0.359	0.051	0.357	0.053
TG	−0.363	0.049	−0.064	0.738

Correlation (PPMC) denoted as "*r*". The correlation (*r*) between low-density lipoprotein (LDL) and BMD in lumbar spine was −0.318 in premenopausal group and −0.358 in postmenopausal female. This indicates that both groups had moderate negative correlation; however, the correlation was statistically not significant in both groups (p = 0.087 and 0.052, respectively). The correlation coefficient (*r*) between very low-density lipoprotein (VLDL) and BMD in lumbar spine was −0.363 in premenopausal group. This indicates a moderate negative correlation, which was statistically significant (p = 0.049). In postmenopausal group, *r* was −0.064 indicating negligible relationship and the correlation was not statistically significant (p = 0.738). PPMC coefficient (*r*) between HDL and BMD in lumbar spine was +0.359 in premenopausal group and 0.357 in postmenopausal females. It indicates a moderate positive correlation; in both the groups the correlation was statistically nonsignificant (p = 0.051 and 0.053). The PPMC coefficient between triglycerides (TGs) and BMD in lumbar spine was −0.363 in premenopausal group. It indicates a moderate negative correlation and the correlation was statistically significant (p = 0.049). In postmenopausal group, "*r*" was −0.064 indicating a negligible relationship and the correlation was not statistically significant (p = 0.738).

DISCUSSION

Our results show that the levels of LDL-C and BMD (lumbar spine) show moderate negative correlation in premenopausal as well as postmenopausal women. An inverse association has been described by Yamaguchi et al[15] between BMDs at two (radius and lumbar spine) of the four sites measured (total body, radius, lumbar spine, and femoral neck) and serum LDL-C levels. However, in the study by Poli et al[16], BMD of only the lumbar spine (2-4) site showed a negative association with serum LDL-C levels in postmenopausal women. The result of these two studies indicating inverse relationship between LDL-C and BMD are similar to our findings but they differ from our results with respect to site of BMD measurement. These differences can be explained by different age distribution, different study population (premenopausal females not included in both studies) and differences in the methodology (skeletal sites of BMD measurement - radius, femoral neck, and spine). Previous studies have also shown differences in age-related BMDs at various skeletal sites in different races[16]. Therefore, it is possible that BMD values at different sites produce different outcomes. Our results indicate that the levels of VLDL-C and BMD show moderate negative correlation in lumbar spine for premenopausal as well as postmenopausal women[17,18].

Literature indicating the effect of serum TGs on BMD is very scarce. Our study shows that the levels of TGs and BMD are also moderately negatively correlated in lumbar spine for premenopausal as well as postmenopausal women. However, Cui et al[19] and Adami et al[3] found a positive correlation between TGs and BMD.

In our study, the levels of HDL-C and BMD show a moderate positive correlation in premenopausal as well as postmenopausal females. Notably, studies conducted by Yamaguchi et al[15] and D'Amelio et al[20] have reported an association between BMD and HDL-C, although these results were not in accordance. Positive relationship was pointed out by Yamaguchi et al[15], while a negative correlation between two parameters was described by D'Amelio et al[20]. However, Poli et al[16] did not find any association between BMD and serum HDL-C levels in postmenopausal women.

CONCLUSION

Our data indicate a relationship between BMD values and serum lipid levels. It suggests that for the lumbar spine, the levels of VLDL-C and serum TGs had negative, while HDL-C had positive association with BMD in premenopausal as well as postmenopausal women. Hence, lipid profile variables show a significant association with BMD and can be used as risk factors for osteoporosis in both premenopausal and postmenopausal women.

However, our study had few limitations. Since this study was conducted in a hospital in a metropolitan city, it might not be representative of the entire female population. Serum vitamin D levels were not considered in the study. The sample size of the study is small and so the power of the study is reduced. Further studies with large sample size are needed to validate the findings of our study.

BENEFITS AND RECOMMENDATIONS OF STUDY

We hypothesized that dyslipidemia is related to BMD and may independently predict the risk for osteoporosis. By controlling dyslipidemia with lifestyle modifications and pharmacotherapy, osteoporosis can potentially be prevented.

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CLINICAL STUDY

Clinicoepidemiological Profile and Micronutrient Deficiencies in Children with Severe Acute Malnutrition

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ABSTRACT

Introduction: Malnutrition is widely prevalent in developing countries and is considered a common denominator in infant and under-5 mortalities. Most child deaths are associated with inappropriate feeding practices and specific micronutrient deficiencies during the first year of life. There is a lack of data about severe acute malnutrition (SAM) and specific micronutrient deficiencies in India; hence, the present study was conducted to study the iron profile, including folic acid, and vitamin B12 levels and their correlation with the clinicoepidemiological profile of children with SAM. **Materials and methods:** This hospital-based cross-sectional study included 95 children with SAM, aged 6 months to 5 years. A predesigned structured proforma was used to collect information. Data concerning clinical examination and history given by the mother and a reliable attendant was collected. The quantitative data were expressed as mean and standard deviation and qualitative data as percentage and proportion. The difference in proportion was analyzed by the Chi-square test and the difference in means was analyzed by ANOVA. P-value <0.05 was taken as significant. All calculations were done by Microsoft Excel, Primer. SPSS Software [version 21] was used for doing statistical analysis. **Results:** In the present study, a total of 95 SAM patients were included with mean age 19.74 months and an F:M ratio of 1.2:1. Weight-for-height was found to be the most reliable criterion to identify children with SAM (78.95%). Edema was present in 18 (18.95%) patients. Around 68.42% of patients had mid-upper arm circumference (MUAC) <11.5 cm; 25.26% of children were found completely immunized, remaining 74.74% were either partially immunized or unimmunized. According to the Kuppuswamy scale for the socioeconomic class, more than two-thirds of the parents belonged to the upper-lower class. About 44.21% of children received exclusive breastfeeding till 6 months of age, while complementary feeding was started in only 25.26% of children at 6 months of age. Anemia was present in 93 children with a prevalence of 97.89%. Of these, 30 patients had vitamin B12 deficiency anemia, 20 patients had iron deficiency anemia, and 6 patients had folate deficiency anemia. **Conclusions:** Severe acute malnutrition is an important preventable and treatable cause of morbidity and mortality in children below 5 years of age in India. Although malnutrition is highly prevalent in Indian children, there are very limited data that use biochemical indexes to characterize the epidemiology of micronutrient deficiencies in children with SAM. A detailed understanding of micronutrient deficiencies and clinical and epidemiological profile of children may help in micronutrient supplementation and fortification programs and targeting the basic causes of pediatric mortalities.

Keywords: Severe acute malnutrition, NFHS-5, iron, folic acid, vitamin B12, wasting, stunting

Childhood undernutrition is an underlying cause of an estimated 45% of all deaths among under-5 children[1]. India has an under-5 mortality rate (U5MR) of 41.9 per 1,000 live births. According to the National Family Health Survey (NFHS-5) 2019-21, 35.5% of children under 5 years are stunted (Below –2 standard deviations [SD], based on the World Health Organization [WHO] standard, height-for-age); 19.3% of children under 5 years are wasted (< –2SD, WHO standard, weight-for-height), 7.7% of children under 5 years are severely wasted (< –3SD, WHO standard; weight-for-height), 32.1% of children under 5 years are underweight (< –2SD, based on the WHO standard, weight-for-age); and 3.4% of children under 5 years

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are overweight (> +2SD, based on the WHO standard, weight-for-height)[2].

It is estimated that 1 in every 3 malnourished children live in India. Malnutrition in children is widely prevalent in developing countries and has been responsible for 60% of the 10.9 million deaths annually among children less than 5 years. Over two-thirds of these deaths, often associated with inappropriate feeding practices, occurred during the first year of life[1]. The infant mortality rate of India is 35.2 per 1,000 live births. As per NFHS-5, in India, 63.7% of children below 6 months of age are exclusively breastfed and 45.9% of children aged 6 to 8 months are receiving solid or semi-solid food and breastmilk[2]. As per NFHS-5, 67.1% of children of age 6 to 59 months in India are anemic. Only 11.1% of breastfeeding and 12.7% of nonbreastfeeding (total 11.3%) children aged 6 to 23 months are receiving an adequate diet[2].

Dietary sources of vitamin B12 are almost exclusively from animal foods. As far as anemia in malnutrition or severe acute malnutrition (SAM) is concerned much emphasis is laid on supplementation of iron and folic acid and not on vitamin B12[3]. Moreover, supplementation of only folic acid in children deficient in both vitamin B12 and folic acid can worsen the neurological status of the child[4]. There is a lack of data about SAM and specific micronutrient deficiencies in India; hence, the present study was aimed to study the iron profile, folic acid, and vitamin B12 levels, and their correlation with the clinicoepidemiological profile of children with SAM.

MATERIALS AND METHODS

This hospital-based cross-sectional study was conducted at the Malnutrition Treatment Center (MNTC), Dept. of Pediatric Medicine of a tertiary care center; children with SAM, aged 6 months to 5 years were included in the study after receiving the requisite clearance from Institutional Ethics Committee. Exclusion criteria were children who were already on hematinics before admission, those aged below 6 months and above 5 years, and refusal for consent. At 95% confidence level and 5% absolute allowable error assuming 94% prevalence of anemia among SAM cases, the required sample size was 91 cases, which was further rounded off to 95 cases of SAM.

A predesigned structured proforma was used to collect information. Basic demographic data, child's profile (address, age, sex, birth spacing, and birth order); education, occupation, and religion of parents; socio-economic details of their parents (family income, caste), breastfeeding (immediate breastfeeding, exclusive breastfeeding, duration of feeding) and introduction of complementary food and child feeding status were collected from all patients. Weight was measured in kilograms using an electronic weighing scale. Mid-upper arm circumference (MUAC) was measured in centimeters using a simple measuring tape. These anthropometric measurements were compared to the WHO reference standards to determine the nutritional status of the child.

Two milliliters of the peripheral venous blood sample was taken with aseptic precautions, in an EDTA vial for determination of complete blood count, 2 mL in the plain vial for C-reactive protein (CRP), and 3 mL in another plain vial for serum iron profile, folic acid, and vitamin B12 estimation. Serum iron profile, folic acid, and vitamin B12 were estimated by using the electrochemiluminescence (ECL) method using VIT B12 600, FOL III 618, and FERRITIN 381 ELECSYS kits for COBASe411 analyzer, Roche diagnostics GmBH Germany distributed by Roche diagnostics GmBH, Sandhofer Strasse 116 Mannheim.

Iron deficiency was defined as ferritin concentration <12 ng/mL, or if the CRP was >5 mg/L, iron deficiency was defined as ferritin concentration <30 ng/mL.[5] Vitamin B12 deficiency was defined as serum or plasma total vitamin B12 concentrations <148 pmol/L, and vitamin B12 insufficiency was defined as vitamin B12 concentrations <221 pmol/L, unless otherwise specified. Folate deficiency was defined as a serum folate concentration <10 nmol/L[6]. Biochemical evidence of inflammation was defined as a CRP concentration >5 mg/L. CRP was measured to evaluate whether systemic inflammation could account for an abnormal ferritin concentration[7].

Data were collected concerning clinical examination and history given by mother and reliable attendant. The quantitative data were expressed as mean and SD and qualitative data as percentage and proportion. The difference in proportion was analyzed by the Chi-square test and the difference in means was analyzed by ANOVA. P-value <0.05 was taken as significant. All calculations were done by Microsoft Excel, Primer. SPSS Software [version 21] was used for doing statistical analysis.

RESULTS

The baseline characteristics of the study participants are depicted in Figure 1. Out of 95 SAM patients, 39 (41.05%) were between 6 to 12 months, 39 (41.05%) between

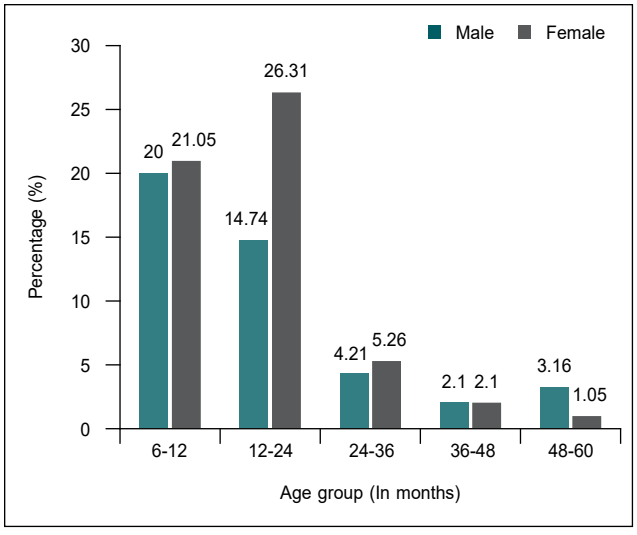

Figure 1. Baseline characteristics of study participants.

Table 1. Weight-for-Height of Study Participants

Age group (In months)	Weight/Height			Total
	<1SD	<2SD	<3SD	
6-12	3 (3.16)	3 (3.16)	32 (33.68)	39 (41.05)
12-24	2 (2.10)	7 (7.37)	30 (31.58)	39 (41.05)
24-36	0 (0.00)	0 (0.00)	9 (9.47)	9 (9.47)
36-48	1 (1.05)	1 (1.05)	2 (2.10)	4 (4.21)
48-60	0 (0.00)	2 (2.10)	2 (2.10)	4 (4.21)
Total	**7 (7.37)**	**13 (13.68)**	**75 (78.95)**	**95 (100.00)**

12 to 24 months, 9 (9.47%) between 24 to 36 months, 4 (4.21%) between 36 to 48 months, and 4 (4.21%) were between 48 to 60 months age group. The mean age of the participants was 19.74 months. Fifty-three (55.79%) were female and 42 (44.21%) were male with a sex ratio (F:M) of 1.2:1.

Out of 95 SAM children, 75 (78.95%) had weight-for-height <3SD, 13 (13.68%) patients had weight-for-height <2SD, and 7 (7.37%) patients had weight-for-height <1SD. Gender-based evaluations concerning weight-for-height suggested that out of 75 having weight-for-height <3SD, 33 (34.74%) were male and 42 (44.21%) were female (Table 1).

Eighteen participants (18.95%) had edema and 77 (81.05%) had no edema. Distribution according to sex and edema shows that out of the 18 patients with edema, 5 were male, and 13 were female. The Chi-square value was 1.679, degree of freedom was 1, and p-value was >0.05, hence not significant.

Out of the 95 study subjects, 68.42% (65) patients had MUAC <11.5 cm, and 31.58% (30) of patients had MUAC >11.5 cm. Twenty-nine patients were male and 36 were female out of the 65 (68.42%) having MUAC <11.5 cm. Thirteen patients were male and 17 were female out of the 30 (31.58%) having MUAC >11.5 cm. The Chi-square value was 0.01, the degree of freedom was 1, and the p-value was >0.05, hence not significant.

Out of 95, 42 (44.21%) children were exclusive breast-feeding, 40 (42.11%) were still predominantly breastfed and 13 (13.68%) were given complementary food besides milk. Out of 95, 24 (25.26%) were completely immunized, 61 (64.21%) were incompletely immunized and 10 (10.52%) were unimmunized.

Out of 95, 93 (97.89%) were anemic, 42 (44.21%) had severe anemia, 39 (41.05%) had moderate anemia, and 8 (8.42%) had mild anemia. Micronutrient deficiency was found in 56 (58.94%). Serum vitamin B12 deficiency was found in 30 (31.58%) patients, serum folate deficiency in 6 (6.32%) patients, and serum iron deficiency in 20 (21.05%) patients. The severity of anemia in study participants is depicted in Table 2.

Mean ± SD of age and severity of anemia analysis suggested 18.00 ± 0.00 for normal hemoglobin (Hb) (n = 2), 30.75 ± 17.17 for anemia (n = 4), 11.00 ± 3.32 for mild anemia (n = 8), 16.82 ± 10.86 for moderate anemia (n = 39), 15.40 ± 7.79 for severe anemia (n = 42).

Gender-wise evaluation suggested that out of the 42 (44.21%) severely anemic children, 20 (47.62%) were male and 22 (52.38%) were female, and out of 39 (41.05%) moderately anemic children, 18 (46.15%) were male and 21 (53.85%) were female. The study of birth order of study subjects showed higher prevalence of severe anemia (42) in the third birth order followed by second birth order, which was 20 and 13, respectively. Moderate anemia (39) was more in the second birth order followed by the fourth birth order, which was 15 and 8, respectively.

Table 3 describes the relationship of the severity of Hb level with weight-for-height of study participants; 34 (35.79%) participants with severe anemia had weight-for-height <3SD. The severity of Hb level analysis concerning feeding history of study subjects suggested that out of 42 exclusive breastfeeding children, 24 had severe anemia, 15 had moderate anemia, and 2 had mild anemia. Mean ± SD of serum iron according to severity of Hb level was 89.00 ± 13.00 for normal Hb (n = 2), 77.50 ± 6.10 for anemic (n = 4), 80.00 ± 29.95 for mildly anemic (n = 8), 110.00 ± 35.94 for moderate anemic (n = 39), 112.12 ± 37.57 for severe anemic (n = 42) patients.

Table 2. Severity of Anemia in Study Participants

Age group (In months)	Normal	Anemic (<11 g/dL)	Mild anemic (10-10.9 g/dL)	Moderate anemic (7-9.9 g/dL)	Severe anemic (<7 g/dL)	Total
6-12	0 (0.00)	0 (0.00)	5 (12.82)	16 (41.02)	18 (46.15)	39
12-24	2 (5.12)	2 (5.12)	3 (7.69)	16 (41.02)	16 (41.02)	39
24-36	0 (0.00)	1 (11.11)	0 (0.00)	3 (33.33)	5 (55.55)	9
36-48	0 (0.00)	0 (0.00)	0 (0.00)	1 (25)	3 (75)	4
48-60	0 (0.00)	1 (25)	0 (0.00)	3 (75)	0 (0.00)	4
Total	**2 (2.10)**	**4 (4.21)**	**8 (8.42)**	**39 (41.05)**	**42 (44.21)**	**95 (100)**

Table 3. Relationship of Severity of Hb Level with Weight-for-Height of Study Participants

Hb	Weight-for-Height			Total
	<1SD	<2SD	<3SD	
Normal	0 (0.00)	0 (0.00)	2 (2.10)	2 (2.10)
Anemic	0 (0.00)	1 (1.05)	3 (3.16)	4 (4.21)
Mildly anemic	2 (2.10)	0 (0.00)	6 (6.32)	8 (8.42)
Moderate anemic	3 (3.33)	6 (6.31)	30 (31.58)	39 (41.05)
Severe anemic	2 (2.10)	6 (6.31)	34 (35.79)	42 (44.21)
Total	**6 (6.31)**	**32 (33.68)**	**57 (60.0)**	**95 (100.00)**

Table 4. Relationship Between Severity of Hb Level as per Vitamin B12 of Study Subjects

Hb	Vitamin B12		Total
	Abnormal	Normal	
Normal	1 (1.05)	1 (1.05)	2 (2.10)
Anemic	4 (4.21)	0 (0.00)	4 (4.21)
Mildly anemic	0 (0.00)	8 (8.42)	8 (8.42)
Moderate anemic	15 (15.79)	24 (25.26)	39 (41.05)
Severe anemic	10 (10.53)	32 (33.68)	42 (44.21)
Total	**30 (31.58)**	**65 (68.42)**	**95 (100.00)**

Out of 95, 20 patients had abnormal iron. Out of 20, 11 (11.58%) patients had MUAC <11.5 cm and 9 (9.47%) patients had MUAC of >11.5 cm. The Chi-square value was 2.110, the degree of freedom was 1, and the p-value was >0.05; hence, not significant.

Analysis of severity of Hb level and serum iron of study subjects suggested that out of 20 children with abnormal serum iron, 10 were severely anemic, 8 were moderately anemic, and 2 were mildly anemic. Distribution according to age and serum iron shows that 20 patients had abnormal iron. Out of 20, 9 patients were in the 6 to 12 months age group and 6 patients were in the 12 to 24 months age group.

Distribution according to sex and serum iron shows that 20 patients had abnormal iron. Out of 20, 9 patients were male and 11 were female. The Chi-square value was 0.01, the degree of freedom was 1, and the p-value was >0.05; hence, not significant. Distribution according to serum iron and feeding history shows that 20 children had abnormal iron. Out of 20, 6 were exclusive breastfeeding, 12 were still predominantly breastfed, and 2 were given complementary food besides milk.

Analysis of severity of Hb level and total iron-binding capacity (TIBC) of study subjects suggested that out of 8 children with abnormal serum TIBC, 3 were severely anemic, 3 were moderately anemic, and 2 were mildly anemic. According to severity of Hb level, the mean ± SD of TIBC was 359.00 ± 9.00 for normal Hb (n = 2), 346.75 ± 34.23 for anemic (n = 4), 362.50 ± 53.84 for mildly anemic (n = 8), 307.31 ± 58.37 for moderately anemic (n = 39), 315.50 ± 59.26 for severely anemic (n = 42) patients (Table 4).

Out of 30 children with abnormal serum vitamin B12, 10 were severely anemic, 15 were moderate anemic, 4 were anemic, and 1 was normal (Table 4).

Analysis of severity of Hb level and serum ferritin of study subjects suggested that out of 52 children with abnormal ferritin, 25 were severely anemic, 25 were moderate anemic, and 2 were mildly anemic. Mean ± SD of serum ferritin according to severity of Hb level was 77.46 ± 47.55 for normal Hb (n = 2), 40.18 ± 17.33 for anemic (n = 4), 64.85 ± 45.56 for mildly anemic (n = 8), 192.04 ± 137.95 for moderate anemic (n = 39), 217.10 ± 187.41 for severe anemic (n = 42) patients.

The relationship between severity of Hb level as per vitamin B12 of study subjects depicted mean ± SD of vitamin B12 of 193.5 ± 7.65 for normal Hb (n = 2), 346.48 ± 258.61 for anemic (n = 4), 323.34 ± 74.71 for mildly anemic (n = 8), 295.29 ± 158.23 for moderately anemic (n = 39), 266.26 ± 106.56 for severely anemic (n = 42) patients. Out of 95, 30 (30.58%) patients had abnormal vitamin B12 levels. Out of 30, 10 (10.53%) were in 6 to 12 months age group and 15 (15.79%) were in 12 to 24 months age group, 3 (3.33%) were in 24 to 36 months age group and 2 (2.1%) were in 48 to 60 months age group. Out of 30, 14 were male and 16 were female; Chi-square value was 0.011, degree of freedom was 1 and p value was >0.05, hence not significant.

Out of 30, 13 (13.68%) were exclusively breastfeeding, 10 (10.53%) were still predominantly breastfed, and 7 (7.37%) were given complementary feeds besides milk; Chi-square value was 3.779, degree of freedom was 2, and p-value was >0.05; hence, not significant.

Out of 30, 19 (20%) patients had MUAC <11.5 cm and 11 (11.58%) patients had MUAC >11.5 cm. The Chi-square value was 0.530, degree of freedom was 1, and p-value was >0.05; hence, not significant. Out of 95, 6 (6.31%) children had abnormal serum folate. Out of 6, 2 (2.10%) were severely anemic, 2 were moderately anemic, and 2 were mildly anemic.

Out of 6 children with abnormal folate, 2 were in the 6 to 12 months age group, 3 were in the 12 to 24 months age group, and 1 was in the 24 to 36 months age group. Out of 6, 2 were male and 4 were female; Chi-square value was 0.017, degree of freedom was 1, and p-value was >0.05; hence, not significant. Out of 6, 2 were exclusive breastfeeding, 3 were still predominantly breastfed, and 1 was given complementary feeds besides milk. Out of 6, 5 had MUAC <11.5 cm and 1 patient had MUAC >11.5 cm. The Chi-square value was 0.128, degree of freedom was 1, and p-value was >0.05; hence, not significant.

The distribution of micronutrient deficiency in the groups based on severity of anemia depicted that in the normal Hb (n = 2) group, 1 child had vitamin B12 deficiency. In anemic group (n = 4), all 4 were vitamin B12 deficient. In mildly anemic (n = 8) group, 2 patients had serum iron deficiency and 2 patients had folate_deficiency; rest 4 were normal. In moderately anemic group (n = 39), 8 patients had serum iron deficiency, 2 patients had folate deficiency, and 15 patients had vitamin B12 deficiency. In severe anemic (n = 42) group, 10 patients had serum iron deficiency, 10 patients had vitamin B12 deficiency, and 2 patients had folate deficiency. Out of 56 SAM patients with micronutrient deficiencies, 30 (31.58%) had serum vitamin B12 deficiency, 20 (21.05%) had serum iron deficiency, and 6 (6.31%) had serum folate deficiency (Table 5).

Table 5. Prevalence of Hematopoietic Factor Deficiency in Relation to Severity of Anemia

	Iron	Folate	Vitamin B12
Normal (n = 2)	0 (0.00)	0 (0.00)	1 (3.33)
Anemic (n = 4)	0 (0.00)	0 (0.00)	4 (13.33)
Mildly anemic (n = 8)	2 (10)	2 (33.33)	0 (0.00)
Moderate anemic (n = 39)	8 (40)	2 (33.33)	15 (50)
Severe anemic (n = 42)	10 (50)	2 (33.33)	10 (33.33)
Total	**20 (21.05)**	**6 (6.31)**	**30 (31.58)**

DISCUSSION

Most of the data on SAM from developing countries is retrospective and descriptive type. The present study was a hospital-based cross-sectional study. Most of the studies were related to infectious comorbidities, while only a few studies were related to micronutrient deficiencies in severely malnourished children.

The present study was undertaken to collect data on demography and micronutrient deficiencies in our area.

The mean age of the study population was 19.74 months. In our study, 39% of the patients were in the age group 6 to 12 months. Another study also found that 50% of SAM patients belonged to the age group 6 to 12 months[8]. The high proportion of SAM patients in the early age group in this region could be due to maternal malnutrition and delayed introduction of complementary feeding[9]. Fifty-three (55.79%) of the patients were female with an F:M ratio was 1.2:1. Various studies have found that males are nearly equally vulnerable to develop SAM as females.

In our study, we found a preponderance of females over males. This may be due to ignorance about the health check-ups and nutrition of female children; however, no definite causal relationship was found for female preponderance.

In our study, 75 (78.95%) children had weight-for-height < –3SD, 40 (42.10%) children had visible severe wasting, 65 (68.42%) had MUAC <11.5 cm, while 18 (18.95%) had bilateral pitting edema of nutritional origin. So, weight-for-height < –3SD appears to be the most reliable criteria to identify children with SAM, while bilateral pitting edema appears to be least reliable. Another study also found similar results that 75.8% of cases had

their weight for height < –3SD, 24.03% cases had severe visible wasting, and 27% had bilateral pitting edema[10].

In our study, 24 (25.26%) children were found completely immunized, 61 (64.21%) were partially immunized, and 10 (10.52%) were unimmunized. In another study, 42.3% of children were completely immunized and 52% had partial immunization, while 5.7% of children had no immunization[10]. According to NFHS-5, the percentage of children aged 12 to 23 months who have received all basic vaccinations increased from 44% in 2005-06 to 76.4% in 2019-21. Between 2005-06 and 2019-21, this percentage increased more in rural areas (from 39% to 76.8%) than in urban areas (from 58% to 75.5%). The proportion of children who received no vaccinations remained low in both surveys (5%-6%). In Rajasthan, the percentage of children aged 12 to 23 months who have received all basic vaccinations increased from 26.5% in 2005-06 to 54.8% in 2015-16 and 80.4% in 2019-21[2,11]. This shows less coverage of immunization in our study area, which is likely due to ignorance and unawareness about immunization.

According to modified Kuppuswamy socioeconomic scale, 74 (77.89%) children in our study belonged to the upper-lower class, 18 (18.95%) belonged to the lower-middle class, while 3 (3.16%) children belonged to the upper-middle class.

In another Indian study, around 75% of families belonged to lower socioeconomic status, which was similar to our study[10]. In another study, 69.4% of children belonged to the lower social class, 19.4% to the middle class while 5.6% was of the upper class, which also correlates with the results of our study[12].

In the present study, 42 (44.21%) children were found to receive exclusive breastfeeding till 6 months of age. In a study by Kumar et al, 6% of babies were found exclusive breastfeeding[10]. The rate of exclusive breastfeeding was more in our study, but weaning does not start at recommended age, which is a predisposing factor for malnutrition. As per NFHS-5, in India, 63.7% of children under age 6 months are exclusively breastfed. About 45.9% of children of age 6 to 8 months are receiving solid or semi-solid food and breast milk. Only 11.1% of breastfeeding children aged 6 to 23 months are receiving an adequate diet and 12.7% of nonbreastfeeding children aged 6 to 23 months are receiving an adequate diet. Total children age 6 to 23 months receiving an adequate diet are 11.3 %[2].

The overlapping nature of protein-energy malnutrition and micronutrient deficiencies is well understood and it is seen that lack of one micronutrient is typically associated with deficiency of others[13].

In the present study, 93 (97.89%) children had anemia. Out of these 8 (8.42%), children had mild anemia, 39 (41.05%) had moderate anemia, while 42 (44.21%) children had severe anemia. The high incidence of anemia in these children could be due to nutritional factors as well as incidental worm infestations. The high prevalence of anemia was also reported by other studies[10,14]. As per NFHS-5, 67.1% of children of age 6 to 59 months in India are anemic[2].

In our study, 56 (58.94%) patients had micronutrient deficiencies. This could be due to chronic disease, worm infestation, and protein-energy malnutrition. In the earlier studies on hematopoietic micronutrient levels in anemic children, iron deficiency was found to be the commonest, whereas in our study on SAM patients serum vitamin B12 deficiency was more common (31.58%) compared to iron (21.05%) and folate (6.32%) deficiency[14,15]. In the study by Yaikhomba et al, serum vitamin B12 deficiency (34%) was more common than iron and folate deficiencies (6% each) in SAM patients, similar to this study[8].

This could be due to routine iron and folic acid supplementation to the pregnant and lactating mothers, whereas higher vitamin B12 deficiency rate could be due to low maternal vitamin B12 levels in a predominantly vegetarian community where no vitamin B12 supplementation is routinely given. Vitamin B12 deficiency is well recognized in exclusively breastfed infants of vitamin B12-deficient mothers[16]. Concentrations of vitamin B12 in breast milk reflect maternal vitamin B12 stores[17], and maternal vitamin B12 stores are depleted in up to one-third of rural Indian women[18].

A study in rural Karnataka also found that the concentration of ferritin and vitamin B12 was decreased in toddlers who continued to receive breast milk[19]. Folate concentration in breast milk is generally high and independent of maternal stores, thus prolonged breastfeeding in most of our patients might protect from folate deficiency[20]. Other studies also found that 58% and 14.4% of the SAM patients were deficient in vitamin B12[10].

CONCLUSIONS

Severe acute malnutrition is an important preventable and treatable cause of morbidity and mortality in children below 5 years of age in India.

Although malnutrition is highly prevalent in Indian children, there are very limited data that use biochemical indexes to characterize the epidemiology of micronutrient deficiencies in children with SAM in rural communities where the burden is highest.

A detailed understanding of how micronutrient concentrations relate to factors such as child feeding practices, maternal health and nutrition, and broader factors such as maternal education and family wealth and food security, together with a detailed model of how these factors are related, would enable improved targeting of resources, including micronutrient supplementation and fortification programs within rural populations where the majority of India's population lives.

Malnutrition is predicted by recurrent hospitalizations, taking an unbalanced diet, lack or incomplete immunization, and lower socioeconomic status. Immunization coverage is not enough in our area, as shown in this study that most children were either partially immunized or unimmunized. So, awareness about immunization needs to be increased. Strengthening of the infant feeding practices needs to be done by promoting exclusive breastfeeding for the first 6 months of life, followed by appropriate complementary feeding with continued breastfeeding. Under-5 children should be screened for protein-energy malnutrition at the community level for early diagnosis and prompt management as a way of reducing the high mortality associated with admitted severe cases. Nearly all SAM patients have micronutrient deficiencies (Iron, folic acid, and vitamin B12). So, micronutrient supplement (Iron, folic acid, and vitamin B12) needs to be given to all SAM patients.

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CASE REPORT

A Unique Case Report on "Bilateral Optic Neuropathy as a Rare Manifestation of Spontaneous Intracranial Hypotension"

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ABSTRACT

Spontaneous intracranial hypotension (SIH) is an uncommon condition characterized by low cerebrospinal fluid (CSF) volume through a dural defect leakage, which results in multiple debilitating clinical manifestations. Although ocular manifestations are common, vision impairment due to SIH is not commonly reported. Optic neuropathy is a rare yet significant complication of SIH. This case documents the association between optic neuropathy and SIH, highlighting the diagnostic challenges and the complexities of managing this condition.

Keywords: Orthostatic headache, bilateral optic neuropathy, subdural hygroma, dural venous thrombosis, epidural blood patch

The clinical characteristics of spontaneous intracranial hypotension (SIH) often result from stretching of the intracranial and cervical dura and dilatation of intracranial venous structures and dural sinuses resulting in orthostatic headache, neck pain, and radicular symptoms[1]. The common ocular manifestations include blurry vision, double vision, and ophthalmoparesis[2]. Visual field deficits are related to stretching of optic nerve over pituitary fossa or vascular congestions of the optic nerve. Optic neuropathy in SIH is a rare and underreported phenomenon. Previously one case reported an association between monocular optic neuropathy and SIH[1]. This is the first case documenting the association of bilateral optic neuropathy in SIH and sheds light on this infrequent complication.

CASE REPORT

A 21-year-old female with no known comorbidities presented with the complaints of insidious-onset, gradually progressive orthostatic headache for 1 year. The headache was holocranial, throbbing type of moderate to severe intensity associated with neck pain. Headache had gradually evolved into nonorthostatic chronic, persistent headache for 5 months. The headache was triggered by coughing and abrupt head movements. She also noticed gradually progressive painless diminution of vision of both eyes (right more than left [R > L]) in the last 4 months with no history of diplopia/lower cranial nerve involvement. There was no relevant medical history or previous trauma or lumbar puncture. On examination, patient was moderately built and nourished. There were no cutaneous or articular stigmata for connective tissue disorder. Cranial nerve examination revealed right eye relative afferent pupil defect (RAPD) (Fig. 1) with perception of light in right eye and visual acuity of 1/60 in left eye. Fundus examination revealed temporal pallor of optic disc (R > L) with well-defined margins with normal retinal vessels with dull macular foveal reflex suggestive of both eye primary optic neuropathy (R > L) (Fig. 2). Ocular movements were full; examination of lower cranial nerves, sensorimotor, cerebellum, and higher mental functions were unremarkable. On investigating, complete blood picture revealed microcytic hypochromic anemia; renal function tests, liver function tests, thyroid profile, urine routine were within limits. Voluntary counseling and testing for human immunodeficiency virus (HIV) was negative. Antinuclear antibody test,

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serum homocysteine, antiphospholipid antibody, serum angiotensin-converting enzyme were negative.

Optical coherence tomography revealed thinning of retinal nerve fiber layer of all quadrants in right eye, and superotemporal and inferotemporal quadrants in the left eye. A visual evoked potential (VEP) revealed no response in the right eye and reduced amplitude and prolonged P100 latency in left eye. A lumbar puncture was performed and the cerebrospinal fluid (CSF) opening pressure measured at the lateral decubitus position was 5 cm of H_2O with normal biochemistry and microbiological analysis including cartridge-based nucleic acid amplification test (CBNAAT) and adenosine deaminase (ADA). Noncontrast CT brain revealed thickened, hyperdense dura along the tentorium (Fig. 3). The contrast-enhanced magnetic resonance imaging (MRI) brain with magnetic resonance venography (MRV) revealed engorged dural spaces, enhancement of pachymeninges, flattening of pons, sagging of bilateral tentorial and cerebellar tonsils (Fig. 4 a-c) with thinning of both optic nerves complicated by chronic dural venous sinus thrombosis.

With the background of orthostatic headache, low CSF opening pressure, neuroimaging suggestive of engorged dural venous sinus and sagging of brain, the probability of SIH was considered. So, a MRI myelogram was done, which demonstrated CSF leak at left lower dorsal level (D11-D12) (Fig. 5). A final diagnosis of SIH was made. Patient was treated with adequate fluids, analgesics, anticoagulants, and subsequently 20 mL epidural blood patch in the lower thoracic region. The headache and general well-being improved and there was no further diminution of visual acuity. Repeat neuroimaging, VEP, visual field charting was planned for during follow-up.

On follow-up, visual field charting showed improvement of visual acuity 1/60 in right eye and 2/60 in left eye. VEP showed P100 latency of 136 ms in right eye and left eye P100 latency of 120 ms with reduced amplitude in both

Figure 1. Right eye RAPD.

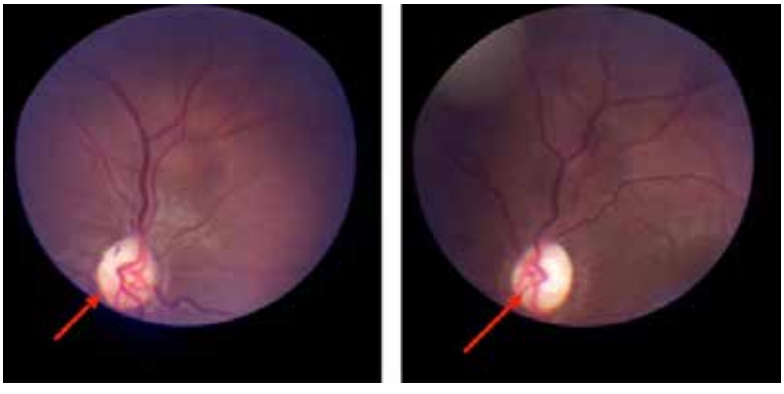

Figure 2. Both eye fundus - pale disc with well-defined margins, normal retinal vessels suggestive of primary optic neuropathy.

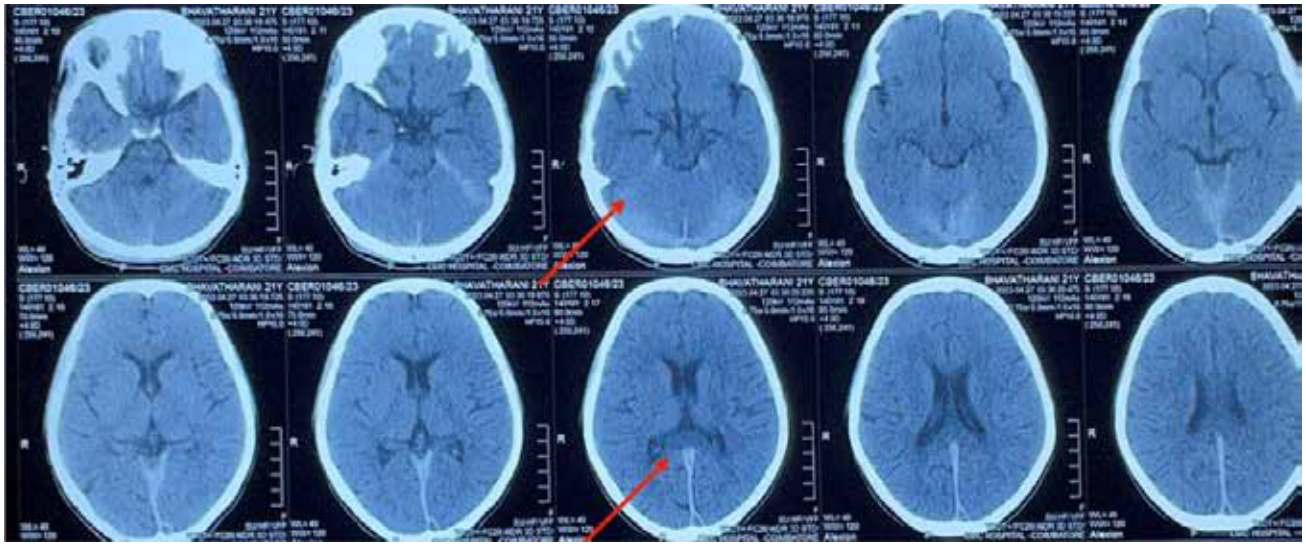

Figure 3. Noncontrast CT brain showing thickened hyperdense dural along posterior falx and tentorium.

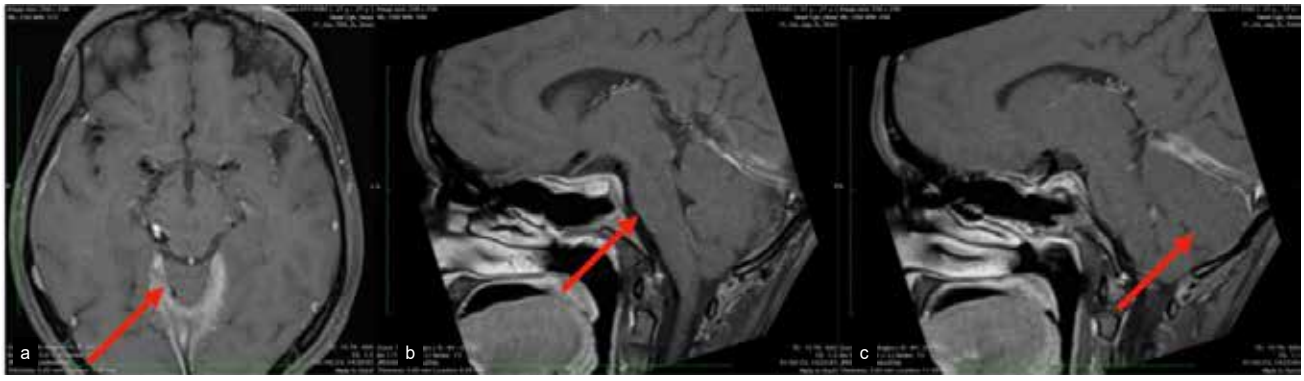

Figure 4. MRI contrast axial-engorged dural venous sinus **(a)**; MRI sagittal contrast flattening of pons **(b)**; and MRI sagittal contrast herniation of cerebellar tonsils **(c)**.

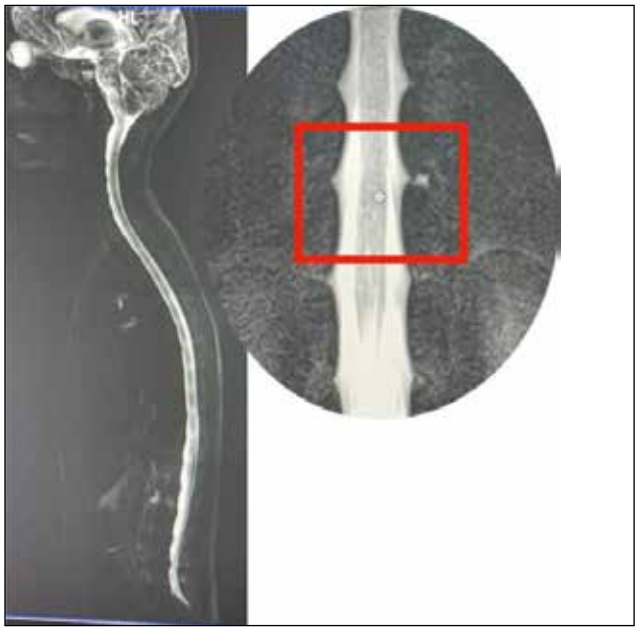

Figure 5. MRI myelography shows CSF leak at lower dorsal level (D11-D12).

eyes. However, MRI showed persistence of sagging of brain and it was planned to repeat in serial follow-ups.

On follow-up visual acuity improved in both eyes. Right eye visual acuity - 20/200 and left eye visual acuity 20/100. Both eye P100 latency is within limits. Neuroimaging findings are static at present.

DISCUSSION

Spontaneous intracranial hypotension is estimated to affect 5 per 1,00,000 people per year with a female preponderance[3]. It occurs when mechanical stressors (spiculated osteophytes, herniated discs, nerve root diverticula) incite small dural tears causing CSF to leak into extradural space[4,5]. It can also occur following lumbar puncture, head trauma, spinal shunts, or rarely spontaneously. It may be exacerbated by connective tissue disorder.

According to Monro-Kellie doctrine, skull is a rigid compartment, which contains brain parenchyma, blood, and CSF compartment[1]. CSF exerts a buoyant force suspending the cranial nerves and brain parenchyma and prevents it from sagging downward[2]. These components are balanced in a state of dynamic equilibrium in normal circumstances. When the volume of CSF decreases in SIH, it is compensated by increase in the volume of other components to maintain the equilibrium, which results in venous sinus engorgement, subdural effusion, enlargement of pituitary gland, pachymeningeal enhancement, vascular congestion of optic nerve[2]. This results in traction of intracranial dura resulting in orthostatic headaches, neck pain, and ophthalmoparesis. Similarly, downward traction of optic nerve causing damage to the sheath of the optic nerve along with vascular congestion of the intracranial portion of the optic nerve can account for optic neuropathy. A case of monocular optic neuropathy associated with SIH has earlier been reported, which was attributed to traction/compression and/or vascular congestion of the intracranial portion of optic nerve[1].

This is the first reported case of bilateral primary optic neuropathy in a patient with SIH and this could be attributed to downward traction of optic nerve resulting in optic nerve damage that would eventually result in optic neuropathy.

CONCLUSION

Postural headache and optic neuropathy could be the presenting symptoms of SIH and early recognition is of paramount importance for preserving vision. Our case underscores the importance of early recognition, and prompt intervention in recognizing optic neuropathy in patients with SIH so that we can prevent the potential

consequences of visual impairment or blindness. This also emphasizes the need for the treating physician to be vigilant in dealing with primary optic atrophy and SIH should be considered as one of the differential diagnoses in cases with the relevant clinical background.

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VIEWPOINT

Unravelling the Complexities of Diabetic Behavior: A Multifaceted Exploration of Psychological, Behavioral, and Societal Factors

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ABSTRACT

Diabetes management is a complex process influenced by various behavioral factors, which are crucial for developing effective interventions that promote optimal disease management and improve patient outcomes. This article explores the diverse behavioral manifestations associated with diabetes, shedding light on the psychological, physiological, and societal factors that underpin this complex interplay. Utilizing the mnemonics "DIABETES" and "DISTORTION", we interpret the behavioral dimensions of diabetes, emphasizing the need for holistic approaches addressing both physical and mental health. Our exploration reveals that diabetic behavior is shaped by a range of factors, including depression, impulsivity, anxiety, binge eating, emotional dysregulation, externalizing problems, somatic symptoms, sleep problems, substance abuse, denial, insulin stigma, suppression, taboo, oppositional behavior, resistance to therapy, template thinking, imitative behavior, oppression, and negativism. These factors interact and influence one another, resulting in a complex web of behavioral challenges that hinder effective diabetes management. By unravelling the underlying psychopathology and cognitive distortions that shape diabetic behavior, we can develop more personalized, holistic, and culturally sensitive approaches to diabetes care. The article highlights the need for integrated interventions that address the psychological, social, and cultural determinants of health, promote patient empowerment, and foster a proactive approach to diabetes management. Ultimately, this multifaceted exploration of diabetic behavior can inform the development of innovative strategies that improve health outcomes, enhance quality of life, and reduce the burden of diabetes on individuals and society.

Keywords: Multifaceted, mnemonic, distortion, stigma, suppression, taboo, holistic

Management of diabetes is a complex process influenced by various behavioral factors. Understanding these factors is essential for developing effective interventions that promote optimal disease management and improve patient outcomes. The intricate relationship between diabetes and human behavior forms a multifaceted domain crucial to understanding disease pathobiology, management, and outcomes[1] (Fig. 1). This article explores the diverse behavioral manifestations associated with diabetes, shedding light on the psychological, physiological, and societal factors that underpin this complex interplay. Utilizing the mnemonics "DIABETES" and "DISTORTION", the authors, hereby, have tried to interpret the behavioral dimensions of diabetes, emphasizing the need for holistic approaches addressing both physical and mental health.

DIABETES MNEMONIC

Depression, Delinquency, and Mood Disorder (D)

Mood disorders, including bipolar disorder, contribute to emotional dysregulation and instability. Depression, prevalent among individuals with diabetes, manifests as persistent sadness, hopelessness, worthlessness, disinterest in activities, along with multitude of somatic manifestations[2].

On the other hand, delinquency encompasses antisocial behavior marked by aggression, rule violation, and

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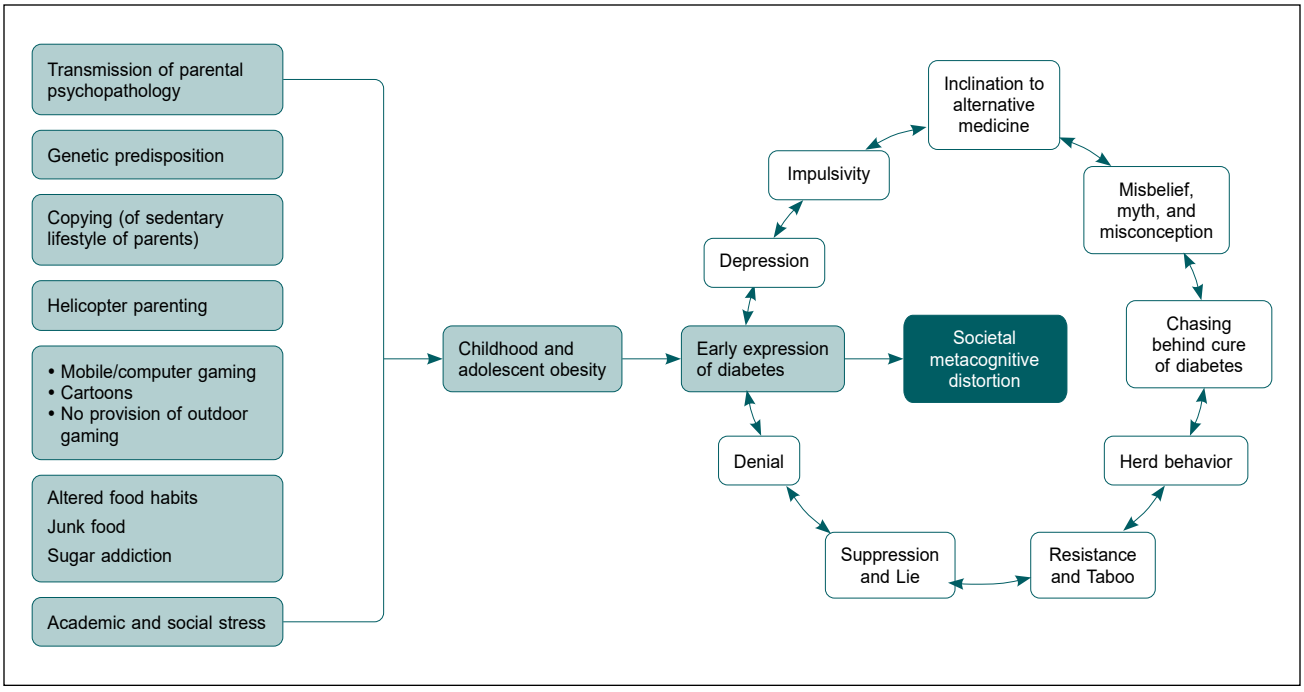

Figure 1. Intricate relationship between social, psychological, and behavioral factors leading to diabetes, and their interplay.

defiance. These psychological challenges compound the complexities of diabetes management, emphasizing the need for holistic approaches addressing both physical and mental health[3].

Impulsivity and Conduct Disorder (I)

Impulsivity, characterized by hasty decision-making and disregard for consequences, poses significant challenges to diabetes self-care. Conduct disorder, typified by antisocial behaviors and rule-breaking conduct, further complicates adherence to treatment regimens and lifestyle modifications[4].

Understanding the underlying drivers of impulsivity and conduct disorder is crucial for developing targeted interventions promoting self-control and adaptive coping strategies in individuals with diabetes.

Anxiety, Anger, Decreased Attention and Concentration, and Hyperactivity (A)

Anxiety disorders, prevalent among individuals with diabetes, exacerbate stress, and metabolic dysfunction. Anger and irritability arise from the frustrations and limitations inherent in diabetes management, impacting emotional well-being and interpersonal relationships. Decreased attention and concentration impair cognitive function, hindering decision-making and self-care behavior. Hyperactivity disrupts daily routines, exacerbating difficulties in managing diabetes effectively[5,6].

Binge Eating and Sugar Addiction (B)

Binge eating disorder, characterized by episodes of uncontrollable eating, contributes to dysregulated eating patterns and weight gain in individuals with diabetes. Sugar addiction, marked by cravings and compulsive consumption of sugary foods, poses challenges to glycemic control and dietary adherence. Addressing binge eating and sugar addiction requires strategies promoting mindful eating, moderation, and healthy coping mechanisms to mitigate their adverse effects on diabetes management[7].

Emotional Dysregulation and Eating Disorders (E)

Emotional dysregulation, characterized by difficulties in managing and expressing emotions, heightens vulnerability to mood disturbances and maladaptive coping strategies in individuals with diabetes[8]. Eating disorders, such as anorexia nervosa and bulimia nervosa, exacerbate metabolic dysfunction and nutritional deficiencies, complicating glycemic control, and overall health[9]. Integrating psychological interventions into diabetes care is essential for addressing emotional dysregulation and eating disorders and promoting holistic well-being.

Temper Tantrums (T)

Temper tantrums, i.e., sudden outbursts of anger or frustration, are common responses to the challenges and limitations of diabetes management. These emotional

reactions may stem from feelings of injustice, perceived restrictions, or conflicts surrounding treatment regimens and lifestyle modifications[5]. Strategies for emotion regulation and conflict resolution are crucial for mitigating the impact of temper tantrums on diabetes self-care and interpersonal relationships.

Externalizing Problems (E)

Externalizing problems, characterized by outwardly directed behaviors such as aggression and defiance, pose significant barriers to effective diabetes management. These behaviors may stem from underlying emotional, cognitive, or social factors and can interfere with treatment adherence and overall well-being[1-6]. Addressing externalizing problems requires a comprehensive approach targeting underlying risk factors, promoting positive coping strategies, and developing social skills.

Somatic Symptoms, Sleep Problems, and Substance Abuse (S)

Somatic symptoms, including pain, fatigue, and gastrointestinal distress, are common complaints among individuals with diabetes and may worsen due to psychological or emotional factors—sleep problems, such as insomnia and sleep apnea, further compromise metabolic health and cardiovascular risk[10]. Substance abuse, including alcohol and illicit drugs, presents additional challenges to diabetes management, contributing to treatment nonadherence and poor health outcomes[11].

DISTORTION MNEMONIC

Denial (D)

Denial emerges as a central theme in the behavioral repertoire of individuals with diabetes, reflecting a psychological defense mechanism characterized by refusal to accept the diagnosis and its implications[5,12]. From a cognitive perspective, denial may be driven by selective attention and memory biases, wherein individuals focus on information that aligns with their desired outcome (i.e., not having diabetes) while disregarding contradictory evidence. Metacognitive distortions, such as overconfidence in one's ability to control the disease through lifestyle modifications alone, may perpetuate denial and hinder efforts to foster acceptance and engagement with diabetes management.

Insulin Stigma (I)

Insulin stigma refers to the negative attitudes and beliefs surrounding insulin therapy among individuals with diabetes, which may stem from misconceptions about its efficacy, safety, or perceived association with disease severity. This stigma can have profound implications for treatment adherence and self-care behavior, as individuals may resist or delay initiation of insulin therapy due to fear of social judgment, injection-related pain, or perceived failure to manage the disease through other means[13,14]. Addressing insulin stigma requires a multifaceted approach that includes patient education, destigmatization efforts, and psychosocial support to promote acceptance and adherence to insulin therapy.

Suppression (S)

Suppression of diabetes-related symptoms and emotions is a common coping mechanism among individuals with diabetes, characterized by efforts to conceal or minimize the impact of the disease on daily functioning and emotional well-being. This may manifest as avoidance of diabetes-related discussions or activities, reluctance to seek medical care, or downplaying the severity of symptoms to oneself and others. However, prolonged suppression of diabetes-related distress can have detrimental effects on mental health and disease management, highlighting the importance of addressing emotional needs and fostering open communication in diabetes care[5,11,15].

Taboo (T)

Taboos surrounding diabetes, particularly in specific cultural or social contexts, may contribute to stigma, misinformation, and reluctance to seek appropriate medical care. Cultural beliefs about the causes and consequences of diabetes, as well as societal norms regarding body image, food, and health, can influence individual attitudes and behavior towards the disease. Addressing diabetes taboos requires culturally sensitive approaches that acknowledge and challenge prevailing beliefs, promote open dialogue, and empower individuals to make informed decisions about their health[16,17].

Oppositional Behavior (O)

Oppositional behavior refers to resistance or defiance towards diabetes management recommendations, often stemming from a sense of frustration, ambivalence, or perceived loss of autonomy. This may manifest as noncompliance with medication regimens, dietary restrictions, or lifestyle modifications, as well as reluctance to engage in self-monitoring or follow-up care[18-20]. Understanding the underlying motivations and psychosocial factors driving oppositional behavior

is essential for tailoring interventions that address individual needs, preferences, and barriers to adherence.

Resistance to Therapy (R)

Resistance to therapy encompasses a spectrum of challenges related to treatment adherence, efficacy, and acceptability among individuals with diabetes. This may include reluctance to initiate or intensify medication regimens, concerns about side effects or long-term consequences, or dissatisfaction with the perceived impact of treatment on quality of life. Addressing resistance to therapy requires a patient-centered approach that considers individual preferences, beliefs, and experiences, as well as ongoing monitoring and support to optimize treatment outcomes[5,11,13,14,18-20].

Template Thinking (T)

Template or block thinking refers to rigid or inflexible cognitive patterns that limit problem-solving abilities and hinder adaptive coping strategies in diabetes management. This may manifest as black-and-white thinking, catastrophizing, or cognitive distortions that impair decision-making and self-regulation. Cognitive-behavioral interventions aimed at challenging and modifying maladaptive thinking patterns can enhance resilience, self-efficacy, and coping skills in individuals with diabetes[5,11,13,14,18-20].

Imitative Behavior (I)

Imitative behavior refers to the tendency to model or mimic the actions and beliefs of others, particularly in social or familial contexts. In the context of diabetes management, imitative behavior may influence treatment adherence, dietary habits, and lifestyle choices through social norms, peer pressure, or familial influences. Understanding the social determinants of health and interpersonal dynamics that shape imitative behavior is essential for developing targeted interventions that promote positive health behaviors and mitigate risk factors for diabetes complications[5,11,13,14,18-20].

Oppression (O)

Oppression encompasses structural barriers, systemic inequalities, and social injustice that disproportionately affect individuals with diabetes, particularly those from marginalized or disadvantaged communities. This may include limited access to health care resources, economic disparities, discrimination in health care settings, or environmental factors that hinder healthy lifestyle choices[21,22]. Addressing oppression requires advocacy, policy change, and community-based initiatives aimed at promoting health equity, social justice, and empowerment for individuals with diabetes.

Negativism (N)

Negativism refers to a pessimistic or defeatist attitude towards diabetes management, characterized by a sense of hopelessness, resignation, or fatalism regarding the ability to control the disease and prevent complications. This may manifest as passive acceptance of diabetes-related symptoms or complications, reluctance to engage in self-care behavior or disengagement from health care services. Psychosocial interventions that enhance resilience, optimism, and self-management skills can mitigate negativism and foster a proactive approach to diabetes care[23,24].

CONCLUSION

The exploration of diabetic behavior demands rigorous scientific inquiry that integrates insights from psychology, neuroscience, endocrinology, and public health. By unravelling the underlying psychopathology and cognitive distortions that shape diabetic behavior, we can pave the way for more personalized, holistic, and culturally sensitive approaches to diabetes care that prioritize patient empowerment, well-being, and health equity[5,25,26].

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■■■■

BRIEF COMMUNICATION

Effect of Background Diuretic Therapy on the Clinical Efficacy of SGLT2 Inhibitors in Patients of Heart Failure with Reduced Ejection Fraction: Current Evidence

KAMAL KISHOR*, DEVENDRA SINGH BISHT†, ASHOK KUMAR‡

ABSTRACT

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a fundamental therapy for heart failure with reduced ejection fraction (HFrEF). The clinical efficacy of SGLT2 inhibitors in the presence of background diuretic therapy has been questioned, mainly because of the overlapping diuretic mechanism of action. However, recently, data analysis from two landmark trials, DELIVER and EMPEROR-Reduced, has attempted to settle this question. Both analyses demonstrate a consistent benefit of SGLT2 inhibitors across a wide range of background diuretic therapy. This brief communication sheds light on the key findings from these scientific studies.

Keywords: SGLT2 inhibitors, heart failure, DELIVER, EMPEROR-Reduced

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have been given class 1 recommendation for managing patients of heart failure with reduced ejection fraction (HFrEF)[1,2]. SGLT2 inhibitor treatment can significantly reduce the rates of cardiovascular death and hospitalization due to heart failure (HF). The beneficial effect of SGLT2 inhibitors is regardless of the patient's glycemia levels and extends even in patients with an estimated glomerular filtration rate (eGFR) as low as 20 mL/min/1.72 m^2 [3,4]. Additionally, the clinical benefits of SGLT2 inhibitors are regardless of the dose or combination of other novel disease-modifying therapies used for HFrEF.

KEY QUESTION

Considering the osmotic diuretic effect of SGLT2 inhibitors, physicians worldwide have expressed concerns that the favorable clinical results demonstrated by SGLT2 inhibitors in patients with HFrEF might be attributed to the concomitant use of loop diuretic therapy. Therefore, there is a debate about how diuretic use affects the effectiveness of SGLT2 inhibitors in patients with HFrEF.

In the context of HFrEF, two scientific papers prespecified the analysis of the DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With Preserved Ejection Fraction Heart Failure) trial[5], and a post-hoc analysis of the EMPEROR-Reduced (EMPagliflozin outcomE tRial in Patients with chrOnic heaRt Failure With Reduced Ejection Fraction) trial[6] recently explored the effect of background diuretic therapy on the clinical efficacy of SGLT2 inhibitors.

The DELIVER trial[7] looked at patients with HF who had mildly reduced to preserved ejection fraction, whereas the EMPEROR-Reduced trial[4] examined patients with more advanced HF. Both analyses showed similar findings regarding the cardiac impact of background diuretic therapy on the clinical effectiveness of SGLT2 inhibitors.

KEY FINDINGS

Four critical findings are worth mentioning.

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Higher Baseline Diuretic Doses Indicate More Advanced HF

Individuals with high initial prescription of diuretics are likely to have more advanced HF, making them more susceptible to various negative clinical outcomes. Such individuals have elevated levels of N-terminal pro–B-type natriuretic peptide levels, higher rates of HF hospitalization, and poor baseline Kansas City Cardiomyopathy Questionnaire (KCCQ) scores. Additionally, these patients also have higher body mass index, higher rates of diabetes, and chronic kidney disease.

Attenuated Efficacy of SGLT2 Inhibitor in the Background of Higher Baseline Diuretic

A post-hoc analysis of the EMPEROR-Reduced trial revealed that empagliflozin was less effective in reducing the number of HF hospitalizations in patients taking high doses of diuretic agents. These patients are typically sicker and have a higher burden of comorbidities. The trial also found that such individuals had higher rates of discontinuing guideline-directed medical treatment. This partially explains why empagliflozin is less effective in individuals of HFrEF on higher baseline diuretics.

The Treatment Effect of SGLT2 Inhibitor Remains Consistent Irrespective of Baseline Diuretic Therapy

SGLT2 inhibitors demonstrated consistent beneficial effects irrespective of the baseline diuretic therapy. SGLT2 inhibitors lead to consistent improvement in cardiovascular death, time-to-first hospitalization for HF, and worsening HF events, including urgent hospital visits for need of intravenous HF therapies. Additionally, benefits did not significantly vary by baseline diuretic use/type or loop diuretic dose. SGLT2 inhibitors result in an improvement of the KCCQ total symptom score across all doses of diuretics.

SGLT2 Inhibitor Exhibited a Diuretic-Sparing Effect

SGLT2 inhibitor exhibits a diuretic-sparing effect. It delays the first diuretic dose increase (except for those taking the highest doses of diuretic agents) and diuretic initiation (in those not taking diuretic agents at baseline). Individuals on dapagliflozin, when compared to placebo, less frequently experience a loop diuretic initiation or dose increase (14.8% vs. 19.6%, $p < 0.001$) and more regularly experience a loop diuretic discontinuation or dose decrease (14.7% vs. 16.5%, $p < 0.001$). Additionally, treatment with dapagliflozin significantly attenuates the rate of rise in loop diuretic dose relative to placebo, resulting in a mean dose reduction over time of 2.5 mg/year (95% confidence interval [CI]: −1.5, −3.7, $p < 0.001$). Similarly, empagliflozin lengthens the time to first diuretic dose increase in all patients taking diuretic agents at baseline (hazard ratio [HR]: 0.68 [95% CI: 0.58-0.80]; $p < 0.001$) and time to diuretic initiation among patients taking no diuretic agents at baseline (HR: 0.62 [95% CI: 0.44-0.88]; $p < 0.01$).

CONCLUSION

To sum up, the results from these analyses confirm the scientific assertion that the positive impact of SGLT2 inhibitors on individuals with HFrEF is consistent across the various doses of background diuretic therapy. Moreover, these insightful analyses allay any apprehensions that certain clinical benefits observed in trials may be attributed to concurrent diuretic therapy.

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Nutritional Recommendations in Gestational Diabetes

SNIGDHA SINGH

- The global rise in the gestational diabetes mellitus (GDM) prevalence and have led to the search for a realistic, feasible, and widely adaptable approach to nutrition therapy to help control maternal glycemia effectively along with promoting normal fetal growth[1].
- Women with GDM have similar nutritional requirements to non-GDM pregnancies but demand a special focus on dietary modification to ensure healthy and mindful eating to achieve and maintain maternal euglycemia, prevent wide glycemic excursions and ensure appropriate gestational weight gain (GWG) and fetal growth[1].

NUTRITIONAL RECOMMENDATIONS

Carbohydrate Restriction

- Carbohydrate restriction is a frequent component of medical nutrition therapy (MNT) in GDM[1].
- The American College of Obstetricians and Gynecologists (ACOG) and the Endocrine Society recommend restricting carbohydrate intake for all GDM women under the MNT program[1].
- The International Federation of Gynecology and Obstetrics (FIGO) recommends monitoring the carbohydrate intake, the quality of carbohydrates consumed and dispersing them throughout the day to achieve and maintain euglycemia[1].
- The amount of permissible carbohydrates varies from 35% to 40% of total calories in the lower carbohydrate range to 50%-60% in the moderate carbohydrate range[1].
- Moreover, the general agreement recommends not limiting carbohydrate intake to <175 g/day[1].

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Reproductive age women who follow a low-carbohydrate dietary pattern are likely to benefit from consuming vegetables rather than animal sources of protein and fat as it minimizes their risk of GDM[1].

Low Glycemic Index Diets

- Diets higher in unrefined/complex carbohydrates can effectively blunt postprandial glycemia, reduce the need for insulin therapy, lower fasting low-density lipoprotein (LDL) cholesterol levels and free fatty acids (FFAs), and improve insulin sensitivity, glycated hemoglobin (HbA1c) and systolic blood pressure in GDM[1].
- Thus a low-to-moderate gastrointestinal diet is recommended in GDM[1].

Dietary Fiber

- Fiber intake helps to lower serum lipid levels and reduce glycemic excursions[1].
- High fiber intake also reduces constipation, a common problem in pregnancy[1].
- Up to 28-g daily fiber intake is recommended for women[1].

Fat

- Increased consumption of total and saturated fat could worsen insulin resistance (IR) and increase fetal nutrient exposure, promoting overgrowth patterns[1].
- The recommendations from most GDM guidelines for fat intake fall in the range of 20% to 35% of daily energy intake (EI)[1].

Protein

- Adequate protein intake during pregnancy is important to rescue maternal stores depletion and muscle breakdown to supply for the fetal needs[1].
- Most nutrition guidelines recommend a protein intake ranging from 10% to 20% of daily EI or about 60 to 80 g of protein intake daily[1].

- The Indian guidelines recommend an additional 23 g of protein intake daily during pregnancy for adult women[1].
- However, it may be restricted in presence of renal failure[1].

Mediterranean Diet

- Mediterranean diet interventions advised early in the pregnancy or to pre-pregnant women can reduce GDM incidence and maternal-fetal adverse outcomes[1].

Non-nutritive Sweeteners

- A few guidelines recommend the use of aspartame, saccharin, acesulfame, and sucralose in moderate amounts[1].
- The Academy of Nutrition and Dietetics also accept using advantame, neotame, luo han guo extracts and steviol glycosides as per the FDA acceptable daily intake limits in women with GDM[1].
- The use of cyclamates is not approved[1].

Interventions to Prevent GDM: Probiotics and Myoinositol

- Studies have shown that probiotics (*Lactobacillus rhamnosus* and *Bifidobacterium lactis* Bb12) can reduce the incidence of GDM[1].
- Probiotic protects against GDM as these micro-organisms can modify intestinal microbiota, altering the fermentation of dietary polysaccharides and improving intestinal barrier function[1].
- Myoinositol, an isomer of inositol, has a potential beneficial effect on improving insulin sensitivity and thus may be useful for women in preventing GDM[1].

In women at high risk of developing GDM, dietary advice, probiotics, and myoinositol supplementation might reduce the incidence of GDM[1].

Carbohydrates

- Opt for high-fiber, whole-grain carbohydrates[2].
- Avoid eating simple carbohydrates like potatoes, french-fries, white rice, candy, soda, etc[2].

Grains, Beans, and Starchy Vegetables

Eat 6 or more servings/day with 1 serving equals[2]:

- 1 slice bread
- 1 ounce (28 g) ready-to-eat cereal
- 1/2 cup (105 g) cooked rice or pasta
- 1 English muffin.

Opt for foods loaded with vitamins, minerals, fiber, and healthy carbohydrates like[2]:

- Whole-grain breads and crackers
- Whole-grain cereals
- Whole grains, such as barley or oats
- Beans
- Brown or wild rice
- Whole-wheat pasta
- Starchy vegetables, such as corn and peas.

Vegetables

Eat 3 to 5 servings/day with 1 serving equals[2]:

- 1 cup (340 g) leafy, green vegetables
- 1 cup (340 g) cooked or chopped raw leafy vegetables
- 3/4 cup (255 g) vegetable juice
- 1/2 cup (170 g) of chopped vegetables, cooked or raw.

Opt for healthy vegetable choices like Fresh or frozen vegetables without added sauces, fats or salt; Dark green and deep yellow vegetables, like spinach, broccoli, romaine lettuce, carrots, and peppers[2].

Fruits

Eat 2 to 4 servings/day with 1 serving equals[2]:

- 1 medium whole fruit (such as a banana, apple or orange)
- 1/2 cup (170 g) chopped, frozen, cooked, or canned fruit
- 3/4 cup (180 mL) fruit juice.

Opt for healthy fruit choices like whole fruits rather than juices; Citrus fruits like oranges, grapefruits and tangerines; Fruit juices without added sugar; Fresh fruits and juices instead of frozen or canned varieties[2].

Milk and Dairy

Eat 4 servings of low-fat or nonfat dairy products/day with 1 serving equals[2]:

- 1 cup (240 mL) milk or yogurt
- 1 1/2 oz (42 g) natural cheese
- 2 oz (56 g) processed cheese.

Opt for healthy dairy choices like low-fat or nonfat milk or yogurt[2].

Protein (Meat, Fish, Dry Beans, Eggs, and Nuts)

Eat 2 to 3 servings/day with one serving equals[2]:

- 2 to 3 oz (55-84 g) cooked meat, poultry or fish
- 1/2 cup (170 g) cooked beans
- 1 egg
- 2 tablespoons (30 g) peanut butter.

Opt for healthy protein choices like fish and poultry (discard the skin from chicken and turkey); Lean cuts of beef, veal, pork, or wild game[2].

Sweets

- Limit the sweet intake with small portion sizes[2].
- Moreover, sugar-free sweets too may not be the best choice[2].

Fats

Limit your intake of fatty foods[2]:

- Spare much use of butter, margarine, salad dressing, cooking oil, and desserts[2].
- Adopt healthy oils, like canola oil, olive oil, peanut oil, and safflower oil. Include nuts, avocados, and olives[2].

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Consent

Consent is crucial to validate any act involving two persons. A valid consent to medical procedures is an essential component for every interaction between all doctors and patients.

Consent is considered as legally valid, if the following hold true:

- The patient is legally competent, i.e., he is an adult, with a healthy mind and understanding
- Consent is given voluntarily
- The person giving consent has been well informed
- Everything told to the patient must be recorded
- Consent is patient-specific
- If a competent adult refuses to get treatment, his decision must be respected.

Consent of the patient or the legal guardian is necessary to conduct an examination. In cases labeled as medicolegal, an informed consent includes the following information:

a) the examination to be conducted is a medicolegal one and would be followed by the preparation of a medicolegal injury report,

b) all the necessary investigations required would be done, and

c) the findings of the report could go against the patient if they are not in line with the history given by the patient.

An accused arrested in a criminal offence can be examined without his consent on the police's request or on the orders of the court, if the examination is believed to provide evidence that the offence has been committed.

While examining a woman, examination by a lady doctor should be preferred. If this is not possible, a female attendant such as a nurse should be present at the time of examination.

IMPORTANCE OF CONSENT

- Consent depicts the right of a patient to make a decision regarding his medical treatment.
- Consent refers to voluntary participation of the patient in his own treatment by a physician or an institute.
- Consent is essential for all diagnostic and therapeutic procedures that are associated with risk/adverse effects or complications.
- Consent is mandatory for all medicolegal cases.

TYPES OF CONSENT

Implied Consent

Implied consent is where the behavior and the conduct of a patient suggest his consent. It implies consent to medical examination in a general sense, for instance, when a patient puts forth his arm for an intramuscular injection. This is the most common form of consent in medical practice. It is not expressed, yet legally effective. However, implied consent is generally limited to common procedures of medical examination.

Expressed Consent

Expressed consent is when a patient clearly expresses his consent to undertake diagnostic or therapeutic treatment. This may be either verbally expressed or may be expressed in writing after the patient is informed about all the aspects of the diagnostic and therapeutic procedure.

When the patient expresses consent to a specific diagnostic or therapeutic procedure verbally, it is termed as oral or verbal expressed consent. When the consent is given in writing, it is called as written expressed consent. Both these forms of expressed consent are acceptable in the court of law as proof of consent; however, written expressed consent is more valuable as it is a permanent written record. To be legally acceptable, expressed consent must agree to the doctrine of informed consent.

Blanket Consent

Blanket consent is taken on a printed form that details almost everything that a doctor or hospital might do to a patient. Blanket consent is legally inadequate for procedures that have risks and alternatives.

ELEMENTS OF INFORMED CONSENT

Disclosure of Information

The following are included in disclosure of information:

- A doctor is required to explain the exact nature of the disease to the patient.

- A doctor should explain the need for the treatment and the nature of the procedure as well as the expectation from the recommended therapeutic intervention besides the probability of success.
- The patient must be informed about the alternative forms of treatment available, with the associated benefits and anticipated adverse effects or risks and complications linked with both the proposed and alternative procedure.
- The patient has the right to choose between proposed and alternative procedure.
- The patient's right to refuse all of these procedures and the medicolegal outcomes of refusal.

Voluntary Consent

The patient's consent must be voluntary and free from any intimidation, force and misrepresentation of facts. A consent is legally valid only if it is informed and voluntary and has been taken freely and exclusively by the patient. No one else has the authority to give consent on behalf of the patient (with few exceptions).

Capacity to Decide

Capacity to decide is a significant aspect of informed consent. An individual who is able to understand the nature of the act/procedure and its probable consequences should give consent. The person giving the consent must be mature enough to understand, evaluate and estimate the risks and benefits associated with the proposed treatment. He should be able to accept the responsibility for the informed consent given to the proposed treatment. Following are the characteristics that describe a competent person:

- A person with a sound mind
- A person with proper reasoning
- One who understands the implications of his consent
- A person who is at least 12 years of age.

The informed consent is considered to be legally valid if all the aforementioned components are fulfilled.

Special Circumstances

- If the patient is a child <12 years of age, consent is taken from the parent or guardian.
- In an emergency involving a child where parents and guardians are not available, consent can be obtained from the person who is in charge of the child at that moment (*Loco Parentis*).
- Consent given for an illegal act is not valid.
- In an emergency where the patient is unconscious and unfit to give consent, emergency doctrine is applicable.
- Consent of spouse for operation and treatment in the routine course is not necessary. However, consent is required if the procedure/instrument used involves danger to life or can impair sexual functions.
- Consent of both the spouses is required in case of an operation involving reproductive and sexual organs, such as sterilization. In cases of artificial insemination donor, consent is need from both the recipient husband and wife and the donor and his wife.
- Under Medical Termination of Pregnancy Act 1972, for MTP, the consent of pregnant woman is sufficient if she is >18 year of age and has sound disposing mind. If the pregnant woman is <18 years old, unconscious or is of unsound mind, consent is taken from her parent or legal guardian.
- Any information pertaining to the nature of illness of the patient can not be disclosed to a third party without his consent except in the following situations:
  - Privileged communication.
  - Case of negligence against the doctor where he can reveal the secrets in his defense.
  - When asked by the honorable court or judge.
- Consent should be taken from the next of kin of a deceased person for performing clinicopathological autopsy. Consent is not required for medicolegal autopsy since the law of the land gives the consent.
- For cadaveric transplantation, consent is taken form the next of kin, who is in possession of the dead body.
- For publication of patient's record or data or photographs, in articles or journals, consent must be taken from them and assurance should be given that their identity will be protected.
- Written informed consent should be obtained from individuals participating in a research program/ clinical trial.

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HCFI Dr KK Aggarwal Research Fund

Minutes of an International Weekly Meeting on "Chronic Kidney Disease and Its Management"

Speaker: Dr DK Sinha, *MD, DM Nephrology. Senior Consultant, Dept. of Nephrology, Heritage Hospitals, Varanasi, Uttar Pradesh*

February 24, 2024 (Saturday, 9.30-10.30 am)

- As the population grows older, the incidence of chronic kidney disease (CKD) is also rising. Most CKD patients are in stages 1 to 3.
- Among adults aged 65 to 74 years, 20% of men and 25% of women have CKD. In persons older than 75 years, 40% of men and 60% of women may have CKD.
- Around 14% of adults in US are estimated to have CKD. The incidence of CKD in the Indian population was determined to be 14% to 16% in the Screening and Early Evaluation of Kidney Disease (SEEK) study.
- CKD is defined as abnormalities in structure and function, which have been present for more than 3 months.
- Markers of CKD include albuminuria, abnormal urinary sediment, electrolyte abnormalities, histological abnormalities and structural abnormalities detected by imaging, or if the patient has persistent fall in estimated glomerular filtration rate (eGFR).
- There are five stages of CKD. Stage 3, which is mild to moderate kidney damage, has been further categorized as stage 3a and 3b. This stage of CKD is usually ignored as the test reports are very close to normal.
- The extent of albuminuria is very important. It has been classified into A1 (urinary albumin-creatinine ratio [UACR] <30 mg/g), A2 (UACR 30-399 mg/g), and A3 (>300 mg/g).
- eGFR and UACR are important in classification of CKD and also its prognosis.
- Most CKD patients do not reach the stage of end-stage renal disease (ESRD) as they usually succumb to complications such as cardiovascular (CV) and cerebrovascular events.
- Patient's history provides clues to the diagnosis of CKD. These include symptoms during urination, recent infection, skin rash or arthritis, any parenterally transmitted diseases, chronic diseases such as diabetes, hypertension, skin disease; past medical history such as nonsteroidal anti-inflammatory drug (NSAID) intake, past urologic evaluation, family history of kidney disease.
- Majority of patients with CKD have diabetes (40%) and hypertension (27%). Hence, more attention has to be paid to manage these conditions. Other causes include glomerulonephritis (11%), interstitial nephritis (4%); around 18% cases may be due to other causes.
- Factors associated with progression include cause of CKD, level of GFR, level of albuminuria, age, sex, race/ethnicity, elevated blood pressure (BP), hyperglycemia, dyslipidemia, smoking, obesity, history of cardiovascular disease (CVD), ongoing exposure to nephrotoxic agents.
- Early treatment can make a difference in CKD. Intervention in the early stage of the disease may allow longer duration of dialysis-free life.
- Approaches to preserving kidney function include symptom management, palliative care and kidney-preserving care.
- Kidney-preserving care aims to slow progression of disease, prevent or delay diagnosis, and improve CV risk. The components of kidney-preserving care include diet and lifestyle, pharmacotherapy for disease progression, for CV risk management, and for other comorbidities such as bone health, anemia. Comprehensive care is needed to retard the progression of CKD.
- A low protein diet is recommended. Protein intake should be lowered to 0.8 g/kg/day in adults with diabetes or without diabetes and GFR <30 mL/min/1.73 m^2. Protein intake >1.3 g/kg/day in adults with CKD at risk of progression should be avoided.
- Salt intake should be lowered to <2 g/day of sodium, unless contraindicated.
- CKD patients should be encouraged to undertake physical activity compatible with CV health and tolerance (at least 30 minutes 5 times in a week), achieve a healthy weight (body mass index [BMI] 20-25), and quit smoking.

- Patients with type 1 diabetes should be screened annually starting 5 years after diagnosis, while type 2 diabetes patients should undergo yearly screening starting at diagnosis. Tests used for screening are eGFR and spot UACR.
- Parameters used to define CKD are persistent UACR >30 mg/g and/or persistent eGFR <60 mL/min/1.73 m^2 and/or other evidence of kidney damage.
- A target glycated hemoglobin (HbA1c) of ~7% is recommended to prevent or delay progression of diabetic kidney disease, including other microvascular complications of diabetes.
- In CKD patients with diabetes, glycemic control should be a part of a multifactorial intervention strategy addressing BP and CV risk, promoting the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), statins and antiplatelet therapy where clinically indicated.
- Sodium-glucose cotransporter-2 (SGLT2) inhibitors are being used to retard the progression of CKD in type 2 diabetes. They act by reducing plasma glucose, body weight, BP, plasma uric, acid and glomerular hyperfiltration. Few landmark trials have shown the benefits of SGLT2 inhibitors.
- The CREDENCE trial has shown that in patients with type 2 diabetes and CKD, canagliflozin reduced the risk of kidney failure and CV events. The risk of primary outcome (doubling of serum creatinine, ESRD and death due to CV, or kidney disease) reduced by 30%, while risk of ESKD reduced by 22%.
- In the DAPA-CKD multicenter, multinational study, dapagliflozin significantly reduced the risk of kidney failure, CV death or hospitalization for heart failure, and all-cause mortality in patients with CKD, with and without type 2 diabetes compared to placebo. It was well-tolerated in keeping with its established safety profile.
- In patients with IgA nephropathy, when added to ACE inhibitor/ARB therapy, dapagliflozin significantly and substantially reduced the risk of CKD progression and major adverse kidney events in a prespecified analysis of DAPA-CKD trial.
- In the EMPA-KIDNEY trial, empagliflozin therapy led to lower risk of progression of kidney disease or death from CV causes compared to placebo in patients with CKD who were at risk of disease progression.
- Glucagon-like peptide-1 (GLP-1) agonists such as semaglutide have also shown beneficial effects in CKD patients.
- Start treatment with renin-angiotensin system (RAS) inhibitors (ACE inhibitors/ARBs) in patients with CKD, high BP, with or without diabetes. The highest approved should be used and gradually tailored. Changes in BP, creatinine and potassium should be monitored regularly, ideally at an interval of 2 to 4 weeks in the initial period.
- Take measures to reduce serum potassium levels to manage the hyperkalemia associated with the use of RAS inhibitor rather than reducing the dose or stopping RAS inhibitor.
- Continue ACE inhibitor/ARB unless the serum creatinine rises by 30% within 4 weeks following initiation of treatment or an increase in dose.
- If case of symptomatic hypotension or uncontrolled hyperkalemia despite medical treatment or to reduce uremic symptoms, while treating kidney failure (eGFR <15), consider reducing the dose or stopping ACE inhibitor/ARB.
- Mineralocorticoid receptor antagonists are effective for management of refractory hypertension but may cause hyperkalemia or a reversible decline in kidney function, especially in patients with low eGFR.
- The 2021 KDIGO guideline recommends treatment to reduce systolic BP to <120 using standardized office BP measurement. It also recommends use of ACE inhibitors/ARBs for adults with albuminuria and high BP (systolic ≥120).
- In the RENAAL trial published in *NEJM*, losartan reduced the primary outcome of doubling of serum creatinine, ESRD and mortality by 43% (vs. 47% with placebo) and ESRD by 19% (vs. 25% with placebo) in patients with type 2 diabetes and nephropathy.
- The Irbesartan Diabetic Nephropathy Trial (IDNT) also demonstrated the renoprotective effect of irbesartan in type 2 diabetic with nephropathy. Irbesartan reduced the primary composite endpoint by 20% (vs. placebo) compared to 23% reduction in risk with amlodipine.
- In CKD patients without anemia, hemoglobin (Hb) should be measured when clinically indicated and at least annually in patients with stage 3 CKD, at least twice per year in patients with CKD4-5 ND (non-dialysis) and at least every 3 months in patients with CKD5-HD (hemodialysis) and at least

every 3 months in patients with CKD5-HD and CKD5-PD (peritoneal dialysis).

- In CKD patients with anemia not being treated with an erythropoiesis-stimulating agents (ESA), Hb should be measured when clinically indicated and at least every 3 months in patients with CKD3-5 ND and CKD5-PD and at least monthly in patients with CKD5-HD.
- Tests in the initial evaluation of anemia included complete blood count, absolute reticulocyte count, serum ferritin, serum transferrin saturation, serum vitamin B12, and folate levels.
- Anemia is diagnosed when Hb is <13 (in males) and <12 (in females) in adults and children older than 15 years of age.
- In children with CKD, anemia is diagnosed when Hb is <11 in children 0.5 to 5 years, <11.5 in children 5 to 12 years, and <12 in children aged 12 to 15 years.
- Easily correctable causes of anemia, in addition to ESA deficiency, are absolute iron deficiency, vitamin B12/folate deficiency, hypothyroidism, ACE inhibitor/ARB nonadherence. Hemoglobinopathies and bone marrow disorders are factors that are impossible to correct.
- In ESA hyporesponsiveness, check for adherence, reticulocyte count (if >130,000/uL, look for blood loss or hemolysis), serum vitamin B12/folate (if low, replenish), iron status (if low, replenish iron), serum parathyroid hormone (PTH) (if elevated, manage hyperparathyroidism), serum C-reactive protein (if elevated, check for and treat infection or inflammation), use of ACE inhibitor/ARB (if yes, consider reducing the dose or stopping the drug), bone marrow biopsy (manage the condition diagnosed).
- ESA should be considered in predialysis patients with Hb levels <10 g/dL and in dialysis patients with Hb 9-10 g/dL. Target Hb for maintenance is 10-11.5 g/dL in CKD patients.
- Serum levels of calcium, phosphate, PTH and alkaline phosphatase (ALP) activity beginning in CKD G3a. In children, this monitoring should begin in CKD G2.
- In patients with CKD G3a-G5D, it is reasonable to base the frequency of monitoring serum calcium, phosphate and PTH on the presence and magnitude of abnormalities and the rate of progression of CKD.
- In CKD G3a-G3b: Measure serum calcium and phosphate every 6 to 12 months and for PTH based on baseline level and CKD progression.
- In CKD G4: Measure serum calcium and phosphate every 3 to 6 months and for PTH every 6 to 12 months.
- In CKD G5 including G5D: Measure serum calcium and phosphate every 1 to 3 months and for PTH every 3 to 6 months.
- In CKD G4-G5D, measure ALP every 12 months or more frequently if PTH is elevated.
- In CKD patients on treatment for CKD-MBD (mineral bone disorder) or in whom biochemical abnormalities are identified, it is reasonable to increase the frequency of measurements to monitor for trends and treatment efficacy and side effects.
- In patients with CKD G3a-G5D, calcidiol levels can be measured. Repeat testing is done based on baseline values.
- Vitamin D deficiency and insufficiency should be corrected using treatment strategies recommended for the general population. Therapeutic decisions should be based on trends rather than on single lab value.
- In patients with CKD G3a-G5D, it is reasonable to perform bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions.
- Multiple new prospective studies have documented that lower dual energy X-ray absorptiometry BMD (bone mineral density) predicts incident fractures in patients with CKD G3a-G5D.
- CKD is closely related to CVD. Chances of having a CVD are 2.5 to 3 times higher in CKD patients; hence, they should be closely watched for CVD.
- Reduction of cardiorenal risk in patients with CKD is through risk factor management (BP target 130/80, HbA1c <7.0, LDL lowering with statins/ezetimibe), use of ACE inhibitors/ARBs, SGLT2 inhibitors, and finerenone.
- Calculation of GFR is very important prior to prescribing any medication. Avoid potentially nephrotoxic drugs. Metformin dose modification should be done based on GFR.
- CKD patients should seek medical advice before using over-the-counter medicines or nutritional protein supplements. Herbal remedies should be avoided.

- CKD patients should be referred for specialist kidney care, in case of acute kidney injury (AKI) or abrupt sustained fall in GFR or GFR <30 mL/min/1.73 m^2 or consistently significant albuminuria or PER or progression of CKD or urinary red cell casts or CKD and hypertension refractory to treatment to ≥4 antihypertensive agents or recurrent nephrolithiasis.
- Patients with progressive CKD in whom the risk of kidney failure within 1 year is 10% to 20% higher should be referred in time for renal replacement therapy (RRT).
- Patients with progressive CKD should be managed in a multidisciplinary setting with access to dietary counseling, transplant options, vascular access surgery. Patient should be prepared for initiation of RRT.
- Dialysis should be initiated when there are symptoms or signs of kidney failure, progressive deterioration in nutritional status refractory to dietary intervention or cognitive impairment.
- Living donor renal transplantation in adults should be considered when the GFR is <20 mL/min/1.73 m^2 and there is evidence of progressive and irreversible CKD over the preceding 6 to 12 months.
- CKD is a silent killer. It needs to be uncovered. CKD progression is preventable-stage the disease and treat it.
- Multi-risk factor intervention is critical.
- Timely referral reduces mortality, reduces cost, and improves planning for RRT.

Participants – Member National Medical Associations: Dr Yeh Woei Chong, Singapore, Chair of Council CMAAO; Dr Angelique Coetzee, South Africa; Dr Ravi Naidu, Malaysia; Dr Wasiq Qazi, Pakistan; Dr Marthanda Pillai, India; Dr Ashraf Nizami, Pakistan; Dr Prakash Budhathoki, Nepal; Dr Mvuyisi Mzukwa, South Africa

Invitees: Dr Monica Vasudev, USA; Dr Brahm Vasudev, USA; Dr Anjali Aggarwal; Dr Colin Goldberg; Dr Manisha Kukreja; Dr S Sharma, Editor-IJCP Group

Moderator: Mr Saurabh Aggarwal

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CSI NIC Mid Term Meet: NIC 2024

SKILLSET AND TOOL KIT OF CHIP PCI AND IMPACT OF INTRAVASCULAR IMAGING IN CHIP PCI

Dr DS Chadha, Bengaluru

- Aging population along with growth of comorbidities will lead to expansion of the CHIP population.
- The CHIP program focuses upon higher-risk patients put on guideline-directed medical therapy, who have the most to gain.
- Need to have a successful CHIP program involving a wide range of specialists, clinical support staff, and administrative personnel.
- The ingredients of a successful CHIP program are: Specialists trained with advanced technical and cognitive skills, availability of the tools on the shelf and well-trained support staff.
- A well-run CHIP program is a "high-risk, higher reward" paradigm that will benefit a traditionally underserved patient population.

ANTEGRADE WIRE ESCALATION AND PARALLEL WIRE TECHNIQUE

Dr Gerald S Werner, Germany

- The antegrade approach is the basis of a successful strategy even in high Japanese chronic total occlusion (J-CTO) score lesions.
- If you cannot manage to advance an antegrade wire, you can neither escalate to retrograde, because you fail to make the wire connection or antegrade dissection and re-entry, because you cannot reach the distal cap within the vessel structure.
- The 20 mm limit for lesion length is rather historic than factual.
- Step down, whenever you make a steep/extra curve e.g., in the GAIA, change to a new one.
- Remember, tip shape is lost rapidly. So, reshape, whenever you get stuck.
- Parallel wire is a logical continuation of antegrade wire escalation.
- Wire manipulation is a basic skill of an interventionist. To manipulate a second wire along a first wire is even easier.
- To take out the "wrong" wire to change for another deprives you of the information already gained. The parallel wire step should not take more than 10 minutes of your wire time. If it fails, move on.
- Always start with an antegrade wire first even in long lesions. The wire left in place is the road map to success. The presence of a wire modifies the vessel architecture, straightens the course for the second wire.

- PWT is quick, efficient, and successful.
- The first wire…straightens the vessel segment, fixes the distal cap and serves as a permanent marker for modifying the course of the second wire.

THE POWER WITHIN: INCLISIRAN AND ACHIEVING OPTIMAL LDL-C IN ESTABLISHED ASCVD RISK

Dr KP Pramod Kumar, Chennai

In patients with established atherosclerotic cardiovascular disease (ASCVD) risk, the "lowest is best" approach for low-density lipoprotein cholesterol (LDL-C) control is crucial. This concept, supported by numerous studies over the years, has shown that significantly lowering LDL-C levels substantially reduces the risk of future cardiovascular events. Traditional statin therapy alone often fails to reach these stringent targets, necessitating the addition of more potent lipid-lowering agents.

Inclisiran, which targets PCSK9 mRNA, has emerged as a powerful adjunct to high-intensity statin therapy. The ORION-10 trial has demonstrated that Inclisiran significantly reduces LDL-C and achieves 52% reduction from baseline levels in patients with established ASCVD risk. Its biannual dosing not only ensures sustained LDL-C reduction but also improves adherence. Incorporating Inclisiran into treatment regimens offers a promising strategy to meet the rigorous lipid goals necessary for high-risk patients.

HOW TO SELECT TECHNIQUE FOR BIFURCATION: OVERVIEW OF EVIDENCE AND PRACTICE

Dr Ajay J Swamy, Secunderabad

- Bifurcation stenting is resource demanding. Results are often less robust than nonbifurcation stenting.
- Anatomical considerations: Is this a significant side branch (SB)? Is this branch easy to win? Is it likely to close if the main vessel is stented? What is the

length of the disease in the SB? Is there significant calcium/thrombus? What is the angle at which it comes off? What is the distribution of plaque in the bifurcation?

- Clinical considerations: What clinical situation are we dealing with (acute coronary syndrome/myocardial infarction [ACS/MI], CSA/silent ischemia)? Are there any other comorbidities (specifically renal function, bleeding risk)? Plan procedure, establish dye limit, procedure endpoint.
- Conceptual considerations: Do we need the SB to merely stay open (LAD-D2, LCx-OM) or do we need an optimal result in the SB (left main [LM] bifurcation, LAD – large D2, LV dysfunction)?
- A provisional one-stent approach remains the most common treatment strategy for bifurcation percutaneous coronary intervention (PCI). Patient selection and meticulous procedure execution are key for acute and long-term clinical success.
- For simple lesions, one stent is always better if feasible. Layered provisional strategy offers best option to implement this strategy. It offers the option to upgrade to second stent to protect/salvage the SB and also use drug-eluting balloon, if feasible.
- For complex lesions, up front two stent strategy.
- Choose the strategy keeping in mind the available resources, expertise, lesion, and patient complexity.
- Try to choose the hardware that has the best chance of crossing in the first attempt.
- In complex lesions, outcomes are worse if two stents not planned. In LM bifurcation, two stents are better.

RETROGRADE COMPLICATIONS

Dr N Prathap Kumar, Kollam

- Vessel perforation is common in retrograde approach and is related to guidewire manipulation, equipment advancement over-the-wire, and balloon inflation.
- Causes of distal vessel perforation: Inadvertent excessive advancement of a guidewire into the distal coronary bed; stiff, tapered or plastic jacket guidewires.
- Collateral perforation – septal is mostly a self-limited event, often ending with drainage in one of the cardiac chambers and negligible clinical consequences. Septal hematoma and dry tamponade may occur.
- Epicardial collateral perforation can rapidly lead to tamponade irrespective of a previous coronary artery bypass grafting. Donor vessel occlusion may occur due to catheter-related injury (during equipment withdrawal or pulling on the retrograde guidewire) or donor vessel thrombosis (long procedures with much intraluminal hardware).
- To prevent donor vessel closure, retrograde approach should be avoided through diseased donor vessels unless PCI is planned ahead. Adequate position of catheter (not too deep) is essential. Position of the retrograde catheter should be confirmed upon guidewire externalization and during procedural steps performed on the externalized wire. Use an additional safety guidewire in donor vessel.
- To prevent aortocoronary dissection, use anchor techniques for catheter support rather than proceeding with deep engagement. Avoid expansion of the dissection plane. Stop injecting contrast.

Key Points

- All these complications can happen.
- Anticipating complications and taking care of them is important.
- Techniques to avoid perforation are: Using Suoh 3 wire with microcatheter without surfing, avoid corkscrew or multiple tortuous channels for wire crossing, excessive manipulation of wire.
- Keeping a safety wire in donor vessel is important.
- Checking ACT every 30 minutes to avoid thrombosis.

GUIDE CATHETER-INDUCED LMCA AND AORTIC DISSECTION: BAILED OUT BY REVERSE CK CULOTTE

Dr Vijayan Ganesan, Kerala

- Avoid deep engagement of the guide catheter.
- If dissection occurs, disengage the catheter and take gentle sinus angiogram to assess the extension. If ostium is involved, use Judkins catheter.
- Limit the angiogram shots.
- If ostium is involved, immediate stenting to seal the entry point is ideal.
- Right coronary artery (RCA) >> left main coronary artery (LMCA) (LMCA has more circular and spiral smooth muscle cells and abundant elastic fibers).
- If progression with hemodynamic instability, acute AR, cardiac tamponade: urgent surgery.

INNOVATION IN PERICARDIOCENTESIS COMPLICATION

Dr Vinay Kumar Sajja

- Right ventricular (RV) punctures can occur as a complication of pericardiocentesis.
- Conventionally open surgical procedures will be needed for RV closure.
- In high-risk surgical patients, a vascular closure device (angioseal) may be helpful in closing the RV puncture site.

CHALLENGING CASE OF SUCCESSFUL PCI OF OSTIAL LAD PCI VIA RETROGRADE EPICARDIAL IPSILATERAL COLLATERALS: SCARY 3-HOUR ROLLER COASTER RIDE ENDING IN THE CLOUD NINE!!

Dr Gaurav Chaudhary, Lucknow

- J-CTO 4 CTO cases are often difficult with lesser success rates.
- In calcified CTO, exteriorization of retrograde micro can be very difficult thus knuckle CART (controlled antegrade and retrograde tracking) and reverse Carlino technique can be used to create subintimal space for antegrade wire.
- Ipsilateral epicardial should negotiated very gently with Sion wire or Suoh 3 wire, which can negotiate acute bends safely.
- Ping-Pong technique may not be successful in calcified long segment as calcium obstruct retrograde microcatheter entry into guide.
- Ostial CTO with good interventionist collaterals are indications of primary retrograde approach, even ILC can be used.
- Failed antegrade CTO are indications of primary retrograde approach.

APPROACH TO BIFURCATION

Dr JS Dugal, Pune

- Provisional stenting is currently recommended as a default strategy for approaching bifurcation PCI.
- It must be kept in mind that the long-term clinical outcomes are mainly dependent on success of main branch (MB) stenting. Therefore, optimization of the result of the MB should be taken priority over the pre-eminence of angiography results in the SB.
- Regardless of the stenting technique, the initial step for a successful bifurcation of PCI strategy begins with a good understanding of bifurcation anatomy.
- The main points when assessing bifurcation anatomy include: assessment of three diameters of bifurcations, assessment of lesion, length and plaque distribution, and assessment of bifurcation angle.
- Appropriate sizing of the MB stent is important for securing favorable long-term outcome and should mainly allow avoiding mala position in proximal SB and scaffolding of SB ostium. Use drug-eluting stents according to the distal MB size. Around 8-10 mm should be kept proximal to the carina.
- Be familiar with maximum stent expansion and stent cell size to avoid SB occlusion and distal dissection.
- Periprocedural occlusion of a large SB, i.e., >2.5 mm has been recognized as a contributor to impaired post-PCI prognosis. The jailed wire has been shown to improve the rate of SB reopening in case of closure.
- The SB wiring prior to MB stenting acts as a marker of rewiring the SB. SB wiring reduces the angle thus setting a more favorable anatomical position for rewiring and advancement of the balloon. Jailed SB wiring may improve its patency after MB stenting.
- Elective SB wiring is recommended in all cases where the operator deems that SB is clinically important and always when treating true bifurcation disease. In case of clinical urgency after failed multiple attempts at SB wiring, a small balloon may be advanced over jailed wire between stent struts and vessel wall to facilitate SB opening.
- Jailed wire may act as anchor for deeper intubation of guide wire and increase support in case of difficult SB crossing.

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News and Views

Balcinrenone + Dapagliflozin: The Next Frontier in Therapy for HF and CKD Patients?

Adding balcinrenone to dapagliflozin did not significantly improve proteinuria in patients with heart failure (HF) and chronic kidney disease (CKD) compared to dapagliflozin alone, according to findings of the MIRACLE (MIneRAlocorticoid reCeptor moduLator and sodium-glucosE cotransporter 2 inhibitor in HF and CKD) published in the *European Journal of Heart Failure*[1].

Balcinrenone is a novel selective mineralocorticoid receptor (MR) modulator, which "separates organ protective effects from acute effects on urinary electrolyte excretion", as shown in preclinical models[2]. Dapagliflozin is an SGLT2 (sodium-glucose cotransporter-2) inhibitor.

This phase 2b trial examined the safety and effectiveness of combination of balcinrenone and dapagliflozin in patients with HF and CKD; 160 sites in Europe, Asia and North America participated in this study, which was conducted from January 2021 to October 2023.

The primary objective of the study was to assess the effect of balcinrenone in combination with dapagliflozin on urinary albumin-to-creatinine ratio (UACR) compared with dapagliflozin + placebo. The dose-response relationship of three doses of balcinrenone (15, 50, or 150 mg/day) + dapagliflozin 10 mg/day on UACR effects was the secondary objective of the study. The assessment of the safety and tolerability of the combination was the safety objective of the study.

The study enrolled 133 patients with symptomatic HF. Participants with an ejection fraction of <60%, an estimated glomerular filtration rate (eGFR) of between 30 and 60 mL/min/1.73 m^2 and UACR of between 30 and 3,000 mg/g were eligible for the study. They were randomized 1:1:1:1 to receive either balcinrenone 15, 50, or 150 mg/day + dapagliflozin 10 mg/day, or dapagliflozin 10 mg/day + placebo, for a duration of 12 weeks. The enrollment was stopped early because of slow recruitment. Safety analysis was done on 131 participants.

Balcinrenone + dapagliflozin groups compared to dapagliflozin + placebo did not vary much in terms of relative reductions in UACR from baseline to week 12. No clear dose-response relationship was observed for balcinrenone.

Possible dose-dependent increases in serum potassium levels, nonsignificant trends towards decreased N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels and decreased eGFR in the highest dose group were noted.

Hyperkalemia occurred in 3.1% of patients receiving the combination treatment and in 9.1% in the placebo. Two participants on balcinrenone + dapagliflozin discontinued due to hyperkalemia (>6.0 mmol/L), while none discontinued the treatment in the dapagliflozin + placebo group. No new safety concerns were observed.

This study indicates that adding balcinrenone to dapagliflozin was comparable to placebo in improving UACR in patients with symptomatic HF, which is a key marker for cardiovascular risk. Also, because of a lack of dose-response relationship, increasing doses of balcinrenone did not provide additional benefits in reducing UACR.

Discontinuation of treatment because of hyperkalemia, especially with higher doses, underscores the necessity for vigilance in monitoring of potassium levels when using balcinrenone, especially when administering higher doses of the drug. The benefits therefore must be carefully weighed against the risks with the use of balcinrenone. The authors, however, suggest further studies to better understand the actions of balcinrenone in patients with HF and CKD to minimize risks while maximizing therapeutic benefits. These findings therefore may be used as a guide to tailor treatment regimens.

References

1. Lam CSP, et al; MIRACLE Study Investigators. Balcinrenone plus dapagliflozin in patients with heart failure and chronic kidney disease: Results from the phase 2b MIRACLE trial. Eur J Heart Fail. 2024;26(8):1727-35.
2. Bamberg K, et al. Preclinical pharmacology of AZD9977: A novel mineralocorticoid receptor modulator separating organ protection from effects on electrolyte excretion. PLoS One. 2018;13(2):e0193380.

Challenges in Adult Vaccination: Perceived Barriers

About 25% of older adults report fear of needles and costs as obstacles to vaccination, according to a study published in the journal *Aging and Health Research*[1]. Lack of a doctor's recommendation, transportation and uncertainty how to schedule vaccines were other

perceived barriers. The less educated, single people and those residing in rural areas were more likely to face barriers in the uptake of vaccines This study focused on identifying the barriers that prevent older adults from accepting vaccines that are recommended for their age group. In addition, the study also explored how demographic factors influence vaccine acceptance.

The study used a mail survey conducted between May and June 2022 to gather data on experiences, perceptions, and behaviors related to vaccination among older adults aged 65 and older in North Dakota, a state in the US. The survey targeted equal numbers of males and females from three distinct strata: urban/high vaccine coverage (1,000 individuals), rural/high vaccine coverage (1,000 individuals), and rural/low vaccine coverage (2,000 individuals). Out of the 4,000 individuals surveyed, 901 (23.4%) responses were received. Their mean age was 75 years. More than half of the respondents were women (53.1%). Majority (~72%) lived in rural areas; one-quarter lived alone and most (86.4%) rated their health as good or better. "Over 90% had received at least one COVID-19 vaccine, nearly 90% had taken at least one flu vaccine in the last 5 years, 70.7% received a pneumococcal vaccine, and 67.8% received a shingles vaccine."

The survey included questions related to barriers to vaccination (such as needle phobia, cost, lacking doctor recommendation, transportation issues, and scheduling uncertainty), vaccine acceptance and various demographic characteristics including age, gender, socioeconomic status, education status, self-rated health, whether living alone. The study also specifically assessed the uptake of four different vaccines among the study population namely Influenza, COVID-19, Shingles, and Pneumococcal vaccines.

Analysis of data revealed cost (27.2%) to be the most common barrier to vaccination followed by needle anxiety (24.1%). Older persons who were single, living in rural areas, with lower levels of education, and who were not white were more likely to encounter obstacles such cost, lack of a doctor's referral, transportation and uncertainty how to schedule vaccines.

Cost was identified as the most prevalent barrier, affecting 27.2% of respondents. This barrier was particularly associated with the uptake of the shingles vaccine. Needle phobia was a significant concern for 24.1% of respondents. It was associated with the uptake of all vaccines except the COVID-19 vaccine. A lack of a doctor's recommendation was a barrier to the uptake of all vaccines except the shingles vaccine. Transportation barrier was particularly associated with the uptake of the pneumococcal vaccine. Participants residing in rural areas were more concerned about costs and also lacked recommendations from their doctor to receive vaccines. Similarly, those with lower educational status also mentioned lack of doctor referral as a hurdle. Transportation as a barrier was more common among those living alone, while the less educated respondents found it difficult to schedule the vaccination.

This study provides valuable insights into vaccination barriers among older persons highlighting how these barriers vary across demographic groups and their specific associations with acceptance of different vaccines. It further underscores the need for multifaceted strategies that address both demographic characteristics and vaccine-specific factors to improve immunization uptake among older adults. Understanding these variations helps tailor interventions and policies to address specific barriers faced by demographic groups. Education and support can enhance the overall vaccine acceptance rates.

Reference

1. Fuller HR, et al. Barriers to vaccination among older adults: demographic variation and links to vaccine acceptance. Aging Health Res. 2024;4(1):100176.

Assessing Risk of Endometrial Hyperplasia and Cancer in Recurrent Abnormal Uterine Bleeding

Older age, nulliparity, a history of endometrial polyps and a sampling interval of <12 months are significant predictors of endometrial hyperplasia and endometrial cancer in women with recurrent abnormal uterine bleeding (AUB) and previous benign endometrial findings, according to a study published August 1, 2024 in the journal *Obstetrics & Gynecology*[1].

In this retrospective study from Thailand, researchers set out to create predictive models for patients with recurrent AUB that would suggest the risk of subsequent development of endometrial hyperplasia and endometrial cancer. The selected participants had undergone endometrial sampling earlier between January 2013 and December 2021 that were benign. Using multivariate logistic regression, a model was built using the important variables linked to endometrial hyperplasia and endometrial cancer. Based on these risk factors, the patients were then further divided into risk categories.

Out of the total 456 patients included in the study, 8.3% developed endometrial hyperplasia and 2.2% developed endometrial cancer. The average interval between the

initial endometrial sampling and the second sampling was 25.1 months.

Patients older than 45 years were nearly 3 times more likely to develop endometrial hyperplasia and endometrial cancer with odds ratio (OR) of 2.86. The risk was increased 3.5 times in nulliparous women (OR 3.50), while a history of endometrial polyps was associated with a more than threefold increased risk of endometrial hyperplasia or cancer (OR 3.69). Among participants who underwent the second sampling in less than a year from the first sampling, the risk was more than doubled with OR of 2.36.

The study developed a scoring system based on the significant predictive factors for endometrial hyperplasia and endometrial cancer. This system allowed for categorization of patients into three distinct risk groups: 0-3 (low risk), 5-8 (intermediate risk), and 9-11 points (high risk), with corresponding probabilities of developing these conditions (4.7%, 15.5%, and 57.1%, respectively). "The area under the curve (AUC) was 73.1%, with a mean absolute error of 0.01."

This study has identified risk factors that indicate the risk of endometrial hyperplasia or endometrial cancer in patients with recurrent AUB and previous benign endometrial findings. Risk stratification also facilitates tailored clinical decision making, with more aggressive management strategies, including frequent follow-ups, investigations or intervention planned for the high-risk group. Counseling patients about their risk also helps them to make more informed decisions about their care.

Reference

1. Veeranaraphanit U, et al. Predicting endometrial hyperplasia and endometrial cancer on recurrent abnormal uterine bleeding. Obstet Gynecol. 2024;144(2):259-65.

Glycemic Variability: A Harbinger of Diabetic Peripheral Neuropathy?

Diabetes patients with increased glycemic variability are at a substantially higher risk of developing diabetic peripheral neuropathy (DPN), as per a study recently published in the journal *Diabetes Research and Clinical Practice*[1].

A systematic review and meta-analysis was conducted to identify any relationship between glycemic variability, as measured by continuous glucose monitoring, and the risk of developing DPN in patients with type 1 and type 2 diabetes. Nine studies with a total of 3,649 patients were included in the meta-analysis.

Analysis revealed a significant association between increased glycemic variability and the incidence of DPN as indicated by various glycemic variability metrics. Patients with higher SD in blood glucose levels are over twice as likely to develop DPN compared to those with lower SD with OR of 2.58. Increased mean amplitude of glycemic excursions was associated with a 90% higher risk of developing DPN (OR 1.90). Higher mean of daily difference was also strongly associated with nearly a threefold increase in the risk of DPN (OR 2.88).

These findings underscore the potential of glycemic variability metrics as potential markers for the onset of DPN. Integrating these metrics into routine diabetes care could serve as an early warning system, allowing for more targeted interventions aimed at mitigating the risk of neuropathy.

Reference

1. Jia Y, et al. Diabetic peripheral neuropathy and glycemic variability assessed by continuous glucose monitoring: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2024;213:111757.

Chronic Obstructive Pulmonary Disease: A Potential Risk Factor for Herpes Zoster

Persons with chronic obstructive pulmonary disease (COPD) nearly 3 times more likely to develop herpes zoster (HZ) compared to those without COPD, according to a study published in the *Clinical Respiratory Journal*[1].

In this retrospective cohort study, the researchers compared the incidence rates of HZ between persons with and without COPD in the United States. Data for the study was obtained from an insurance database from January 2013 to December 2018.

A total of 161,970 participants with a diagnosis of COPD were categorized as COPD+, while 9,643,522 participants without COPD diagnosis were grouped as COPD−. Those with a history of HZ, prior HZ vaccination, postherpetic neuralgia (PHN), or herpes zoster ophthalmicus were excluded from the study. Participants with COPD tended to be older in age, have more comorbid conditions and also used steroids more frequently than those without COPD.

The incidence rate of HZ was significantly higher in the COPD+ cohort (13.0 per 1,000 person-years) compared to the COPD− cohort (2.3 per 1,000 person-years) with an adjusted incidence rate ratio (aIRR) of 2.77. COPD patients had a 5.7-fold higher incidence rate of HZ compared to those without COPD, even after adjustment. The unadjusted incidence rate of PHN was 1.7 times higher in the COPD+/HZ+ group

(64.8 per 1,000 person-years) compared to the COPD−/HZ+ cohort (37.1 per 1,000 person-years). However, after adjustment, this association was not statistically significant with aIRR of 1.07. The incidence rates of HZ and PHN increased with age across the cohorts. After adjusting for potential confounders, adults with COPD were found to have a 2.8-fold increased risk of developing HZ compared to those without COPD.

These findings underscore the need for greater awareness about the risk of HZ, which is a very painful condition, in COPD patients. They also establish the importance of proactive targeted prevention strategies, including Shingles vaccination for those at higher risk.

Reference

1. Thompson-Leduc P, et al. Chronic obstructive pulmonary disease is associated with an increased risk of herpes zoster: a retrospective United States claims database analysis. Clin Respir J. 2022;16(12):826-34.

Long-Term Lung Damage among COVID-19 Survivors

Over one-third of patients who had residual lung abnormalities at discharge after being hospitalized for COVID-19 continue to experience respiratory symptoms and lung abnormalities even 3 years after discharge, according to a study published in the *European Respiratory Journal*[1].

The study followed a group of 728 patients who had earlier been hospitalized with COVID-19 and had residual lung abnormalities at discharge from January to April 2020. It tracked the progression of residual lung abnormalities such as ground-glass opacities, reticulation and fibrotic-like changes, and pulmonary function over a period of 3 years. The participants were evaluated at multiple time points post-discharge: 6 months, 12 months, 2 years, and 3 years from the onset of symptoms. The tests undertaken included pulmonary function tests, 6-minute walk distance (6MWD), chest computed tomography (CT) scans including a self-reported questionnaire to assess the respiratory symptoms. A total of 792 persons who had tested negative for COVID-19 were also included in the study as the control group.

The proportion of patients with reduced diffusing capacity of the lung for carbon monoxide (D_{LCO}) (<80% of the predicted value) decreased from 49% at 6 months to 38% at 3 years (p = 0.001). The average 6MWD improved from 496 m in 6 months to 510 m in 3 years (p = 0.002). The prevalence of residual lung abnormalities decreased from 46% at 6 months to 36% at 3 years. These changes were evident regardless of the severity of disease.

Patients with residual lung abnormalities at 3 years were more likely to report respiratory symptoms (32%) compared to those with complete resolution (16%) (p < 0.001). They also had a lower average 6MWD (494 m) than those without abnormalities (510 m) (p = 0.003). A higher percentage of patients with residual lung abnormalities had abnormal D_{LCO} (57%) versus those with complete resolution (27%) (p < 0.001).

Regardless of the initial severity of the disease, COVID-19 survivors showed the highest prevalence of nonfibrotic changes 6 months after discharge, which progressively declined over the 3-year period. At 6 months, fibrotic changes were most common in patients with severity scores of 5 to 6, which remained for the 3 years of the study. Patients with fibrotic-like changes experienced more respiratory symptoms (44% vs. 25%) and had a lower D_{LCO} (57% vs. 50%) compared to those with nonfibrotic changes. A comparison of COVID survivors and controls revealed that around 38% of COVID-19 survivors had impaired D_{LCO} (<80% of predicted) compared to only 17% in the control group (p < 0.001). Also, 23% of COVID-19 survivors reported at least one respiratory symptom compared to just 2.2% of the control group (p < 0.001). The most common symptoms at 3 years were cough, dyspnea, and expectoration.

The study points out a clear distinction in the long-term pulmonary outcomes of COVID-19 survivors based on the initial severity of their illness. While many patients show improvement in radiological abnormalities and pulmonary function over time, those with severe initial disease remain at risk for persistent fibrotic lung changes that were associated with increased symptoms, lower 6MWD and abnormal pulmonary function, underscoring the importance of tailored post-recovery management.

Reference

1. Han X, et al. Long-term radiological and pulmonary function abnormalities at 3 years after COVID-19 hospitalisation: a longitudinal cohort study. Eur Respir J. 2024;64(1):2301612.

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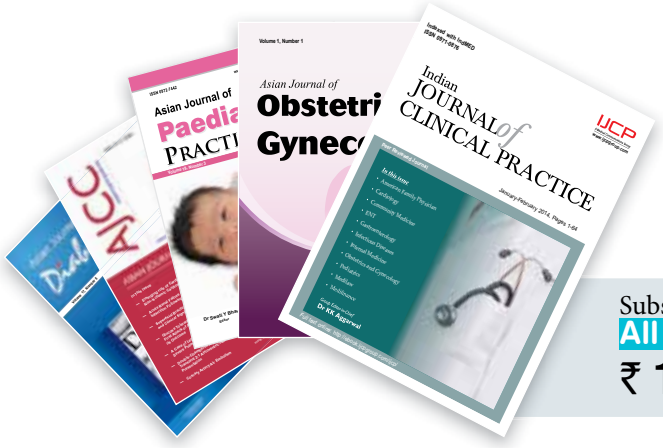

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Lighter Side of Medicine

HUMOR

SALES PRACTICE

The out-of-work newlywed took a temporary job as a vacuum cleaner salesman to make ends meet.

After 3 days of intensive training, the sales manager told him to go home and practice his pitch on his wife.

The next morning, the manager asked the novice how he made out.

"Well," the man began, "I did what you said, and after I finished, I asked her if she would buy the vacuum cleaner from me. She said 'Yes.' Then I asked her 'Why?' She replied, 'Because I love you'."

TELL HIM I CAN'T SEE HIM

While he was talking to me, his nurse came in and said, "Doctor, there is a man here who thinks he's invisible."

The doctor said, "Tell him I can't see him."

GETTING THREATENING LETTERS

A man stormed into the postmaster's office in a fury. "I've been getting threatening letters in the mail for months and I want them stopped."

"Of course," said the postmaster. "Sending threatening letters through the mail is a serious offense.

Do you know who's sending them?"

"Yes," shouted the man. "It's those idiots down at the Income Tax Department."

STANDING THERE ALL BY YOURSELF

One day, there were a couple of kids in a psychology class. The teacher stands up and says to the class "stand up if you think you're stupid!" After about 5 minutes, Little Johnny stood up and the teacher says "do you think you're stupid Johnny?" To which Little Johnny replies "No miss I just hate to see you standing there all by yourself!!!

THE LAW OF COFFEE

If you sit down to enjoy a hot cup of coffee, then your boss will ask you to do something that will last until the coffee is cold.

Patient: Doctor, tell me how I can repay you for your kindness?

Doctor: You can pay by cash, card, or check!

Q: What do you call a doctor who fixes websites?

A: URL-ologist!

Q: Why is a doctor always calm?

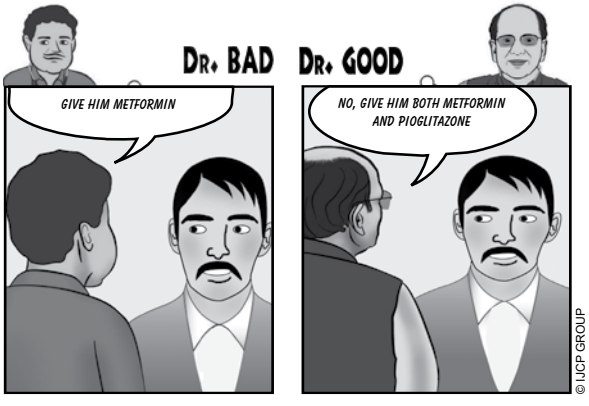
A: Because they have a lot of patients!

Patient: Doctor, I'm going to die in 59 seconds!

Doctor: Hang on, I'll be there in a minute!

Dr. Good and Dr. Bad

SITUATION: A type 2 diabetic patient was advised antioxidants.



LESSON: Pioglitazone was superior to metformin to improve oxidative stress as reflected by reduction in malondialdehyde but the antioxidant effect i.e., increase in superoxide dismutase was seen with metformin only. The differing mechanism of actions of the two drugs on oxidative stress favors co-prescription of these drugs for better outcome in improving insulin resistance and diabetic complications.

Diabetes Metab Syndr. 2016;10(2):102-4.

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- Method of selecting the sample (cases, subjects, etc. from the statistical universe).
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- Statistical methods used for presentation and analysis of data i.e., in terms of mean and standard deviation values or percentages and statistical tests such as Student's 't' test, Chi-square test and analysis of variance or non-parametric tests and multivariate techniques.
- Confidence intervals for the measurements should be provided wherever appropriate.

Results

- These should be concise and include only the tables and figures necessary to enhance the understanding of the text.

Discussion

– This should consist of a review of the literature and relate the major findings of the article to other publications on the subject. The particular relevance of the results to healthcare in India should be stressed, e.g., practicality and cost.

References

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Examples of common forms of references are:

Articles

Paintal AS. Impulses in vagal afferent fibres from specific pulmonary deflation receptors. The response of those receptors to phenylguanide, potato S-hydroxytryptamine and their role in respiratory and cardiovascular reflexes. Q. J. Expt. Physiol. 1955;40:89-111.

Books

Stansfield AG. Lymph Node Biopsy Interpretation Churchill Livingstone, New York 1985.

Articles in Books

Strong MS. Recurrent respiratory papillomatosis. In: Scott Brown's Otolaryngology. Paediatric Otolaryngology Evans JNG (Ed.), Butterworths, London 1987;6:466-470.

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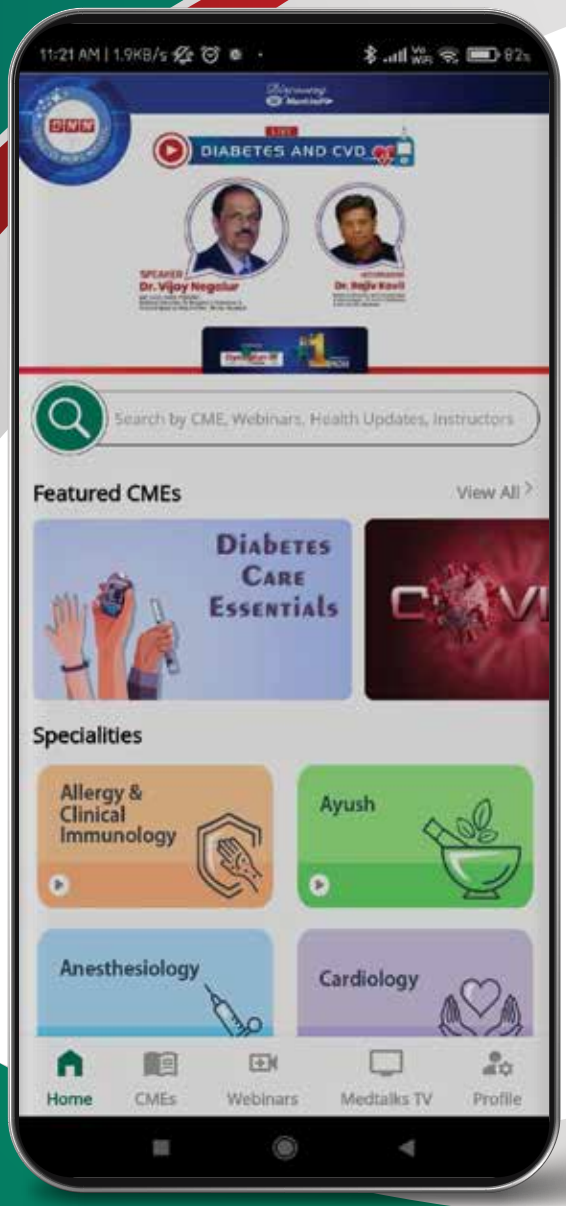

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