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Contents

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Editorial Board (2025–2026)

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Human Metapneumovirus—Is It a Cause for Concern?

Shobha Manish Itolikar[1*], Milind Nadkar[2]

Emerging Infections and the New World

"Infectious disease is one of the few genuine adventures left in the world…. however secure and well regulated civilized life may become, bacteria, protozoa, viruses, infected fleas, lice, ticks, mosquitoes and bedbugs will always lurk in the shadows and pounce upon us when our defenses are down."[1] These words by microbiologist Hans Zinsser in 1934 could be considered even more relevant and relatable today, nearly a century after he made these observations. Emerging infectious diseases continue to be a threat to our progress even though civilization and mankind have taken giant leaps toward development.

Just when we thought we could breathe easy having seen the end of the COVID-19 pandemic, we are holding our breath again in apprehension of a similar situation. The end of 2024 announced the outbreak of human metapneumovirus (HMPV) cases in China, raising global concerns. The virus that made headlines and is reported to have spread to other parts of the world is rather a well-known virus that has been in the seasonal flu landscape for several decades and has marked its presence in nearly every continent in the world. Since it has been in circulation for many years, experts are well aware of its genetic makeup and disease characteristics, unlike the COVID-19 virus, which was a novel coronavirus about which very little was known.

The Anthropo-zoonotic Interface

The evolution of present-day birds from dinosaurs took several million years to yield the thousands of avian species that are the epicenter of emerging infections today. By virtue of their migratory behaviors as well as environmental exposure to other biodiversity, birds tend to acquire viruses from multiple sources. These viruses tend to render the hosts into viral reservoirs. When anthropocenic man ventures into ornithogenic territory, the bird–man interface is breached, and zoonotic transfer occurs. Thus, the virus finds a new host in humans, and we witness frequent outbreaks of different respiratory pathogens from time to time.[2] In this way, HMPV has evolved from its avian counterpart, the avian pneumovirus (APV). Though first detected in the year 2001 in nasopharyngeal aspirates from 28 Dutch children, there is evidence that the virus has been circulating among the human population for at least half a century.[3] With 60% of known infections and 75% of emerging infections in humans being zoonotic, it is of utmost importance that we understand how these illnesses behave and how to empower ourselves with the knowledge to fight them.[4]

HMPV Current Scenario

China, from where the initial outbreak was reported in December 2024, has stated that cases of HMPV are in decline as of late January 2025. Although India has reported few cases of mild HMPV infection in some of its states, the situation is not alarming as the numbers do not portend a lurking epidemic. As per government directives, states have stepped up surveillance of respiratory illnesses, and measures are being taken to spread awareness about how to prevent the transmission of HMPV.[5]

Decoding HMPV

Virus characteristics: HMPV is a large ribonucleic acid (RNA) virus such as influenza, parainfluenza, respiratory syncytial virus (RSV), and coronavirus. After its discovery, genetic studies were used to classify it as the first mammalian member of the genus *Metapneumovirus*, which until then had only APV as the sole species. Belonging to the recently assigned Pneumoviridae family of viruses, the lesser-known HMPV bears resemblance to its more famous cousin, the RSV, in more ways than one.[6]

Prevalence: Today, HMPV is quickly emerging as a significant respiratory pathogen in humans. Second to RSV, it is the cause of both upper and lower respiratory tract infections in all age groups with a more significant impact on children, the elderly, and immunocompromised individuals. Statistics show that HMPV accounts for about 5–10% of all pediatric respiratory infections during any given flu season in the United States. Data available from the National Institute of Virology, Pune, suggests an overall prevalence rate of HMPV to be 8% in India and 3% globally. Seroprevalence studies indicate that there is almost universal infection with HMPV in children by the age of 5 years. Yet reinfections can occur throughout an individual's life due to waning immunity levels.[7,8]

Mode of transmission: This virus primarily spreads through aerosols and secretions from infected persons and can survive outside the host for several hours, thus enabling transmission through fomites. Additionally, many nosocomial infections have been documented.[6]

Clinical features: Distinguishing HMPV infections from other respiratory viruses based on symptomatology alone is virtually impossible. It shares a similar constellation of symptoms and radiologic features with other viruses such as influenza virus, parainfluenza virus, RSV, and novel coronavirus. Clinical manifestations of HMPV range from mild flu-like illness to more serious pneumonia and acute respiratory distress syndrome. Patients with an upper respiratory tract infection will present with fever, cough, nasal congestion, rhinorrhea and sore throat along with other constitutional symptoms. Clinical features of a lower respiratory tract infection will also include wheezing, dyspnea, chest discomfort and hypoxia. HMPV is associated with acute exacerbations of asthma and chronic obstructive pulmonary disease (COPD) in predisposed individuals, which may necessitate hospitalization. Extrapulmonary complications described in literature are otitis media and HMPV encephalitis.[3]

Prognosis: Most of the cases (95%) are mild self-limiting influenza-like illnesses.[3] There is increased mortality in patients with hematological malignancies, especially in hematopoietic stem cell transplant recipients. The risk factors postulated to predict poor outcomes are the presence of lymphopenia, neutropenia, low monocyte counts, use of high dose steroids, history of smoking and the presence of coinfections.[9]

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Management: Though HMPV infection does not require confirmatory testing and a clinical diagnosis is sufficient in a mild flu-like condition, reverse transcriptase polymerase chain reaction (RT-PCR) from nasopharyngeal swabs remains the most widely accepted investigation of choice.[3] The mainstay of treatment is symptom-based care with antipyretics, antihistamines, and hydration. Critically ill cases warrant early intensive management with oxygen support and pharmacotherapy. Although there is no specific antiviral therapy against HMPV, there has been some success reported with the use of either ribavirin alone or in combination with polyclonal intravenous immunoglobulins.[10] Futuristically, monoclonal antibodies against fusion proteins of HMPV might turn out to be game changers in the therapeutic armamentarium.

How is HMPV Different from COVID?

Human metapneumovirus has already been in circulation in most parts of the world; hence, there is more herd immunity against it than there would be against a novel virus, such as COVID-19 at the beginning of the pandemic. Moreover, it is less contagious and milder than the COVID-19 virus.

Conclusion

The fear over the spread of HMPV has led to worldwide fear that it might trigger a health situation similar to the COVID-19 pandemic. Although vigilance is advised, there is no reason to panic at the moment. A more cautious approach is advised in high-risk patients. There is no better time than this to advocate the importance of prophylactic measures in the form of stringent hand hygiene, cough etiquette, masking up, and contact isolation.

Additionally, such frequent health scares should foster anthropological research focusing on the human–animal link that forms the etiological site of zoonotic infection in order to redefine contemporary practices of global health.

References

1. Weissmann G. Rats, lice, and Zinsser. Emerg Infect Dis 2005;11(3):492–496.
2. Chan JF, To KK, Chen H, et al. Cross-species transmission and emergence of novel viruses from birds. Curr Opin Virol 2015;10:63–69.
3. Broor S, Bharaj P, Chahar HS. Human metapneumovirus: a new respiratory pathogen. J Biosci 2008;33(4):483–493.
4. United Nations Environment Programme Handbook - UNEP Frontiers Report 2016. pp. 18–25.
5. https://www.chinacdc.cn/jksj/jksj04_14249/
6. Rima B, Collins P, Easton A, et al. ICTV virus taxonomy profile: Pneumoviridae. J Gen Virol 2017;98(12):2912–2913.
7. Wang X, Li Y, Deloria-Knoll M, et al. Global burden of acute lower respiratory infection associated with human metapneumovirus in children under 5 years in 2018: a systematic review and modelling study. Lancet Glob Health 2021;9(1):e33–e43.
8. Waghmode R, Jadhav S, Nema V. The burden of respiratory viruses and their prevalence in different geographical regions of India: 1970-2020. Front Microbiol 2021;12:723850.
9. Waghmare A, Englund JA, Boeckh M. How I treat respiratory viral infections in the setting of intensive chemotherapy or hematopoietic cell transplantation. Blood 2016;127(22):2682–2692.
10. Wyde PR, Chetty SN, Jewell AM, et al. Comparison of the inhibition of human metapneumovirus and respiratory syncytial virus by ribavirin and immune serum globulin in vitro. Antiviral Res 2003;60(1):51–59.

ORIGINAL ARTICLE

Urinary Levels of Neutrophil Gelatinase-associated Lipocalin and Cystatin C in Patients with Hepatitis B on Tenofovir Treatment

Shivani Rani[1], Himanshu Dandu[2], Ambuj Yadav[3*], Mahak Lamba[4], Amit Goel[5], Wahid Ali[6], Virendra Atam[7], Sumit Rungta[8], Medhavi Gautam[9], Atin Singhai[10]

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Abstract

Introduction: Tenofovir disoproxil fumarate (TDF) is a third-generation nucleoside analogue commonly used as a first-line therapy for chronic hepatitis B virus (HBV) infection. However, it is associated with nephrotoxicity, which can occur through mechanisms such as mitochondrial deoxyribonucleic acid (DNA) depletion and damage to renal tubules. This nephrotoxic effect typically manifests as a mild increase in serum creatinine and a decrease in serum phosphate, usually within 4–12 months after starting treatment. Recent studies suggest that novel biomarkers, such as urinary neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C, may predict acute kidney injury (AKI) earlier and more accurately than traditional markers like serum creatinine. In line with this, we investigated NGAL and cystatin C levels in HBV patients receiving TDF therapy to assess their potential in monitoring kidney function.

Materials and methods: The study included 350 cases in total. Each participant underwent a thorough assessment, including a detailed medical history, clinical examination, and routine blood tests, as outlined in the study's working proforma. Based on the above details, 226 cases fulfilling the inclusion criteria were enrolled for the second step of the study, where a 5 mL urine sample from each case was taken and sent to the pathology laboratory for estimation of cystatin C and NGAL by the ELISA method with the help of a kit.

Results: The average age of the participants was 37.93 years, with 124 individuals falling within the 18–35-year age-group. After accounting for confounding factors, 87 cases were identified, predominantly young males, who exhibited elevated levels of both urinary NGAL and cystatin C.

Conclusion: In this cross-sectional study, after controlling for confounding factors, we observed that TDF treatment was linked to elevated levels of urinary NGAL and cystatin C in 87 (38.4%) of the cases. Notably, increased levels of these biomarkers were also found in the younger age-group (18–35 years). These findings suggest the need for further prospective studies with larger sample sizes to better understand the direct impact of TDF on kidney function in hepatitis B patients.

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Introduction

Hepatitis B virus (HBV) continues to be a major global health concern, affecting around 3.5% of the population with chronic infection.[1] Tenofovir disoproxil fumarate (TDF), a third-generation nucleoside analogue, is used as a first-line treatment for chronic HBV. While effective, TDF is associated with nephrotoxicity, which can occur through various mechanisms, including mitochondrial deoxyribonucleic acid (DNA) depletion and damage to renal tubules.[2–4] Nephrotoxicity is often marked by mild increases in serum creatinine and a reduction in serum phosphate, typically manifesting 4–12 months after initiating TDF therapy.[5] Although renal impairment related to TDF is more frequently observed in HIV patients, there have been reports of significant kidney dysfunction in individuals with chronic hepatitis B as well.[6–8]

Acute kidney injury (AKI) is a clinical condition marked by a sudden deterioration in kidney function, often resulting from changes in blood flow or damage to the kidney's structures.[9] Directly measuring the glomerular filtration rate (GFR) is widely regarded as the most precise method for identifying alterations in kidney function. Serum creatinine is commonly considered a delayed biomarker, as it typically begins to increase only after a significant decline of approximately 50% in kidney function. The diagnosis of AKI traditionally relies on elevated serum creatinine levels or reduced urine output, both of which have limitations. As a result, extensive research over recent decades has focused on identifying and validating new biomarkers for the early detection of AKI. Evidence suggests that these novel biomarkers can predict AKI development and outcomes more effectively and sooner than serum creatinine. For instance, cystatin C and neutrophil gelatinase-associated lipocalin (NGAL) have been identified as independent early predictors of AKI.[9] NGAL, in particular, is useful for the early detection and risk assessment of kidney damage caused by tenofovir.[10] Both NGAL and cystatin C levels tend to rise in response to proximal tubular injury, such as that induced by tenofovir. Looking at the literature, we tested the presence of urinary NGAL and cystatin C molecules in HBV patients who had been taking TDF.

Materials and Methods

This cross-sectional study was conducted at the Department of Internal Medicine, King George's Medical University (KGMU), in collaboration with the Departments of Gastromedicine and Pathology at KGMU, as well as the Department of Gastromedicine at Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow. Ethical clearance was approved by the Institutional Ethics Committee, KGMU (reference code VII-PGTSC-IIA/P4). After receiving approval, cases were enrolled from June to December 2022. This study included all patients above the age of 18 years with Hepatitis B-induced chronic liver disease on tenofovir treatment for 4 months or more. Patients not giving consent,

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those with a history of hypothyroidism and hyperthyroidism, renal disease or deranged renal function as per AKIN (Acute Kidney Injury Network) criteria, history of dialysis in the past, diabetes mellitus, hypertension, and chronic obstructive pulmonary disease (COPD) were excluded. Sample size was calculated using the formula $n = (z_{1-\alpha/2})^2 \times p \times q / d^2$, where n = sample size, $z_{1-\alpha/2}$ = value of normal deviate at a 95% confidence interval, p = prevalence of AKI, q = 1 – prevalence, d = absolute error, and the final sample size came to 233.

The study included 350 cases in total. Each case underwent a thorough evaluation, including a detailed history, clinical examination, and routine blood tests, in accordance with the established study protocol. Based on the results of the above details, 226 cases fulfilling the inclusion criteria were enrolled for the second step of the study, where a 5 mL urine sample from each case was taken and sent to the pathology laboratory for estimation of urinary cystatin C and urinary NGAL by the kit (Elabscience Biotechnology Inc.) *via* the ELISA method. Those cases with a raised level of NGAL and cystatin C were referred to a nephrologist for further monitoring and treatment of the patient. The cutoff for both NGAL and cystatin C levels was >12.5 ng/dL after dilution.

Categorical variables were presented as numbers and percentages, while continuous variables were reported as means with standard deviations (SD). Comparisons of quantitative variables between two groups were performed using the Mann–Whitney *U* test, and between three groups using the Kruskal–Wallis *U* test. Qualitative variables were analyzed using the Chi-squared test or Fisher's exact test, as appropriate. The Spearman correlation coefficient was employed to evaluate the strength of the association between two continuous variables. A p-value of <0.05 was considered statistically significant.

Table 1: Sex distribution in study distribution

Sex	*Frequency*	*Percent*
Male	184	81.4
Female	42	18.6
Total	226	100.0

Table 2: Age distribution in study population

Age intervals	*Frequency*	*Percent*
18–35 years	124	54.9
36–50 years	51	22.6
51–65 years	42	18.6
>65 years	9	4.0
Total	226	100.0

Table 3: Association of raised level of both urinary NGAL and cystatin C with age intervals and sex

		Urinary NGAL and cystatin C				*p-value*
		≥12.5		*<12.5*		
		N	*%*	*N*	*%*	
Age intervals	18–35 years	48	55.2%	76	54.7%	0.780
	36–50 years	20	23.0%	31	22.3%	
	51–65 years	17	19.5%	25	18.0%	
	>65 years	2	2.3%	7	5.0%	
Sex	Male	78	89.7%	106	76.3%	0.012
	Female	9	10.3%	33	23.7%	

After removing maximum confounding factors, we found that 87 cases had raised levels of urinary NGAL and cystatin C and out of these 87, 78 were male. We found a significant association of raised level of urinary NGAL and cystatin C with sex with p-value of 0. 012. We also found that 48 patients out of 87 were belong to age-group of 18–35 years

Table 4: Association of raised level of both urinary NGAL and cystatin C with duration of tenofovir

Duration of tenofovir	*Urinary NGAL and cystatin C*			
	≥12.5		*<12.5*	
	N	*%*	*N*	*%*
4–12 month	70	80.5%	117	84.2%
12–24 months	7	8.0%	6	4.3%
>24 months	10	11.5%	16	11.5%

Above table shows that out of 87 cases with raised level of both urinary NGAL and cystatin C 70 (80.5%) cases had 4–12 months treatment duration, 7 cases (8.0%) in 12–24 months duration belong, 10 (11.5%) cases >24 months duration

Results

In this study, 226 cases were enrolled. Of these, 184 were male and 42 were female (Table 1). The average age was 37.93 years, with the majority of participants falling within the 18–35 year age-group (54.9%). This was followed by 22.6% in the 36–50 year range, 18.6% in the 51–65 year range, and 4% aged over 65 years. The mean age was 37.69 ± 14.65 years with a median of 33 years. The minimum age was 19 years, and the maximum age was 81 years (Table 2). Clinical features of the study population showed pallor in 63 cases (27.9%), icterus in 25 (11.1%) cases, pedal edema in 77 (34.1%) cases, ascites in 44 (19.5%) cases, and hepatomegaly in 129 (57.1%) cases. It was observed that the maximum number of cases (74.8%) were in class A, 23% in class B, and 2.2% in class C of the Child-Pugh Score. After excluding confounding factors, out of 226 cases, 87 had raised levels of both urinary NGAL and cystatin C. Of these 87 cases, the majority were male and were in the age-group of 18–35 years (Tables 3 and 4).

Discussion

Studies indicate that renal dysfunction is associated with TDF. However, renal impairment occurs more frequently in HIV patients than in chronic hepatitis B patients receiving TDF treatment.[8,11] Multivariate analysis identified several risk factors linked to a decline in estimated glomerular filtration rate (eGFR) among patients treated with TDF, including advanced age, preexisting renal failure, comorbid conditions, a history of transplant, use of concurrent nephrotoxic drugs, advanced HIV coinfection, and male gender.[10,12–14]

A literature review conducted by Yang and Choi, available on PubMed, found that patients treated with TDF experienced a more significant reduction in eGFR compared to those on entecavir (ETV), with the decline occurring in a time-dependent manner.[15] According to the European Association for the Study of the Liver (EASL) guidelines, patients starting TDF should have their serum creatinine levels tested prior to treatment. Additionally, baseline renal risk should be assessed, considering factors such as decompensated cirrhosis, creatinine clearance below 60 mL/minute, poorly controlled hypertension, proteinuria, uncontrolled diabetes, use of nephrotoxic drugs, active glomerulonephritis, and solid-organ transplantation.[16] These confounding factors, which can cause raised levels of NGAL and cystatin C, have been excluded *via* exclusion criteria in our study.

Our study is a cross-sectional study in which 226 cases were enrolled. Of 226 cases,

184 (81.4%) were male, and 42 (18.6%) were female. In these 226 cases, the mean age was 37.93, and 124 (54.9%) were in the age-group of 18–35 years.

Urinary biomarkers of kidney damage could serve as potential indicators for detecting subclinical injury caused by TDF toxicity.[17] Urinary levels of NGAL and cystatin C can be influenced by various factors. Cystatin C tends to be lower in African populations, and elevated levels are linked to higher CRP, elevated white blood cell counts, and lower albumin levels.[16] Urinary NGAL levels are typically increased in patients with conditions like COPD, sepsis, and cardiac dysfunction. In our study, we accounted for these potential confounding factors during participant enrollment. We found that out of the total cases, 90 exhibited elevated urinary NGAL, while 113 showed increased cystatin C levels. Notably, 87 cases (38.49%) had elevated levels of both NGAL and cystatin C. Among these 87 cases, 78 were male and 9 were female, with 48 cases falling within the age-group of 18–35 years. Additionally, we observed a significant association between urinary NGAL and cystatin C levels and sex, with higher levels in males. However, other studies have reported urinary NGAL levels tend to be higher in males, whereas cystatin C levels are not influenced by age or sex.[18,19]

Our study found a positive correlation between urinary NGAL and cystatin C with the duration of treatment, but it was weak. NGAL and cystatin C had a correlation coefficient of 0.01 and 0.021, respectively. We also observed that out of 87 cases, 70 cases with raised levels of both urinary NGAL and cystatin C belonged to the treatment group of early duration (4–12 months), which means renal injury is not time dependent. TDF can even cause renal dysfunction in the initial duration of treatment (Table 4).

Data indicate that elevated urinary levels of NGAL and cystatin C may serve as predictors of acute-on-chronic liver failure (ACLF) and its impact on mortality in patients with chronic liver disease.[20] In our study, we didn't include those patients who were fulfilling the ACLF criteria. Further studies can be done to see the correlation between levels of NGAL and cystatin C with mortality outcome in patients with ACLF.[21,22]

Conclusion

In this cross-sectional study, after accounting for confounding factors, we found that TDF use is linked to increased urinary NGAL and cystatin C in 87 (38.4%) patients, including those aged 18–35. Given that these biomarkers are indicators of AKI, further prospective studies with larger samples are needed to evaluate the direct impact of TDF in hepatitis B patients.

As NGAL and cystatin C are elevated in patients on tenofovir, we recommend regular kidney function testing, including urine protein and serum creatinine levels. If kidney damage is detected, TDF dosage may need adjustment or a switch to another antiviral. Other potential causes of renal dysfunction, such as dehydration or nephrotoxic drugs, should also be considered. Further research with larger sample sizes is needed for confirmation.

Since NGAL and cystatin C can rise before serum creatinine, they could serve as early markers for kidney injury, but more studies are required to assess their role in diagnosing AKI. These biomarkers are currently available only in specific centers but may become more accessible and useful for early detection in the future.

Regular follow-ups are essential for monitoring kidney function, and patients should promptly report symptoms like edema or reduced urine output. With proper management, the risk of kidney injury in patients on tenofovir can be minimized.

References

1. Zhang K, Lin S, Wang M, et al. The risk of acute kidney injury in hepatitis B virus-related acute on chronic liver failure with tenofovir treatment. Biomed Res Int 2020;2020:5728359.
2. Chan HLY, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol 2016;1(3):185–195.
3. Birkus G, Hitchcock MJM, Cihlar T. Assessment of mitochondrial toxicity in human cells treated with tenofovir: comparison with other nucleoside reverse transcriptase inhibitors. Antimicrob Agents Chemother 2002;46(3):716–723.
4. Martin JL, Brown CE, Matthews-Davis N, et al. Effects of antiviral nucleoside analogs on human DNA polymerases and mitochondrial DNA synthesis. Antimicrob Agents Chemother 1994;38(12):2743–2749.
5. Cho H, Cho Y, Cho EJ, et al. Tenofovir-associated nephrotoxicity in patients with chronic hepatitis B: two cases. Clin Mol Hepatol 2016;22(2):286–291.
6. Tourret J, Deray G, Isnard-Bagnis C. Tenofovir effect on the kidneys of HIV-infected patients: a double-edged sword? J Am Soc Nephrol 2013;24(10):1519–1527.
7. Goicoechea M, Liu S, Best B, et al. Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. J Infect Dis 2008;197(1):102–108.
8. Lampertico P, Soffredini R, Viganò M, et al. 525 tenofovir monotherapy for naïve patients with chronic hepatitis B: a multicenter European study in clinical practice in 302 patients followed for 30 months. J Hepatol 2012;56(Suppl 2): S208.
9. Jo SK, Yang J, Hwang SM, et al. Role of biomarkers as predictors of acute kidney injury and mortality in decompensated cirrhosis. Sci Rep 2019;9(1):14508.
10. Tsai MC, Chen CH, Tseng PL, et al. Comparison of renal safety and efficacy of telbivudine, entecavir and tenofovir treatment in chronic hepatitis B patients: real world experience. Clin Microbiol Infect 2016;22(1):95.e1–95.e7.
11. Fontana RJ. Side effects of long-term oral antiviral therapy for hepatitis B. Hepatology 2009;49(5 Suppl):S185–S195.
12. Ha NB, Ku K, Ha NB, et al. Renal function in chronic hepatitis B patients treated with tenofovir disoproxil fumarate or entecavir monotherapy: a matched case-cohort study. J Clin Gastroenterol 2015;49(10):873–877.
13. Gish RG, Clark MD, Kane SD, et al. Similar risk of renal events among patients treated with tenofovir or entecavir for chronic hepatitis B. Clin Gastroenterol Hepatol 2012;10(8):941–946.
14. Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB, et al. Tenofovir nephrotoxicity: 2011 update. AIDS Res Treat 2011;2011:354908.
15. Yang YM, Choi EJ. Renal safety of tenofovir and/or entecavir in patients with chronic HBV monoinfection. Ther Clin Risk Manag 2017;13:1273–1285.
16. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. J Hepatol 2012;57:167–185.
17. Zhang WR, Scherzer R, Estrella MM, et al. Tenofovir disoproxil fumarate initiation and changes in urinary biomarker concentrations among HIV-infected men and women. AIDS 2019;33(4):723–733.
18. Chakraborty S, Kaur S, Guha S, et al. The multifaceted roles of neutrophil gelatinase associated lipocalin (NGAL) in inflammation and cancer. Biochim Biophys Acta 2012;1826:129–169.
19. Lima C, de Fatima Vattimo M, Macedo E. Neutrophil gelatinase-associated lipocalin as a promising biomarker in acute kidney injury. In: Inflammation in 21st Century; 2020.
20. Li J, Hu C, Chen Y, et al. Short-term and long-term safety and efficacy of tenofovir alafenamide, tenofovir disoproxil fumarate and entecavir treatment of acute-on-chronic liver failure associated with hepatitis B. BMC Infect Dis 2021;21(1):567.
21. Ariza X, Sola E, Elia C, et al. Analysis of a urinary biomarker panel for clinical outcomes assessment in cirrhosis. PLoS One 2015;10:e0128145.
22. Ariza X, Graupera I, Coll M, et al. Neutrophil gelatinase-associated lipocalin is a biomarker of acute-on-chronic liver failure and prognosis in cirrhosis. J Hepatol 2016;65:57–65.

ORIGINAL ARTICLE

Impact of Blood Glucose Level on Hematological Indices in Patients with Type 2 Diabetes Mellitus

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Abstract

Background: The severity and complications of type 2 diabetes mellitus (T2DM) are the most important preventable health burdens. This study was undertaken to assess the impact of hyperglycemia on hematological indices in patients with T2DM.

Materials and methods: This study was conducted on 300 patients with T2DM, which included group A having controlled diabetes [hemoglobin A1c (HbA1c) <7%] and group B having uncontrolled diabetes (HbA1c >7%). Information concerning medical history, physical examination, diabetic parameters, hematological indices, and laboratory findings was extracted for interpretation and association between both groups.

Results: About 115 patients (38.33%) had HbA1c <7% and 185 patients (61.67%) had HbA1c >7%. Total leukocyte count (TLC), monocytes, basophils, red cell distribution width (RDW-CV), platelet distribution width (PDW), mean platelet volume (MPV), platelet large cell ratio (P-LCR), plateletcrit (PCT), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were significantly higher among patients with uncontrolled T2DM compared to those with controlled T2DM ($p < 0.05$), while red blood cells (RBC) count, hemoglobin, mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) were significantly lower in the uncontrolled diabetic group compared to the controlled diabetic group ($p < 0.05$). HbA1c had a significant positive correlation coefficient with TLC, neutrophil count, basophil count, PDW, MPV, PCT, PLR, and NLR, while RBC count, hemoglobin, hematocrit (HCT), and MCV showed significant negative correlation coefficients ($p < 0.05$).

Conclusion: This study concluded that inflammation, tendency to coagulation, and thrombosis can be detected with easily accessible and inexpensive hematological indices. Therefore, hematological indices can be used as a direct measure to detect the severity of T2DM and its complications.

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Introduction

The term "diabetes mellitus" describes a metabolic ailment of a couple of etiology characterized by persistent hyperglycemia due to defective secretion and/or action of insulin, which leads to an imbalance in carbohydrate, fat, and protein metabolism. Diabetes mellitus is one of the most common chronic illnesses in almost all nations. It is increasing rapidly in every part of the world, to the extent that it has now assumed an epidemic proportion.

It is estimated that 54 crore adults in the age-group of 20–79 years are living with (T2DM). This number is expected to rise to 64.5 crore by 2030 and 78.4 crore by 2045.[1] DM caused 6.7 million deaths in 2021.[1] The prevalence of type 2 DM varies significantly from one geographical location to another due to environmental and lifestyle risk factors.[2] Several sedentary lifestyle-related factors are responsible for the increasing prevalence of T2DM in developing countries, including overweight [body mass index (BMI) = 25 kg/m^2], obesity (BMI = 30 kg/m^2), physical inactivity, and increased caloric intake. These are all shown to be primary risk factors for the onset of T2DM, irrespective of age and sex.[3]

Diabetes mellitus is a very common metabolic disease worldwide and, particularly in India, where it has been called "The Diabetes Capital of the World." Diabetes mellitus itself results in a range of complications affecting all major systems of the body.

Diabetes mellitus is associated with macrovascular as well as microvascular complications. Type 2 diabetic patients are at a higher risk of developing cardiovascular diseases (CVDs) and stroke. T2DM is the most common risk factor for the development of coronary artery disease (CAD), along with other risk factors like hypertension, increased low-density lipoprotein cholesterol (LDL), and weight gain.[4,5]

Inflammation is closely related to the secretory defect of beta cells as well as insulin resistance. Circulating markers of inflammation can reduce the function of beta cells through secretory dysfunction or uncontrolled apoptosis.[6] A classical inflammatory marker includes total leukocyte count (TLC); it alters carbohydrate metabolism and increases insulin resistance, which predisposes individuals to T2DM and various cardiovascular risks.[7] In addition to atheroma formation, the combination of hypercoagulability, impaired fibrinolysis, and impaired vasodilation may further increase the risk of vascular occlusion and cardiovascular events in diabetes.[8]

Large platelets are more active than smaller platelets and carry more pro-thrombotic factors, including thromboxane A2, thromboxane B2, platelet factor 4, serotonin, and platelet-derived growth factor.[9] This suggests that changes in platelet count and mean platelet volume (MPV) reflect the state of thrombogenesis. It has been shown that MPV is significantly higher in diabetic populations.[10] Platelet activity and aggregation ability, which are important in atherogenesis and thrombogenesis, can be easily predicted through various hematological indices, such as MPV, plateletcrit (PCT), and platelet count as part of a complete blood count.

Within the closing many years, platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) were introduced as capability markers to determine inflammation in cardiac and noncardiac issues.[11] Starting from this point, we hypothesized that the elevated hazard of diabetic vascular complications in sufferers with bad glycemic manage can be associated with impaired numerous hematological indices, which can be recovered through tight glycemic control. Consequently, we need to evaluate the association among hematological indices, glycemic control, and microvascular complications in type 2 diabetic sufferers.

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Materials and Methods

Study Design

This cross-sectional, observational, comparative analysis was conducted on a total of 300 patients with T2DM from January 2020 to December 2022, who visited for outpatient department (OPD) or inpatient department (IPD) at SMS Medical College and Hospitals, Jaipur, India. This study was permitted by the Institutional Ethics Committee of this institute. In this study, apparently healthy diabetic sufferers were included. About 115 sufferers with type 2 DM and controlled sugar [hemoglobin A1c (HbA1c) <7%] were considered in group A, and 185 patients with uncontrolled T2DM (HbA1c >7%) were considered in group B. Informed consent was received from each subject included in the study.

Patients with a history of hematological disease and thrombotic disease, on anticoagulant medications, chronic kidney disease, chronic liver disease, malignancy including leukemia and lymphoma, male patients with Hb <12.5 gm/dL, female patients with Hb <11.5 gm/dL, current or former smokers, pregnancy, and acute infectious disease altering these indices were excluded from this study.

Methods

Patients presenting or diagnosed with T2DM coming to the outpatient or emergency department were identified and enrolled in the study. Any patients with an HbA1c level >6.5 gm% or a history of taking any oral hypoglycemic agents and/or insulin were considered diabetic patients.

Data including blood pressure, height and weight measurements, age, gender, accompanying disease history, smoking habits, medication, and medical history were recorded. The Quetelet index formula was used to calculate BMI. Complete blood count from the advanced hematology lab, biochemical profile including blood glucose, creatinine, total lipid profile, HbA1c, and spot urinary albumin creatinine ratio were obtained. NLR and PLR were calculated as the ratio of neutrophils to lymphocytes and platelets to lymphocytes, respectively.

Sufferers with DM have been evaluated concerning metabolic regulation and nephropathy on the premise of morning spot urinary albumin/creatinine ratio. All of the data were gathered on a predesigned proforma. Information thus accrued has been entered in the form of a master chart. The information has been categorized and analyzed according to the objectives and goals of the study. Inferences were drawn using suitable tests of significance.

Statistical Analysis

Collected data were tabulated in Microsoft Excel and arranged for analysis. Quantitative data were expressed as mean ± SD, and qualitative data as percentages. For the comparison of quantitative and qualitative data, the *t*-test and Chi-squared test were used, respectively. The Pearson correlation coefficient was used to determine correlations between variables. A *p*-value of <0.05 was considered significant.

Results

A total of 300 patients enrolled in this study. On the basis of their glycemic control, the study population was divided into two groups, that is, group A with controlled sugar (HbA1c <7%) and group B with uncontrolled sugar (HbA1c >7%). Among the selected study population, 115 patients (38.33%) have controlled blood sugar with HbA1c <7 gm%, and 185 (61.67%) patients have uncontrolled blood sugar with HbA1c >7 gm%.

The mean age was significantly higher in the uncontrolled diabetic group (55.56 ± 15.58 years) as compared to the controlled diabetic group (50.94 ± 11.4 years) with a *p*-value of 0.0063 (Table 1). Men are able to control their diabetes efficiently as compared to their female counterparts ($p < 0.001$). The duration of diabetes and systolic blood pressure were found to be significantly higher in the uncontrolled diabetic group as compared to the controlled diabetic group ($p < 0.001$).

Laboratory Findings

As per indicators of glycemic control, blood glucose and HbA1c were found to be significantly higher among patients with poorly controlled T2DM as compared to those with well-controlled T2DM ($p < 0.001$). Diabetic risk factors like total cholesterol, triglycerides, and LDL cholesterol were also found to be significantly higher among patients with poorly controlled T2DM as compared to those with well-controlled T2DM ($p < 0.05$). Diabetes-related microvascular complications like urine albumin-to-creatinine ratio (UACR) were significantly higher among patients with poorly controlled T2DM as compared to those with well-controlled T2DM ($p < 0.001$). Among white blood cell indices, inflammatory markers like total WBC count, monocyte count, and basophil count were significantly higher in patients with poorly controlled T2DM as compared to those with well-controlled T2DM ($p < 0.05$) (Table 1).

Red blood cell indices like RBC count, hemoglobin, mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) were significantly lower among the uncontrolled diabetic group as compared to the controlled diabetic group ($p < 0.05$), while red cell distribution width (RDW-CV) was found to be significantly higher among the uncontrolled diabetic group (14.24 ± 2.87%) as compared to the controlled diabetic group (13.12 ± 2.56%) ($p = 0.0007$). Other indices like platelet distribution width (PDW), MPV, platelet large cell ratio (P-LCR), PCT, NLR, and PLR were also significantly higher among patients with poorly controlled T2DM as compared to those with well-controlled T2DM ($p < 0.001$).

Association of Hematological Indices with Parameters of Glycemic Index

Fasting blood glucose has a significant positive correlation coefficient with TLC, neutrophil count, monocyte count, basophil count, RDW-CV, RDW-SD, PDW, MPV, P-LCR, PCT, PLR, and NLR, while RBC count, hemoglobin, hematocrit (HCT), MCV, and MCH showed significant negative correlation coefficients ($p < 0.05$). HbA1c showed a significant positive correlation coefficient with TLC, neutrophil count, basophil count, PDW, MPV, PCT, PLR, and NLR, while RBC count, hemoglobin, HCT, and MCV showed significant negative correlation coefficients ($p < 0.05$). BMI showed a significant positive correlation coefficient with TLC, neutrophil count, monocyte count, basophil count, PCT, and PLR, while RBC count, hemoglobin, HCT, MCV, and MCH showed significant negative correlation coefficients ($p < 0.05$) (Table 2).

Discussion

Diabetes mellitus is a persistent condition that could result in several complications over the years. The diabetes-related microvascular complications are highly prevalent in individuals with poor glycemic control, longer duration of T2DM, associated high blood pressure, and obesity. This leads to elevated morbidities and mortalities in T2DM.[12] Persistent hyperglycemia results in a series of interrelated changes that could cause evident endothelial dysfunction and diabetes-related vascular complications. The formation of advanced glycation end products, protein kinase C activation, and polyol pathway defects are the possible mechanisms through which elevated sugar levels produce vascular complications.[13]

Sufferers with T2DM have an elevated risk of coagulation defects and thromboembolic events. The activation, increased adhesion,

Table 1: Characteristics and hematological indices in patients with T2DM

Parameters	*Group A HbA1c <7 gm/dL (n = 115)*	*Group B HbA1c >7 gm/dL (n = 185)*	*p-value*
Age (year)	50.94 ± 11.4	55.56 ± 15.58	0.0063
Gender			
Male	102 (88.69%)	108 (58.38%)	<0.001
Female	13 (11.31%)	77 (41.62%)	
Duration of diabetes (years)	4.6 ± 1.4	6.8 ± 2.1	<0.001
BMI (kg/m^2)	28.44 ± 1.29	28.57 ± 1.37	0.4146
Systolic blood pressure (mm Hg)	131.50 ± 5.10	137.29 ± 5.83	<0.001
Diastolic blood pressure (mm Hg)	88.88 ± 10.56	89.17 ± 6.35	0.7666
Fasting blood glucose (mg/dL)	103.6 ± 8.64	165.4 ± 25.76	<0.001
Postprandial blood glucose (mg/dL)	153.5 ± 10.65	214 ± 32.44	<0.001
HbA1c (%)	6.32 ± 0.64	8.94 ± 2.37	<0.001
UACR (mg/gm)	247 ± 139.06	704.24 ± 231.61	<0.001
Total cholesterol (mg/dL)	174.94 ± 15.78	183.00 ± 10.83	<0.001
Triglycerides (mg/dL)	94.55 ± 13.69	98.81 ± 14.28	0.0112
LDL-C (mg/dL)	125.06 ± 19.59	137.18 ± 22.68	<0.001
HDL-C (mg/dL)	41.88 ± 5.07	41.10 ± 6.36	0.2665
White blood cells indices			
Total WBC count (10^9/L)	6.60 ± 1.88	7.15 ± 1.91	0.0153
Neutrophil count (10^9/L)	3.74 ± 1.34	4.12 ± 2.33	0.1124
Lymphocyte count (10^9/L)	2.20 ± 1.01	2.01 ± 1.29	0.1800
Monocyte count (10^9/L)	0.42 ± 0.34	0.71 ± 0.51	<0.001
Eosinophil count (10^9/L)	0.13 ± 0.21	0.16 ± 0.12	0.1165
Basophil count (10^9/L)	0.11 ± 0.07	0.15 ± 0.13	0.0026
Red blood cells indices			
RBC count (10^{12}/L)	4.31 ± 1.12	3.98 ± 1.17	0.0164
Hemoglobin (gm/dL)	13.05 ± 2.33	12.3 ± 2.42	0.0086
HCT (%)	46.14 ± 9.62	44.29 ± 10.31	0.1222
MCV (fL)	89.12 ± 15.32	84.25 ± 22.87	0.0444
MCH (pg)	28.89 ± 3.91	27.98 ± 3.84	0.0484
MCHC (%)	34.50 ± 3.38	34.12 ± 3.53	0.3576
RDW-CV (%)	13.12 ± 2.56	14.24 ± 2.87	0.0007
Platelet indices			
Platelet count (10^9/L)	246.50 ± 19.52	251.87 ± 26.58	0.0618
PDW (fL)	9.32 ± 1.82	10.11 ± 1.98	0.0006
MPV (fL)	9.12 ± 2.12	9.74 ± 2.54	0.0296
P-LCR (%)	16.94 ± 4.12	19.84 ± 5.24	<0.001
PCT (%)	0.22 ± 0.04	0.25 ± 0.05	0.0037
NLR	1.70 ± 1.33	2.04 ± 1.50	0.0473
PLR	112.04 ± 19.33	125.30 ± 20.60	<0.001

BMI, body mass index; HCT, hematocrit; Hgb, hemoglobin; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; NLR, neutrophil to lymphocyte ratio; PDW, platelet distribution width; PLC-R, platelet large cell ratio; PLR, Platelet to lymphocyte ratio; RBC, red blood cells; RDW-CV, red cell distribution width coefficient of variation; RDW-SD, red cell distribution width standard deviation; SD, standard deviation; UACR, urine albumin creatinine ratio; WBC, white blood cells; *p*-value < 0.05, statistically significant

and aggregation of platelets due to metabolic disturbances, insulin resistance, high blood sugar, and elevated cholesterol levels have been observed in T2DM.[14] Various factors, including systemic inflammation, impaired calcium metabolism, reduced nitric oxide, and increased phosphorylation and glycosylation of cell proteins, are responsible for prolonged platelet activation and increased release of pro-thrombotic factors in T2DM.[15]

The affiliation of elevated MPV with prediabetes, diabetes, and vascular diabetic complications is mentioned in the literature.[16] Furthermore, the affiliation of MPV and impaired glucose regulation in diabetic patients is also stated.[17] As with MPV, elevated PDW is also reported to be related to diabetes and vascular complications.[18] Several studies reported no relation, while some reported positive affiliations between diabetes and platelet count.[19]

Increased TLC is a standard marker of inflammation, and it recruits inflammation with hyperglycemia and insulin resistance.[20] In recent years, PLR and NLR have been identified as novel markers of inflammation in various metabolic disorders.[21] Moreover, increased levels of PLR and NLR have been reported in T2DM and diabetes-related nephropathy.[21] Besides thromboembolic issues, associations of platelet indices with inflammation and disordered activity of anti-inflammatory factors have also been demonstrated.

In the present study, a total of 300 patients with T2DM were enrolled. Elderly people and female patients had poorly controlled diabetes, and the difference was significant.

In our study, the mean BMI among both groups did not differ significantly. This suggests that cases with poorly controlled diabetes are more obese than those in the well-controlled diabetic group, but the difference is statistically nonsignificant (p = 0.4146). This was similar to the study done by Demirtas et al.,[22] where the difference in mean BMI between the two groups was statistically nonsignificant. In our study, uncontrolled diabetics had a longer history of diabetes compared to the controlled diabetic group. Indices of glycemic control, including duration of diabetes, blood sugar level, HbA1c, and systolic blood pressure, were significantly higher among those with uncontrolled diabetes compared to the controlled diabetic group. In our study, the mean SBP of the good glycemic control group (HbA1c <7%) was 131.50 ± 5.10 mm Hg, and that of the poor glycemic control group (HbA1c >7%) was 137.29 ± 5.83 mm Hg. A significant difference was observed (<0.001) between the groups.

Diabetes-related microvascular complications, like UACR, were significantly higher in patients with poorly controlled T2DM compared to those with good control (p < 0.001). Thus, patients with poorly controlled diabetes had significantly more albuminuria than those with good control, further increasing the risk of nephropathy. In this study, the mean values of total cholesterol, triglycerides, and LDL levels were significantly higher in patients with poorly controlled T2DM compared to those with good control (p < 0.001). Therefore, patients with poorly controlled diabetes had a significantly more deranged lipid profile than those with good control,

Table 2: Pearson correlation coefficient "r" (*p*-value) of hematological indices with diabetic parameters

Hematological indices	*FBG (mg/dL)*	*PPG (mg/dL)*	*HbA1c (gm/dL)*	*BMI (Kg/m^2)*
White blood cells indices		DBP		
Total WBC count (10^9/L)	0.21 (0.0006)	–0.013 (0.8091)	0.272 (<0.001)	0.289 (<0.001)
Neutrophil count (10^9/L)	0.198 (0.0005)	0.022 (0.6915)	0.280 (<0.001)	0.311 (<0.001)
Lymphocyte count (10^9/L)	–0.044 (0.4686)	–0.109 (0.0547)	0.035 (0.5459)	–0.042 (0.4686)
Monocyte count (10^9/L)	0.29 (<0.001)	–0.013 (0.7825)	0.091 (0.1157)	0.130 (0.0243)
Eosinophil count (10^9/L)	0.110 (0.0617)	–0.038 (0.5009)	0.095 (0.1005)	0.111 (0.05479)
Basophil count (10^9/L)	0.432 (<0.001)	0.101 (0.0837)	0.314 (<0.001)	0.329 (<0.001)
Red blood cells indices				
RBC count (10^{12}/L)	–0.325 (<0.001)	–0.135 (0.193)	–0.131 (0.0232)	–0.181 (0.0016)
Hemoglobin (gm/dL)	–0.438 (<0.001)	–0.175 (0.0023)	–0.185 (0.0012)	–0.279 (<0.001)
Hematocrit (%)	–0.401 (<0.001)	–0.172 (0.0028)	–0.160 (0.0054)	–0.230 (<0.001)
MCV (fL)	–0.396 (<0.001)	0.121 (0.0361)	–0.54 (<0.001)	–0.218 (<0.001)
MCH (pg)	–0.337 (<0.001)	–0.090 (0.1198)	–0.070 (0.2267)	–0241 (<0.001)
MCHC (gm/dL)	0.068 (0.2403)	0.25 (<0.001)	0.001 (0.9862)	–0.087 (0.1327)
RDW-CV (%)	0.138 (0.0167)	0.0075 (0.897)	0.020 (0.7300)	0.151 (0.0088)
RDW-SD (fL)	0.162 (0.0049)	0.281 (<0.001)	0.086 (0.1372)	0.105 (0.0693)
Platelet indices				
Platelet count (10^9/L)	–0.28 (<0.001)	0.161 (0.0053)	0.062 (0.2844)	0.078 (0.1778)
PDW (fL)	0.271 (<0.001)	0.076 (0.1892)	0.136 (0.0184)	0.085 (0.1418)
MPV (fL)	0.295 (<0.001)	0.002 (0.9724)	0.101 (0.0807)	0.030 (0.6047)
PLC-R (%)	0.177 (0.0020)	–0.031 (0.5927)	0.071 (0.2201)	–0.035 (0.5459)
PCT (%)	0.151 (0.0088)	0.101 (0.0807)	0.102 (0.0777)	0.120 (0.0377)
NLR	0.125 (0.0304)	0.106 (0.0667)	0.156 (0.0067)	0.095 (0.1005)
PLR	0.187 (0.0011)	0.115 (0.0465)	0.123 (0.0332)	0.224 (<0.001)

further increasing the risk of atherosclerotic burden. A study by Petitti et al. suggests that hematological indices and blood sugar levels may be correlated due to diabetes-related dyslipidemia.[23] In this study, we found that among white blood cell indices, inflammatory markers such as total WBC count, monocyte count, and basophil count were significantly higher in patients with poorly controlled T2DM compared to those with good control ($p < 0.05$).

FBG has a direct significant positive correlation coefficient with TLC ($r = +0.21$, $p = 0.0006$), neutrophil count ($r = +0.198$, $p = 0.0005$), monocyte count ($r = +0.29$, $p < 0.001$), and basophil count ($r = +0.432$, $p < 0.001$). HbA1c has a direct significant positive correlation coefficient with WBC count ($r = +0.272$, $p < 0.001$), neutrophil count ($r = +0.280$, $p < 0.001$), and basophil count ($r = +0.314$, $p < 0.001$). BMI has a direct significant positive correlation coefficient with WBC count ($r = +0.289$, $p < 0.001$), neutrophil count ($r = +0.311$, $p < 0.001$), monocyte count ($r = +0.130$, $p = 0.0243$), and basophil count ($r = +0.329$, $p < 0.001$). The differential WBC counts are probably deranged due to high blood sugar levels in patients with T2DM. Elevated TLC is an important marker of inflammation, and evidence from epidemiological research studies suggests that complications of T2DM are directly correlated with WBC count.[24]

Insulin resistance at peripheral tissues produces continuous low-grade inflammation and secretes proinflammatory cytokines.[25] Moreover, in high glycemic conditions, WBCs are stimulated through oxidative stress, and simultaneously, inflammation-associated growth of cytokines produces vascular complications in diabetes. Another marker of inflammation, including neutrophils and monocytes, is also related to the development of vascular complications in T2DM.[26]

Red blood cell indices, like RBC count, hemoglobin, MCV, and MCH, were significantly lower in the uncontrolled diabetic group compared to the controlled diabetic group ($p < 0.05$), while RDW-CV was found to be significantly higher in the uncontrolled diabetic group (14.24 ± 2.87%) compared to the controlled diabetic group (13.12 ± 2.56%) ($p = 0.0007$). FBG has a direct significant negative correlation coefficient with RBC count ($r = -0.325$, $p < 0.001$), hemoglobin ($r = -0.438$, $p < 0.001$), HCT ($r = -0.401$, $p < 0.001$), MCV ($r = -0.396$, $p < 0.001$), and MCH ($r = -0.337$, $p < 0.001$), while a positive correlation coefficient is found with RDW-CV ($r = 0.396$, $p = 0.0167$) and RDW-SD ($r = 0.162$, $p = 0.0049$). HbA1c has a direct significant negative correlation coefficient with RBC count ($r = -0.131$, $p = 0.0232$), hemoglobin ($r = -0.185$, $p = 0.0012$), HCT ($r = -0.160$, $p = 0.0054$), and MCV ($r = -0.54$, $p < 0.001$). BMI, a most important risk factor of diabetes, has a direct significant negative correlation coefficient with RBC count ($r = -0.181$, $p = 0.0016$), hemoglobin ($r = -0.279$, $p < 0.001$), HCT ($r = -0.230$, $p < 0.001$), MCV ($r = -0.218$, $p < 0.001$), and MCH ($r = -0.241$, $p < 0.001$), while a positive correlation coefficient is found with RDW-CV ($r = 0.151$, $p = 0.0088$).

Every other study has found that diabetics are at risk of anemia because of decreased kidney capabilities and reduced production of erythropoietin hormone, which ultimately results in reduced RBC count within the body.[27] The possible explanation for this difference is probably that chronic hyperglycemia causes nonenzymatic glycosylation of RBC membrane proteins, leading to increased aging of RBCs. Enormous elevations of HCT and MCV are likely due to the type of morphological changes exhibited by RBCs and compositional changes in plasma associated with T2DM.[28] In diabetic patients, a number of risk factors, including hyperglycemia, hyperosmolarity, oxidative stress, inflammation, and lipid metabolic disease, may affect RBC metabolism

as they increase aggregation, reduce cell deformability, and decrease membrane fluidity. Subsequently, the overall process affects the physiological functions of RBCs, which may in turn increase diabetes-related complications.[29]

Indices like PDW, MPV, P-LCR, PCT, NLR, and PLR were observed to be significantly higher in the uncontrolled diabetic group compared to the controlled diabetic group ($p < 0.001$). In addition, other concordant findings were reported in South Korea, India, and Turkey, where MPV, PDW, and P-LCR showed a significant increase in poorly glycemic-controlled diabetes patients.[30] FBG has a direct significant negative correlation coefficient with platelet count ($r = -0.28$, $p < 0.001$), while a positive correlation coefficient is found with PDW, MPV, PLCR, PCT, NLR, and PLR. HbA1c has a direct significant positive correlation coefficient with PDW, NLR, and PLR.

We examine exhibits that inflammation, tendency to coagulation, and thrombosis may be detected with those smooth-on-hand and cheaper hematological indices. Furthermore, a number of these parameters can also assist to conscious clinicians about impaired glucose regulation and vascular diabetic complications. These assessments are easy, cheaper, and carried out routinely. They may be an alternative to other more expensive inflammatory markers, such as ILs, TNF, and cytokines. Improved glycemic control decreases these indices and can prevent microvascular complications of diabetes.

Limitations

The sample size was limited, and for confirmation of results, we need a larger sample size. It was a single-center, observational, cross-sectional study, and if it had been multicentric, we might have had different results due to a different study population.

References

1. Global Burden of Diabetes. International Diabetes Federation. IDF Diabetes Atlas, 10th ed. Brussels, Belgium. 2021. Available at: https://www.diabetesatlas.org
2. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001;414(6865):782–787.
3. Kopelman PG. Obesity as a medical problem. Nature 2000;404(6778):635–643.
4. Fox CS, Coady S, Sorlie PD, et al. Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. Circulation 2007;115(12):1544–1550.
5. Preis SR, Pencina MJ, Hwang SJ, et al. Trends in cardiovascular disease risk factors in individuals with and without diabetes mellitus in the Framingham Heart Study. Circulation 2009;120(3):212–220.
6. Agrawal NK, Kant S. Targeting inflammation in diabetes: newer therapeutic options. World J Diabetes 2014;5:697–710.
7. Horne BD, Anderson JL, John JM, et al. Which white blood cell subtypes predict increased cardiovascular risk? J Am Coll Cardiol 2005;45:1638–1643.
8. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA 2002;287:2570–2581.
9. Gasparyan AY, Ayvazyan L, Mikhailidis DP, et al. Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des 2011;17:47–58.
10. Zaccardi F, Rocca B, Pitocco D, et al. Platelet mean volume, distribution width, and count in type 2 diabetes, impaired fasting glucose, and metabolic syndrome: a meta-analysis. Diabetes Metab Res Rev 2015;31:402–410.
11. Ergelen M, Uyarel H, Altay S, et al. Predictive value of elevated neutrophil to lymphocyte ratio in patients undergoing primary angioplasty for ST-segment elevation myocardial infarction. Clin Appl Thromb Hemost 2014;20:427–432.
12. O'Malley T, Langhorne P, Elton RA, et al. Platelet size in stroke patients. Stroke 1995;26:995–999.
13. Vernekar PV, Vaidya KA. Comparison of mean platelet volume in type 2 diabetics on insulin therapy and on oral hypoglycaemic agents. J Clin Diagn Res 2013;7(12):2839–2840.
14. Kim JH, Bae HY, Kim SY. Response: clinical marker of platelet hyperreactivity in diabetes mellitus (Diabetes Metab J 2013;37:423-8). Diabetes Metab J 2014;38:160–161.
15. El Haouari M, Rosado JA. Platelet signalling abnormalities in patients with type 2 diabetes mellitus: a review. Blood Cells Mol Dis 2008;41:119–123.
16. Zuberi BF, Akhtar N, Afsar S. Comparison of mean platelet volume in patients with diabetes mellitus, impaired fasting glucose and non-diabetic subjects. Singapore Med J 2008;49:114–116.
17. Ozder A, Eker HH. Investigation of mean platelet volume in patients with type 2 diabetes mellitus and in subjects with impaired fasting glucose: a cost-effective tool in primary health care? Int J Clin Exp Med 2014;7:2292–2297.
18. Bekler A, Ozkan MTA, Tenekecioglu E, et al. Increased platelet distribution width is associated with severity of coronary artery disease in patients with acute coronary syndrome. Angiology 2015;66:638–643.
19. Erdogan S, Ozdemir O, Dogan HO, et al. Liver enzymes, mean platelet volume, and red cell distribution width in gestational diabetes. Turk J Med Sci 2014;44:121–125.
20. Twig G, Afek A, Shamiss A, et al. White blood cells count and incidence of type 2 diabetes in young men. Diabetes Care 2013;36:276–282.
21. Akbas EM, Demirtas L, Ozcicek A, et al. Association of epicardial adipose tissue, neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio with diabetic nephropathy. Int J Clin Exp Med 2014;7:1794–1801.
22. Demirtas L, Degirmenci H, Akbas EM, et al. Association of hematological indices with diabetes, impaired glucose regulation and microvascular complications of diabetes. Int J Clin Exp Med 2015;8(7):11420–11427.
23. Petitti DB, Imperatore G, Palla SL, et al. Serum lipids and glucose control: the Search for Diabetes in Youth study. Arch Pediatr Adolesc Med 2007;161:159–165.
24. Vozarova B, Weyer C, Lindsay RS, et al. High white blood cell count is associated with a worsening of insulin sensitivity and predicts the development of type 2 diabetes. Diabetes 2002;51:455–461.
25. Jiang H, Yan WH, Li CJ, et al. Elevated white blood cell count is associated with higher risk of glucose metabolism disorders in middle-aged and elderly Chinese people. Int J Environ Res Public Health 2014;11:5497–5509.
26. Hamed NAM. Alterations in hematological parameters: could it be a marker in diabetes mellitus? BAOJ Diabet 2016;2(1):1–9.
27. Cawood TJ, Buckley U, Murray A, et al. Prevalence of anaemia in patients with diabetes mellitus. Ir J Med Sci 2006;175:25–27.
28. Marcinkowska-Gapinska A, Kowal P. Blood fluidity and thermography in patients with diabetes mellitus and coronary artery disease in comparison to the healthy subject. Clin Hemorheol Microcirc 2006;35:473–479.
29. Wang Y, Yang P, Yan Z, et al. The relationship between erythrocytes and diabetes mellitus. J Diabetes Res 2021;2021:6656062.
30. Bhattacharjee P, Datta A, Debbarma RK, et al. Platelet indices in diabetics and influence of glycemic control—a hospital-based study in North-East India. Int J Med Res Rev 2016;4(12):2186–2192.

ORIGINAL ARTICLE

Clinical Profile, Prognosis, and Outcome of Acute Kidney Injury Patients Admitted in Medical Intensive Care Unit

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Abstract

Background: Acute kidney injury (AKI) is one of the poor prognosticating conditions in the intensive care unit (ICU). It increases mortality. Its pathophysiology involves various aspects, such as prerenal, renal, and postrenal components. Many times, it is a combination of one or more etiologies. Its management is a challenge, as no agent is approved for its prevention or treatment. It is the comprehensive treatment and timely institution of renal replacement therapy (RRT) that matter most. To understand the prognosis and outcome of patients with AKI, we conducted this observational analytical study.

Materials and methods: It was a observational study. To analyze the effect of loop diuretics, we grouped the patients into two: one group received furosemide, and the other did not.

Results: There was a male preponderance among AKI patients. Hypertension and diabetes were the most common comorbidities. About 44.1% of patients received diuretics. There was no significant difference among patients in the requirement for RRT or the need for vasopressors; however, the outcome of patients who received diuretics was worse.

Conclusion: The use of diuretics did not improve the outcome of acute kidney injury.

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Introduction

Acute kidney injury (AKI) is one of the common complications of any critical illness. It is defined by the Kidney Disease Improving Global Outcomes (KDIGO) Society as an acute decrease in renal function, a rise in serum creatinine of 0.3 mg% or more within 48 hours, or an increase in serum creatinine to 1.5 times baseline or more within the last 7 days, or urine output <0.5 mL/kg/hour for 6 hours. The incidence varies from 20 to 70%.[1,2] Risk factors for developing AKI include sepsis, diabetes, hypertension, use of mechanical ventilators, and use of vasopressors. AKI in intensive care units (ICU) can be sub-grouped into two: one with those who have AKI at admission to the hospital, and the second with those who develop AKI during the hospital course. The second category has a worse prognosis.[3,4] In a study by Kellum et al., 16,000 patients were observed for 1 year who suffered AKI in the ICU. Classically, according to pathophysiology, AKI is divided into prerenal, renal (intrinsic), and postrenal. Prerenal, the most common form in the ICU, usually develops secondary to low blood pressure, sepsis causing vasodilation, and hypoperfusion. Intrinsic renal disease is caused by parenchymal involvement, tubular necrosis, interstitial nephritis, and glomerulonephritis. The most common cause of intrinsic AKI is acute tubular necrosis (ATN). ATN in the ICU can be divided into three categories: ischemia-reperfusion injury, nephrotoxic, and septic. Septic ATN is unique, and it can develop in the absence of overt renal ischemia.[5] Postrenal causes are due to obstruction in the urinary tract.

They observed five types of outcome: patients with early recovery (<7 days), patients with late recovery (>7 days), relapse with or without altered renal function at discharge, and sustained renal failure.[6] Patients developing AKI in critical care units are relatively younger in age, male predominant, and have multiorgan dysfunction.

The role of diuretics in prevention and treatment is always debatable. In the AKIGUARD Trial, the investigator found a significant reduction in contrast-induced nephropathy in the group that received saline plus diuretics compared to those who received sodabicarb/N-acetyl cysteine/vitamin C.[7] Kleinknecht et al., Shilliday et al., and van der Voort et al. did prospective placebo-controlled studies to look for the therapeutic effect of loop diuretics on AKI, and all of these found neither advantage nor disadvantage of LD on AKI outcome.[8–10]

In this study, we observed the clinicopathologic profile of AKI in patients admitted to the ICU and compared the outcome of patients who received diuretics with those who did not receive them.

Materials and Methods

It was an observational study, where medical records of patients who were admitted or developed AKI in the medical ICU during January to June 2022 were included, and relevant data were collected. Ethical approval was taken from the Institutional Ethics Committee (AIIMS/Pat/IEC/2022/867).

Inclusion Criteria

Patients developing or admitted with AKI in the ICU.

Exclusion Criteria

Burn patients, surgical patients, known or diagnosed CKD, and CLD.

Appropriate statistical analysis was done using SPSS. For analysis purposes, patients were divided into two groups depending on the use of diuretics. The independent *t*-test and Chi-squared test of proportions were used to compare continuous and categorical variables, respectively, between the groups.

Results

A total of 77 patients were recruited; of these, five patients were excluded because they were found to have chronic kidney disease on evaluation. The mean age of patients who developed AKI was 55.3 ± 16.2 years. About 54.2% of them are males. The mean length of stay was 12.58 ± 7.63 days.

Baseline characteristics of patients are summarized in Table 1. Comorbidities like hypertension, diabetes, coronary artery disease, cerebrovascular accident (CVA), infection, malignancy, and chronic obstructive pulmonary disease (COPD) were present in 33.3, 33.3, 16.7, 20.1, 11.1, 9.7% of patients, respectively. About 44.1% of patients had diuretics use during their course of treatment. 66.7% ($n = 48$) of patients were

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oliguric/anuric. 68.1% of patients expired during their course.

Table 2 shows the comparison of groups who received diuretics in their treatment vs those who did not. There was no clinically significant difference in mean SOFA score, APACHE II score, and total length of stay. There was no significant difference in the need for renal replacement therapy (RRT) and the need for vasopressors between the two groups. When we compared the outcome between these two groups, it was higher in the group that received diuretics ($p < 0.001$).

The association between the use of diuretics and outcome was compared using the Chi-squared test and found that the use of diuretics was associated with poor outcome (df = 13.776, $p < 0.001$) (Table 3).

Table 1: Baseline characteristics of patients ($n = 72$)

Characteristics	*Mean ± standard deviation*	
Age (in years)	55.3 ± 16.2	
Length of stay (in days)	12.58 ± 7.63	
	Frequency	*%*
Gender		
Male	39	54.2
Female	33	45.8
Hypertension	24	33.3
Diabetes mellitus	24	33.3
Coronary artery disease	12	16.7
Contrast induced	7	9.7
Cardiovascular accident infection	15	20.1
Malignancy	8	11.1
COPD	7	9.7
Use of diuretics	32	44.1
Need of vasopressors	31	43.1
Need of RRT	25	34.7
Urine output		
Anuric/oliguric	48	66.7
Non oliguric	24	33.3
Outcome of patient		
Discharge	19	26.4
LAMA	4	5.5
Death	49	68.1

Discussion

The kidney is a highly differentiated organ in the body, consisting of nearly 30 different cell types. Its main functions include endocrine function, maintenance of blood pressure, solute and water transport, acid-base balance, and removal of drug metabolites. Blood flow in both kidneys is around 1000 mL per minute, that is, around 20% of cardiac output. Impairment of kidney function over days to weeks (generally known or expected to have occurred within 7 days) results in the accumulation of nitrogenous waste products. AKI is not a single disease but rather a designation for a heterogeneous group of conditions that share a common diagnostic feature. The epidemiology of AKI differs in developed and developing countries, with infections, sepsis, snake bites, and crush injuries being the most common causes. In our study, the most common cause appeared to be infection and sepsis. The most common associated chronic illnesses were diabetes and hypertension. We had 9.7% ($n = 7$) patients with drug-induced nephropathy—four cases of contrast-induced nephropathy and three cases due to injection colistin. The mean age of patients was 55 years, and there was a male preponderance. Gender distribution was similar to admissions in the ICU. Although a clear-cut demarcation of the pathological cause was not possible, almost 45% had prerenal, 35% had renal, and 20% had postrenal causes. These differentiations were not strict, and many patients had two or more types of pathophysiology contributing to their overall situation. In this study, 48 patients (66.7%) were anuric

Table 2: Distribution of the clinical parameters and treatment requirement in ICU according to use of diuretics ($n = 72$)

		Diuretics used (n = 32)	*Diuretics not used (n = 40)*	*p-value*
Mean ± SD				
SOFA score*		7.84 ± 4.54	6.50 ± 2.86	0.151
APACHE-II score**		23.22 ± 21.76	21.90 ± 14.51	0.424
Length of stay (days)*		11.34 ± 6.31	13.75 ± 8.47	0.186
Frequency (%)				
Need of RRT†	Yes	11 (44.0)	14 (56.0)	0.956
	No	21 (44.7)	26 (55.3)	
Need of vasopressors†	Yes	13 (41.9)	18 (58.1)	0.709
	No	19 (46.3)	22 (53.7)	

*Independent *t*-test; **Mann–Whitney *U* test; †Chi-squared test of proportion

Table 3: Association between diuretic use and outcome of patients ($n = 72$)

Use of diuretics	*Outcome of patients*			*Total*	*Chi-square (df)*	*p-value*
	Discharge	*LAMA*	*Death*			
Diuretics not used	17 (42.5)	3 (7.5)	20 (50.0)	40	13.776 (2)	0.001
Diuretics used	2 (6.2)	1 (3.1)	29 (90.6)	32		

or oliguric, and the rest were nonoliguric. While analyzing the outcome, we found that 49 patients (68%) died, and 4 patients left the hospital against medical advice as they were not improving. Only 19 (26%) patients improved and were discharged. Of these, 16 patients reached normal values for creatinine and urea, and the remaining 3 showed a downward trend but still had higher-than-normal levels of blood urea and creatinine. AKI is considered to be an independent risk factor for poor prognostication in intensive care patients.[11]

For further analysis, we divided the patients into two groups: one who received diuretics for AKI and another who did not. The use of diuretics in AKI treatment is a controversial issue. Loop diuretics increase the tubular flow, which decreases the tubular obstruction, decreases the medullary oxygen consumption by decreasing the net electrolyte reuptake, and increases tubular cell survival. They cause volume depletion and can increase the prerenal component of AKI. Diuretics were given to 32 patients (44%). Severity scores, like SOFA and APACHE II scores, were not significantly varied between the two groups. The need for RRT and use of vasopressors among the two groups were also not significantly different, but the outcome of patients was significantly varied and was better in the patient group who did not receive diuretics. Mortality was higher in the diuretics group. This high mortality can be multifactorial, and AKI is one of the factors.

Loop diuretics have a controversial role in the prevention and treatment of AKI. In a few previous studies, loop diuretics proved to be beneficial in the prevention of contrast-induced nephropathy and postangiography AKI.[12–14] Furosemide stress test (FST) is used to predict the progression of AKI. It also guides the time to start RRT.[15] In this, 1–1.5 mg/kg of furosemide is given, and urine output in the next 2 hours should be 200 mL for a positive test. This test was not found to be effective in showing the appropriate time for RRT in a recent study by Lumlertgul et al.[16] However, this test was found to be advantageous in deciding RRT in postrenal transplant AKI patients, as shown by Udomkarnjananun et al.[17] The preventive role of diuretics was assessed in postcardiac surgery patients by Lassnigg et al. in 2000. They concluded that although urine output was higher in the diuretics group, renal dysfunction did not vary significantly between the groups with or without diuretics.[18]

Studies focusing on the treatment of AKI with diuretics are mostly neutral regarding renal outcome, except for the study by Cantarovich et al., in which patients who received loop diuretics had improved diuresis and a shorter period of oliguria.[19]

To summarize, the development of AKI in ICU patients contributes to poor prognosis. Prevention is desirable, but at times it develops as part of multiorgan dysfunction. The use of diuretics is controversial and is mostly associated with poor outcomes.

Conclusion

Hypertension and diabetes are the most common comorbidities associated with AKI. The use of diuretics did not reduce the need for RRT, but it was associated with poorer outcomes.

References

1. Susantitaphong P, Cruz DN, Cerda J, et al. World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol 2013;8:1482–1493.
2. Hoste EAJ, Bagshaw SM, Bellomo R, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015;41:1411–1423.
3. Hsu C-N, Lee C-T, Su C-H, et al. Incidence, outcomes, and risk factors of community-acquired and hospital-acquired acute kidney injury: a retrospective cohort study. Medicine (Baltimore) 2016;95:e3674.
4. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Am J Kidney Dis 2002;39:930–936.
5. Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005;294:813–818.
6. Kellum JA, Sileanu FE, Bihorac A, et al. Recovery after acute kidney injury. Am J Respir Crit Care Med 2017;195(6):784–791.
7. Usmiani T, Andreis A, Budano C, et al. AKIGUARD (Acute Kidney Injury GUARding Device) trial: in-hospital and one-year outcomes. J Cardiovasc Med (Hagerstown) 2016;17(7):530–537.
8. Kleinknecht D, Ganeval D, Gonzalez-Duque LA, et al. Furosemide in acute oliguric renal failure. A controlled trial. Nephron 1976;17(1):51–58.
9. Shilliday IR, Quinn KJ, Allison ME. Loop diuretics in the management of acute renal failure: a prospective, double-blind, placebo-controlled, randomized study. Nephrol Dial Transplant 1997;12(12):2592–2596.
10. van der Voort PHJ, Boerma EC, Koopmans M, et al. Furosemide does not improve renal recovery after hemofiltration for acute renal failure in critically ill patients: a double blind randomized controlled trial. Crit Care Med 2009;37(2):533–538.
11. Hashemian SM, Jamaati H, Bidgoli BF, et al. Outcome of acute kidney injury in critical care unit, based on AKI network. Tanaffos 2016;15(2):89–95.
12. Dussol B, Morange S, Loundoun A, et al. A randomized trial of saline hydration to prevent contrast nephropathy in chronic renal failure patients. Nephrol Dial Transplant 2006;21(8):2120–2126.
13. Gu GQ, Lu R, Cui W, et al. Low-dose furosemide administered with adequate hydration reduces contrast-induced nephropathy in patients undergoing coronary angiography. Cardiology 2013;125(2):69–73.
14. Marenzi G, Ferrari C, Marana I, et al. Prevention of contrast nephropathy by furosemide with matched hydration: the MYTHOS (induced diuresis with matched hydration compared to standard hydration for contrast induced nephropathy prevention) trial. JACC Cardiovasc Interv 2012;5(1):90–97.
15. Chawla LS, Davison DL, Brasha-Mitchell E, et al. Development and standardization of a furosemide stress test to predict the severity of acute kidney injury. Crit Care 2013;17(5):R207.
16. Lumlertgul N, Peerapornratana S, Trakarnvanich T, et al. Early versus standard initiation of renal replacement therapy in furosemide stress test non-responsive acute kidney injury patients (the FST trial). Crit Care 2018;22(1):101.
17. Udomkarnjananun S, Townamchai N, Iampenkhae K, et al. Furosemide stress test as a predicting biomarker for delayed graft function in kidney transplantation. Nephron 2019;141(4):236–248.
18. Lassnigg A, Donner E, Grubhofer G, et al. Lack of renoprotective effects of dopamine and furosemide during cardiac surgery. J Am Soc Nephrol 2000;11(1):97–104.
19. Cantarovich F, Galli C, Benedetti L, et al. High dose frusemide in established acute renal failure. Br Med J 1973;4(5890):449–450.

ORIGINAL ARTICLE

The Effect of Clinical Decision Support Tools on Physicians' Practices

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Abstract

Objective: The objective of this research is to assess the impact of clinical decision support (CDS) tools on the practices of Indian physicians.

Methods: Descriptive statistics and frequency distributions are used to assess the data.

Results: Through a primary survey, it was found that about 69% of the physicians frequently use clinical decision tools in their practice. The author found that the clinical decision tools affect 1–5 decisions every week (for about 54% of the sample). Nonetheless, a great many (31%) stated that they do not use the tools frequently; therefore, none of their decisions are affected by the technology on a usual basis. There is a slight improvement in diagnosis post the use of the app. Although 46% of doctors stated that they have made zero errors in decision making post the use of the application, 54% admitted making errors in 1–5 decisions per week. This shows that the tool has not been able to address all the needs of the doctors. A great many agreed that the tool helped in reducing diagnostic tests. Although a majority of doctors stated that they order fewer than five diagnostic tests post the use of the application, a great many doctors agreed that they order >10 tests after using the application. This could be due to less faith in the technology or could be an attribute of a small sample. The author intended to assess whether clinical decision tools are cost-effective. The author found that not all decision tools are cost-effective. The variation could be due to differences in comprehensiveness of information, product features, and area of practice.

Conclusion: This study exhibits that there is less faith in the technology and the application is favored by younger doctors. By and large, doctors agreed that the tool provides quicker diagnosis and is user-friendly.

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Introduction

The potential of information technology (IT) to improve process and delivery of care has been persistently discussed in the literature. Domain scholars opine that IT has been underutilized in managing healthcare and that IT is a critical tool in improving efficiency and quality.[1] Evidence shows that doctors spend 64% of their time online surveying for information that could support their clinical decisions.[2] IT tools are being increasingly used by physicians to lessen administrative burden and to improve the quality of their care services. In this paper, an attempt is made to assess the impact of one of the IT tools—clinical decision support (CDS) tools—on the practices of Indian physicians.

The literature has identified several benefits of the use of clinical decision tools. These include reducing toxic drug levels and lessening the time to achieve therapeutic control,[3,4] reducing medication errors,[5,6] modifying prescriptions as per the guidelines, and increasing diagnostic testing.[7] In addition to their potent benefits, CDS tools can be used for a variety of purposes. CDS software can be used to surf literature, ask for recommendations based on patients' characteristics, receive notifications when health parameters cross certain limits, receive critiques of recommended therapies, and access programs that describe the pros and cons of alternative outcomes.[8]

The preventive healthcare market size in India will reach $169 billion by 2025.[9] Of this, the diagnostic and therapeutic market will consume 32%. Given the sheer size of the market and the potent benefits that physicians accrue due to the use of CDS tools, a study analyzing the impact of the tools on physicians' practices becomes imperative. The CDS tools are a part of a larger domain of evidence-based practice (EBP).

The paper is organized as follows: First, relevant literature is examined. Then, methodology and findings are discussed.

What Does the Literature Say?

Primarily, CDS systems are used in the domain of diagnosis and therapy. Of the two, CDS tools are more prevalent in diagnosis; therefore, this study focuses on CDS tools in the domain of diagnosis. First, this paper describes the history of clinical decision support systems (CDSS) in diagnosis and then explores general literature relating to CDSS.

History

Diligent attempts have been made in the literature to describe, model, and critique medical diagnostic decision support (MDDS) systems.[10] An author[10] studied papers from 1954 to 1992 and asserted that the academic literature has extensively studied MDDS systems. He traces the history of academic research on MDDS systems and reveals that the current system is a product of the laborious attempts of mathematical formulations of the past.

In the initial stages, MDDS systems were articulated using logic and probabilistic reasoning.[10] Later, heuristic reasoning developed, which not only combined the features of the two models but also enabled the physician to formulate "short-cut mental strategies"[11] that facilitated swift decision making. Heuristic reasoning was followed by rule-based systems, where software fed with human-curated rules was used to diagnose diseases. This was followed by Bayesian belief networks, which enabled the detection of diseases using probabilities of certain symptoms.

The beginning years of diagnostic decision support systems were dominated by the "Greek oracle" model.[10] Under this model, the physician was required to feed historical and physical health examination data into the system, and the system was expected to provide a correct diagnosis to the patient and explain its reasoning. The role of the physician was that of a passive observer, and he was solely required to provide "yes" and "no" answers to the system's questions.[10] There were fatal flaws in the "Greek oracle" model. The system neglected the ability of the physician to diagnose patients who were under the direct observation of the physician.[10] In addition, the system was restricted by the type of questions it asked. Not all relevant information could be fed into

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the system. Eventually, the "Greek oracle" was abandoned, and the developers focused on creating systems that allowed greater flexibility in terms of exploiting both the physician's intellect and the system's capability.[10]

Recent CDS tools, provided by startups, are based on artificial intelligence. Millions of medical cases are fed into the computers, and the computers, based on patient characteristics and the best evidence available, suggest recommendations to physicians. The endeavor of this paper is to assess the impact of such CDS tools on physicians' practices.

General Literature Relating to the Effectiveness of Clinical Decision Support Systems

Clinical decision support systems have been extensively explored in the literature. Many systematic reviews have identified the benefits of such tools. These include reducing toxic drug levels and lessening the time to achieve therapeutic control,[3,4] reducing medication errors,[5,6] modifying prescriptions as per the guidelines, and increasing diagnostic testing.[7] In addition to their potent benefits, CDS tools can be used for a variety of purposes. CDS software can be used to surf literature, ask for recommendations based on patients' characteristics, receive notifications when health parameters cross certain limits, receive critiques of recommended therapies, and access programs that describe the pros and cons of alternative outcomes.[8]

The academic literature related to CDSS has examined two aspects of the system: factors affecting the adoption of the system and the effectiveness of CDSS in affecting physicians' performance and patient outcomes.

Two studies[12,13] attempted to identify features of CDSS that significantly affect clinical practice. They found that factors such as the ability of CDSS to provide automatic recommendations, provision at the time and location of care, provision of recommendations along with assessments, automatic prompts, and integration of CDSS with other software affect the performance of CDSS. In addition, direct experimental evidence[12] found that effectiveness was enhanced when clinicians were asked to document the reason for not following the system recommendation and when clinicians were provided with feedback on their compliance with recommendations.

Studies[14–18] attempted to analyze the effectiveness of CDSS on physicians' performance and patient outcomes. A majority of the studies included in the systematic reviews were randomized controlled trials (RCTs), and the reviews found that CDSS brought significant positive changes in physicians' performance. Papers assessing the effects of CDSS on patient outcomes were limited, and therefore, no robust conclusion can be drawn.

Although the systematic reviews found positive evidence, the authors cautioned against accepting the positive results uncritically. A paper[17] stated that most of the studies included in their review lacked generalizability. The studies had smaller sample sizes and were poorly designed. Contamination of control groups, irregular use of CDSS by providers, selection bias, and the presence of uncontrolled confounding factors could have affected the results of the studies. Qualitative studies included in the review were nonrandom and did not consider baseline differences between measurement groups.

A paper[16] reported that all their RCTs were unblinded. In addition, participants were briefed about CDSS and the effect of their compliance with it in advance, which could have affected the robustness of the studies.

All the systematic reviews mentioned above, with the exception of some reviews,[15–17] did not consider qualitative studies, which would have provided greater depth in understanding the factors affecting the effectiveness of CDSS.

There was just one paper that discussed the cost-effectiveness of CDSS. The paper[16] reported that only 15% (6/41) of the studies reported costs, and a majority of them carried out cost comparisons of interventions rather than assessing cost-effectiveness. Reporting on cost was often incomplete. At best, studies focused on calculating operating expenses and varied significantly in terms of calculating costs.

Further, they stated that a majority of studies were conducted in high-income countries and that the implementation of CDSS in resource-poor settings is doubtful. Moreover, patients' and organizational culture and values would further affect the implementation of CDSS.

Although many studies attempted to determine the effectiveness of CDSS, studies examining barriers to adoption were far and few between. A paper[19] endeavored to identify barriers and facilitators in the adoption of CDSS. They included healthcare professionals working in hospitals to assess barriers to adoption and found that at lower levels of technological integration, healthcare professionals perceived CDSS as a tool that could reduce professional autonomy and cause medicolegal problems. However, as technological integration improved, these concerns were replaced by usability and technical barriers. They further stated that barriers to technology adoption may exist prior to the introduction of technology. Forming a static list of barriers without considering the context and phase of implementation will not prove useful. Diverse factors such as the attitude of healthcare professionals toward guidelines and evidence, interdisciplinary relationships, and the culture of the organization may affect the adoption of CDSS.

Clinical Decision Support Systems and Evidence-based Care

Decision support systems are tools of EBP. They present relevant evidence to physicians at the time of care and therefore have the capability to improve efficiency and quality of care. Evidence-based care—existing in the form of scientifically robust academic studies—has the potential to improve healthcare, but there exists a gap between evidence and practice.[20] The academic literature states that there is a 17-year delay between new evidence appearing in the literature and its application into practice.[20] A pertinent question arises: Why does the gap persist? First, there are limited resources at institutions' disposal.[20] This holds institutions back from implementing any new practice. Next, there exists a discrepancy between the needs of physician decision-makers and the priorities set by clinical researchers.[20] This "knowledge chasm" has widened the gap between theory and practice. Thirdly, inappropriate and infrequent availability of evidence-based content at the point of care limits the use of evidence.[20] Finally, it is argued that advancement in the knowledge base alone will not be sufficient to bring about changes in practice and policy; therefore, scholars have called for a systems approach.[21] Research has highlighted that the application of EBP principles on a system-wide scale requires strong leadership, acceptance by local leaders, and intense resources for the development, adoption, and implementation of the principles into clinical practice.[21]

Why is EBP important? Advocates of EBP have stated that, in addition to providing up-to-date information to physicians, EBP can make healthcare cost-effective and safer, which is the ultimate goal of healthcare policies across the world. Clinicians need copious information to treat different patients, and reliance on human memory alone tends to pose limitations.[21] Textbooks are outdated and, at times, even inaccurate[22]; journals provide vast amounts of information, but culling relevant ones becomes laborious[23]; and medical education courses are taught with obsolete teaching modes[24] without practical evidence. All these factors necessitate the use of EBP. EBP has also been found to reduce medical errors. A study[25] stated that there were "6.5 adverse drug events per 100 admissions, and 28% were preventable." There have been instances of misuse,[26] overuse,[27] and underuse[27] of

pharmaceuticals and health technology, which has resulted in a substantial increase in cost.[21] Aligning practice with evidence will guarantee the optimum use of resources.

Problems with Evidence-based Practice and Recommendations

Evidence-based practice is not free from problems, but there have been suggestions to improve the software and systems that provide EBP.[21] It has been argued that research related to a large segment of the population cannot always be applied to individual patients, as they differ in clinical context and baseline characteristics. A proposed solution is to use novel statistics, such as "numbers needed to treat" and likelihood ratios, to individualize treatment.[21] Secondly, studies have strict inclusion criteria to be included in evidence-based systems, and "pigeon-holing" patients into a few categories does not reflect the complex real situations in which they are based.[21] It is suggested to integrate external evidence with patient-specific circumstances and characteristics of local health systems to provide individualized treatments.[21] It has been argued that EBP puts heavy emphasis on quantitative data and neglects the experiences and values of clinicians and patients.[21] A suggestion put forth is to include qualitative information in the system to be used in "interpretive and communicative" aspects of care.[21] It is said that EBP systems flood clinicians with a huge amount of information, and relevant information is not always available when urgently needed.[21] Studies state that there have been software solutions providing preappraised, ready-to-use clinical knowledge specifically designed for physicians' practice, which will ease the burden on physicians.[21] It is also noted that there is a paucity of sturdy scientific literature substantiating the benefits of EBP to clinicians' practice and patient outcomes. However, studies assessing the effectiveness of EBP have been rapidly growing. Finally, it is contended that EBP does not provide strong evidence for some important clinical problems. But advocates argue that "EBP never promised clear-cut solutions to clinical problems"[21]; instead, a mix of system-based recommendations with the clinical expertise of physicians is needed to solve complex medical problems.[21]

Research Gap

The academic literature on CDSS assesses the impact of CDSS on physicians' performance in developed countries. Studies in the context of developing countries are few. Secondly, there are few studies that assess the performance of CDSS tools in general diagnosis. This research is a humble attempt in this direction.

Methods

For the purpose of this study, a CDSS is defined as "any software designed to directly aid in clinical decision making in which characteristics of individual patients are matched to a computerized knowledge base for the purpose of generating patient-specific assessments or recommendations that are then presented to clinicians for consideration."[14] The respondent group includes physicians who use clinical decision applications in their practice. An interview schedule was prepared and circulated on social media websites in the form of Google Forms. Convenience sampling was followed. Altogether, 13 responses were received. Descriptive statistics were used to analyze the data. In the interview schedule, there was no provision to identify either the doctor or the company whose products were being used due to ethical concerns and the reluctance of the doctors to share personal details about the company.

Findings

Table 1 exhibits that the sample primarily consists of doctors who are middle-aged and have spent <10 years in practice. The doctors were predominantly based in Bangalore.

Figure 1 shows that most physicians reported their tool is not powered by artificial intelligence. In the history of CDS tools, clinical decision systems were articulated using logic and probabilistic reasoning.[10] Recent CDS tools are powered by artificial intelligence, where millions of medical cases are fed into computers, and recommendations are provided based on patients' characteristics and the best evidence available. Tools backed by artificial intelligence are more effective than the traditional ones.

Figure 2 exhibits that about 69% of the physicians frequently use clinical decision tools in their practice.

Studies have shown that mobile devices have been pervasively used by faculty, students, and residents of medical schools.[28] Mobile devices are significant as they improve access to point-of-care tools and enhance decision-making and patient outcomes.[29]

Evidence shows that doctors spend 64% of their time online surveying for information that could support their clinical decisions.[2]

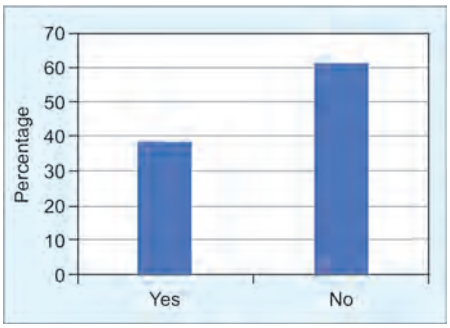

Fig. 1: Is the diagnostic tool powered by artificial intelligence? *Source*: Author (Fieldwork)

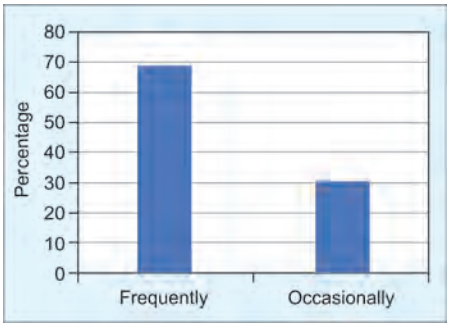

Fig. 2: To what extent do you use clinical decision technology in your practice? *Source*: Author (Fieldwork)

Table 1: Sociodemographic profile of doctors

Age-group			*Number of years of practice*		
Age	*No. of respondents*	*Percentage*	*Years of practice*	*No. of respondents*	*Percentage*
20–30	2	15.4	<10	7	53.8
31–40	6	46.2	11–30	2	15.4
41 and above	5	38.5	31 and above	4	30.8
Total	13		Total	13	
Location of the clinic					
Location	No. of respondents	Percentage			
Bangalore	4	30.8			
Delhi	1	7.7			
Mumbai	1	7.7			
Others	2	15.4			
No answer	5	38.5			
Total	13				

Source: Author (Fieldwork)

Figure 3 shows that doctors accept the recommendations provided by the CDS tool to a great extent. The faith in the decision tool, although not prominent, is improving. This could be due to the fact that the sample is dominated by young physicians who are more open to accepting technology.

The literature has identified several benefits of using clinical decision tools. In one instance, the use of electronic tools resulted in twice as many modifications in patient management decisions compared to when paper resources were used.[30]

Figure 4 reveals that the clinical decision tool affects 1–5 decisions every week for about 54% of the sample. Nonetheless, a great many (31%) stated that they do not use the tool frequently; therefore, none of their decisions are affected by the technology on a regular basis.

The primary benefit of a CDS tool is to reduce diagnostic errors. An endeavor was made to assess whether the use of the CDS tool improved diagnoses provided by the doctors.

Figure 5 exhibits that there is a slight improvement in diagnosis following the use of the app. Although 46% of doctors stated that they have made 0 errors in decision-making after using the application, 54% reported making errors in 1–5 decisions per week. This indicates that the tool has not fully addressed the needs of the doctors. Nonetheless, no physician reported making >5 errors per week after using the application.

One of the questions in the interview schedule was about the benefits of the CDS tool as perceived by doctors. The doctors stated that the tool improves the accuracy of diagnosis and helps in complicated cases. One physician mentioned that its accuracy rate is 92%. However, one doctor noted that the tool is used only in the preliminary stages of diagnosis, while another mentioned that the diagnosis provided by the tool is sometimes inaccurate. By and large, doctors agreed that the tool provides quicker diagnosis and is user-friendly.

The author wanted to assess whether the use of the clinical decision tool helped avoid unnecessary medical tests.

Figure 6 demonstrates that a large number of doctors agreed that the tool contributed to reducing diagnostic tests. Nonetheless, the data in Figure 7 shows otherwise.

Although a majority of doctors stated that they order fewer than 5 diagnostic tests after using the application, a great many doctors reported ordering >10 tests after using the application. This could be due to less faith in the technology or could be an attribute of a small sample.

Studies have shown that IT investments have both short-run and long-run payoffs.[31]

The author intended to assess whether clinical decision tools are cost-effective. Figure 8 exhibits that not all decision tools are cost-effective. The variation could be due to differences in the comprehensiveness of information, product features, and area of practice.

By and large, through the data analysis, the author concludes that the CDS applications are not immensely effective, are cost-inefficient, and are not popular among older physicians.

Discussion

The academic literature has underscored various benefits of CDS applications. Retrieval of information from an electronic drug database has been shown to improve decision-making and patient care.[30] Access to patient information and reports on mobile devices has improved care coordination.[30] In one instance, mobile devices were found to reduce doctor-patient encounter time.[30] Nonetheless, data on the effectiveness of CDS applications is limited.[32]

Nonetheless, studies conducted in the Indian context show optimistic results. A paper[33] assessed the effectiveness of a CDS tool in diagnosing and managing cardiovascular disease in rural India. The findings revealed that the CDS tool provided timely guidance, accurate diagnosis, and appropriate treatment recommendations to

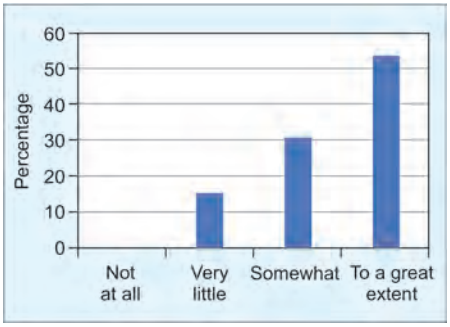

Fig. 3: To what extent do you accept the recommendations provided by the clinical decision software? *Source*: Author (Fieldwork)

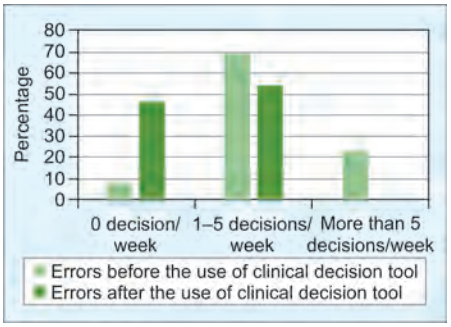

Fig. 5: Diagnostic errors before and after the use of the clinical decision tool; *Source*: Author (Fieldwork)

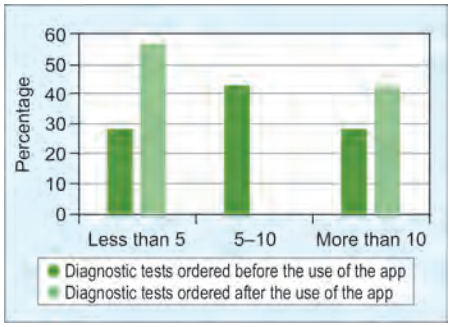

Fig. 7: Number of diagnostic tests ordered before and after the use of the tool; *Source*: Author (Fieldwork)

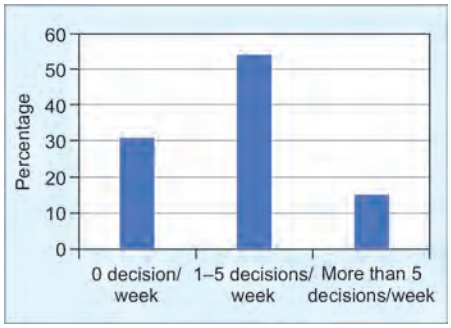

Fig. 4: Clinical decisions affected by the clinical decision technology; *Source*: Author (Fieldwork)

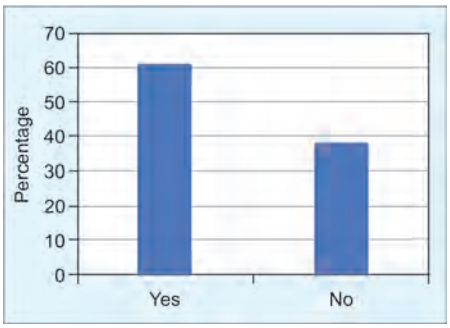

Fig. 6: Has the use of the CDS tool helped avoid unnecessary medical tests? *Source*: Author (Fieldwork)

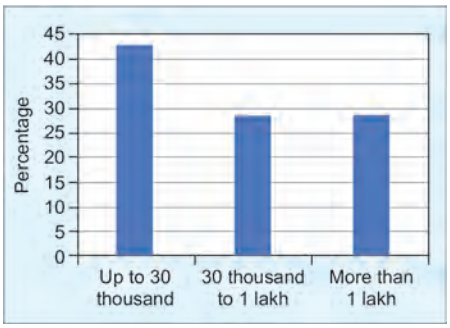

Fig. 8: Subscription cost of the clinical decision tool (per year); *Source*: Author (Fieldwork)

nonphysician healthcare workers. Another study[34] introduced a CDS tool to improve care during labor and childbirth in two Indian states. It found that CDS tools enhanced intrapartum and postpartum care by providing timely and accurate interventions. A study[35] conducted in rural parts of India assessed the effectiveness of a CDS tool in managing cardiovascular diseases. It found that the CDS tool enhanced the ability of nonphysician healthcare workers to detect the disease; nonetheless, network connectivity remains a pertinent issue. Another paper[36] carried out an experimental study on the effectiveness of a CDS tool in managing hypertension in rural India. The study found that compared to standard care, the CDS tool helped in making more informed decisions regarding medication, lifestyle changes, and follow-up care, resulting in better control of patients' blood pressure.

Although studies have shown positive outcomes, they are tainted by limitations. The studies might have sampling bias as they are conducted in specific regions or with limited sample sizes, thereby restricting generalizability. The studies are of short duration, limiting insights into the long-term effectiveness and adoption of CDS tools. Additionally, studies have highlighted issues such as network connectivity and lower user acceptance of the tool. Most studies focus on process outcomes, such as diagnostic accuracy and usage rates, but do not delve into patient outcomes, limiting the assessment of CDS tools' impact on patient health.

This study exhibits that there is less faith in the technology and the application is favored by younger doctors. The academic literature states that the adoption of evidence-based technology is affected by various factors, including culture, context, regional laws, competing considerations, patients' preferences, and clinical circumstances.[20,37] The literature also expresses concerns regarding the reliability of the tools, lack of standard content, absence of oversight on the applications, and protection of patients' data.[20] Nonetheless, health apps are significant as they enable remote monitoring of patients. The literature calls for rigorous evaluation of clinical decision tools before they are introduced into clinical practice.[14]

References

1. Richardson WC, Berwick D, Bisgard J, et al. (2001). Institute of medicine. Crossing the Quality Chasm: A New Health System for the 21st Century.
2. Chase J. (2013). IPads and other drugs. Medical Marketing & Media: The Interactive Guide. 10–11.
3. Walton RT, Harvey E, Dovey S, et al. Computerised advice on drug dosage to improve prescribing practice. Cochrane Database Syst Rev 2001;(1):CD002894.
4. Durieux P, Trinquart L, Colombet I, et al. Computerized advice on drug dosage to improve prescribing practice. Cochrane Database Syst Rev 2008;(3):CD002894.
5. Eslami S, Abu-Hanna A, De Keizer NF. Evaluation of outpatient computerized physician medication order entry systems: a systematic review. J Am Med Inform Assoc 2007;14(4):400–406.
6. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. Arch Intern Med 2003;163(12):1409–1416.
7. Bennett JW, Glasziou PP. Computerised reminders and feedback in medication management: a systematic review of randomised controlled trials. Med J Aust 2003;178(5):217–222.
8. Clayton PD, Hripcsak G. Decision support in healthcare. Int J Biomed Comput 1995;39(1):59–66.
9. In 42. India's healthtech landscape in a post-COVID-19 world. 2020.
10. Miller RA. Medical diagnostic decision support systems—past, present, and future: a threaded bibliography and brief commentary. J Am Med Inform Assoc 1994;1(1):8–27.
11. O'Neill ES. Heuristics reasoning in diagnostic judgment. J Prof Nurs 1995;11(4):239–245.
12. Kawamoto K, Houlihan CA, Balas EA, et al. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. BMJ 2005;330(7494):765.
13. Mollon B, Chong JJ, Holbrook AM, et al. Features predicting the success of computerized decision support for prescribing: a systematic review of randomized controlled trials. BMC Med Inform Decis Mak 2009;9(1):1–9.
14. Hunt DL, Haynes RB, Hanna SE, et al. Effects of computer-based clinical decision support systems on physician performance and patient outcomes: a systematic review. JAMA 1998;280(15):1339–1346.
15. Garg AX, Adhikari NK, McDonald H, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. JAMA 2005;293(10):1223–1238.
16. Souza NM, Sebaldt RJ, Mackay JA, et al. Computerized clinical decision support systems for primary preventive care: a decision-maker-researcher partnership systematic review of effects on process of care and patient outcomes. Implement Sci 2011;6(1):1–14.
17. Bryan C, Boren SA. The use and effectiveness of electronic clinical decision support tools in the ambulatory/primary care setting: a systematic review of the literature. Inform Prim Care 2008;16(2):79–91.
18. Pearson SA, Moxey A, Robertson J, et al. Do computerised clinical decision support systems for prescribing change practice? A systematic review of the literature (1990-2007). BMC Health Serv Res 2009;9:154.
19. Liberati EG, Ruggiero F, Galuppo L, et al. What hinders the uptake of computerized decision support systems in hospitals? A qualitative study and framework for implementation. Implement Sci 2017;12(1):1–13.
20. Clancy CM, Cronin K. Evidence-based decision making: global evidence, local decisions. Health Aff (Millwood) 2005;24(1):151–162.
21. Leung GM. Evidence-based practice revisited. Asia Pac J Public Health 2001;13(2):116–121.
22. Antman EM, Lau J, Kupelnick B, et al. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts: treatments for myocardial infarction. JAMA 1992;268(2):240–248.
23. Haynes RB. Some problems in applying evidence in clinical practice. Ann N Y Acad Sci 1993;703:210–225.
24. Davis DA, Thomson MA, Oxman AD, et al. Changing physician performance: a systematic review of the effect of continuing medical education strategies. JAMA 1995;274(9):700–705.
25. Bates DW, Ebell M, Gotlieb E, et al. A proposal for electronic medical records in US primary care. J Am Med Inform Assoc 2003;10(1):1–10.
26. Siegel D, Lopez J. Trends in antihypertensive drug use in the United States: do the JNC V recommendations affect prescribing? JAMA 1997;278(21):1745–1748.
27. Leung GM, Johnston JM, Ho LM, et al. Computerization of clinical practice in Hong Kong. Int J Med Inform 2001;62(2–3):143–154.
28. Wallace S, Clark M, White J. 'It's on my iPhone': attitudes to the use of mobile computing devices in medical education, a mixed-methods study. BMJ Open 2012;2(4):e001099.
29. Aungst TD. Medical applications for pharmacists using mobile devices. Ann Pharmacother 2013;47(7–8):1088–1095.
30. Mickan S, Tilson JK, Atherton H, et al. Evidence of effectiveness of health care professionals using handheld computers: a scoping review of systematic reviews. J Med Internet Res 2013;15(10):e212.
31. Kauffman RJ, Weill P. An evaluative framework for research on the performance effects of information technology investment. 1989.
32. Blackmore CC, Mecklenburg RS, Kaplan GS. Effectiveness of clinical decision support in controlling inappropriate imaging. J Am Coll Radiol 2011;8(1):19–25.
33. Praveen D, Patel A, Raghu A, et al. SMARTHealth India: development and field evaluation of a mobile clinical decision support system for cardiovascular diseases in rural India. JMIR Mhealth Uhealth 2014;2(4):e3568.
34. Usmanova G, Lalchandani K, Srivastava A, et al. The role of digital clinical decision support tool in improving quality of intrapartum and postpartum care: experiences from two states of India. BMC Pregnancy Childbirth 2021;21:1–12.
35. Raghu A, Praveen D, Peiris D, et al. Lessons from the evaluation of a clinical decision support tool for cardiovascular disease risk management in rural India. In: Technologies for Development: What is Essential? Springer International Publishing; 2015. pp. 199–209.
36. Anchala R, Kaptoge S, Pant H, et al. Evaluation of effectiveness and cost-effectiveness of a clinical decision support system in managing hypertension in resource constrained primary health care settings: results from a cluster randomized trial. J Am Heart Assoc 2015;4(1):e001213.
37. Rehnquist J. The globalization of clinical trials: a growing challenge in protecting human subjects. Department of Health and Human Services, Office of Inspector General; 2001.

ORIGINAL ARTICLE

Evaluation of the Relationship between Procalcitonin and Total Leukocyte Count, Neutrophil and Neutrophil/Lymphocyte Ratio in Patients with Systemic Inflammatory Response Syndrome and Sepsis: A Hospital-based Observational Study

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Abstract

Introduction: An elevated defensive reaction of the body to a harmful stressor like infection, trauma, surgery, acute inflammation, ischemia, reperfusion, or malignancy to localize and eliminate the endogenous or exogenous source of the injury is known as systemic inflammatory response syndrome (SIRS). Sepsis is a term used for SIRS with suspected or documented sources of infection. It is characterized by the fulfillment of any two of the following conditions: white blood cell (WBC) count ≥4000/µL or >10% immature forms or bands; body temperature over 38°C or below 36°C; pulse rate above 90 beats per minute; tachypnea (respiratory rate greater than 20 breaths per minute); or partial pressure of CO_2 below 32 mm Hg. Procalcitonin (PCT) is one of the more complex and expensive lab indicators used to diagnose and prognosticate this disorder. Less expensive tests include total leukocyte count (TLC), neutrophil count, and neutrophil/lymphocyte ratio (NLR).

Objectives: To ascertain the correlation between procalcitonin and TLC, neutrophil count, and NLR in patients with SIRS without documented infection and SIRS with infection (sepsis), and to evaluate TLC, neutrophil count, and NLR ratios between SIRS without infection and sepsis.

Materials and methods: Acutely ill patients aged 18 years or older who fulfilled the criteria for SIRS were included in this study. The serum PCT value, TLC, and blood culture were done within 12 hours of admission. All other relevant investigations at the time of admission were also noted.

Results: Out of 282 patients with SIRS, 194 patients had no documented infection (group I), whereas 88 patients had a documented infection (sepsis group II). The difference in age and sex between both groups ($p < 0.05$) was found to be statistically significant. All four markers—PCT, TLC, neutrophils, and NLR—were significantly higher in the sepsis group.

Conclusion: PCT is the best biomarker to predict sepsis, and it correlated significantly with TLC, neutrophil count, and NLR in SIRS without infection, and with neutrophil count and NLR in sepsis in our study. Secondly, TLC and NLR are also good predictors of sepsis and can diagnose sepsis in resource-poor settings.

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Introduction

An elevated defensive reaction of the body to a harmful stressor, like infection, trauma, surgery, acute inflammation, ischemia, reperfusion, or malignancy, to localize and eliminate the endogenous or exogenous source of the injury, is known as systemic inflammatory response syndrome (SIRS). Sepsis is a term used for SIRS with suspected or documented sources of infection. It is characterized by the fulfilment of any two of the following conditions: white blood cell (WBC) count ≥4000/µL or >10% immature forms or bands; body temperature above 38°C or below 36°C; pulse rate above 90 beats per minute; tachypnea (respiratory rate greater than 20 breaths per minute); or partial pressure of CO_2 below 32 mm Hg.[1] A prompt clinical and laboratory diagnosis, along with appropriate therapeutic therapy, are critical factors that determine the prognosis and death rate of patients with this life-threatening illness. Procalcitonin (PCT) is one of the more complex and expensive lab indicators used to diagnose and prognosticate this disorder. Less expensive tests include total leukocyte count (TLC), neutrophil count, and neutrophil/lymphocyte ratio (NLR).[2] The complete blood counts (CBC) test, the most popular and straightforward laboratory test that offers a plethora of information about a person's health state, can be used to assess any one of these three assays. Usually, an increase in TLC indicates an infection or inflammation. In a similar vein, during an infection, the neutrophil count rises significantly and is typically correlated with the overall severity of the infection. Neither of the tests is specifically designed to detect infections. Due to delayed neutrophil apoptosis, the value of the neutrophil count in severe sepsis is restricted. Notably, a variety of stressors, including physical and psychological strain, physiological conditions like pregnancy and obesity,[3] and some other illnesses like smoking, can cause neutrophilia.[4] Periodically, low TLC counts can also occur in sepsis.[5]

One consistent biomarker for sepsis that has surfaced is NLR. The equilibrium between neutrophil and lymphocyte numbers can be inferred from changes in NLR. NLR correlates with SOFA score, APACHE I, and sepsis severity scores, and has been demonstrated in multiple studies to be an early indicator of sepsis, regardless of the etiology of sepsis.[6–8] The effectiveness of PCT as a marker of bacterial infection and critical disease has been demonstrated by a wealth of research. A sensitive biomarker aids in treatment decision-making because positive bacteriological results can be

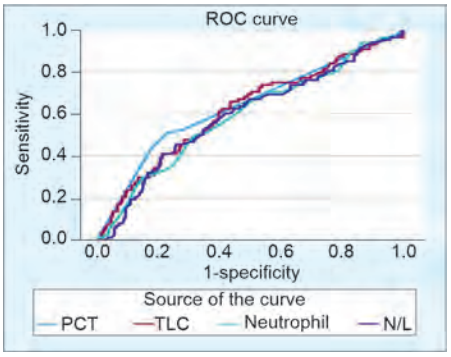

Fig. 1: ROC curve showing the AUC of all the four biomarkers

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attributed to contamination, while negative results do not rule out sepsis. We attempted to assess PCT's correlation with the other three sepsis biomarkers in the current study. These biomarkers can be easily obtained by simply doing a CBC count. These can be a cheaper alternative to costly tests and are done routinely in resource-poor settings as well.

Study Objectives

To determine the relationship between procalcitonin and TLC, neutrophil count, and NLR in patients with SIRS without documented infection and SIRS with infection (sepsis).

To evaluate the TLC, neutrophil count, and NLR between SIRS without infection and sepsis.

Materials and Methods

Data Source and Collection

All adult patients aged 18 years or more who presented to the emergency unit of Central Referral Hospital (CRH) or were directly admitted to the intensive care unit (ICU) or wards, and who fulfilled the criteria of SIRS between January 2022 and October 2023 and gave consent for the study, were considered. Prior ethical approval of the research was obtained from the research ethical committee of the Sikkim Manipal Institute of Medical Sciences.

Study Design

Observational cross-sectional study.

Site and Population

All adult patients aged 18 years or older, who presented either to the emergency unit of CRH or were directly admitted to the medicine ICU or wards and fulfilled the criteria of SIRS, were included in this study. CRH is a 500-bed hospital in Gangtok, Sikkim, a small northeastern state of India.

Sample Size and Sampling Method

According to a hospital-based study in North India, the prevalence of SIRS was found to be 23%. So, a sample size of 282 was taken.

Inclusion Criteria

All acutely ill, hospitalized medical patients aged 18 years or older, who presented to the emergency department of CRH or were directly admitted to the ICU or wards and fulfilled the inclusion criteria of SIRS or sepsis, were included. Consent was taken from the patient's attendant if the patient was not fit to give consent.

Exclusion Criteria

- Unwilling patients.
- Individuals transferred from other hospitals or wards.
- Patients with untreated end-stage renal failure not on dialysis, medullary thyroid carcinoma, or islet cell tumors.
- Severe pancreatitis, postliver transplantation, severe and prolonged cardiogenic shock, or heat shock.

Patients who were admitted to the department more than once during the inclusion period were counted only once, at the time of their initial admission, and not again during future admissions.

Study

The serum PCT value, checked using the semiquantitative PCT test kit (Med Source Ozone Biomedicals Pvt. Ltd., Procalcitonin Semi-Quantitative Assay Kit) within 12 hours of admission to the hospital, was noted. The kit, an antigen-capture immunochromatographic assay, provided qualitative/quantitative PCT values within 20–30 minutes. A PCT value of ≥0.5 was considered significant, as per the manufacturer's instructions. TLC was measured by an automated hematology analyzer. Blood cultures were done using the automated BacT/ALERT BD system under strict aseptic precautions. All pertinent investigation reports were recorded, including blood investigations performed upon admission, such as CBC, LFT, KFT, and sugar, among others.

The demographic profile and medical examination findings of all the patients were registered. A detailed medical history, including comorbidities like hypertension (HTN), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), pulmonary tuberculosis (PTB), malignancy, coronary artery disease (CAD), chronic kidney disease (CKD), chronic liver disease (CLD), cerebrovascular accident (CVA), etc., was noted along with the complete medical examination findings.

The identification of a pertinent pathogen by microscopy, cultures in blood, urine, sputum, or tissue biopsy samples, or polymerase chain reaction, constituted the basis for documenting sepsis.

Analysis

Patients with confirmed SIRS were included in the study and divided based on negative and positive culture reports into group I and group II. All the data were analyzed using IBM Statistical Package for the Social Sciences (SPSS) Statistics 23.0 (IBM Corp., Armonk, NY, USA). Mann–Whitney *U* tests were used to compare the medians of PCT, TLC, and NLR. The Chi-squared test was used to compare categorical variables. The correlation between PCT and the abovementioned other three biomarkers of sepsis was determined with the help of Pearson's test.

Results

Out of a total of 282 patients with SIRS, there was no documented infection in 194 patients (group I), whereas 88 patients had documented infection (sepsis group II). The difference between age and sex in both groups ($p < 0.05$) was found to be statistically significant. All four markers, PCT, TLC, neutrophils, and NLR, were significantly higher in the sepsis group (Table 1).

In Pearson's correlation analysis, except for PCT and WBC in sepsis, significant correlations were found between PCT and WBC, neutrophil count, and N/L ratio in both groups of SIRS (Table 2).

Area under the Receiver Operating Characteristic Curve

Test result variable(s)	*Area*
PCT	0.638
TLC	0.618
Neutrophil	0.594
NLR	0.595

The area under the curve (AUC) of PCT was 0.638, with an interval from 0.565 to 0.711, and a cutoff point of 6 was obtained at 95% significance. Similarly, the AUC of TLC was 0.618, with an interval from 0.546 to 0.691, and a 95% significance obtained a cutoff of 7.3500. For neutrophils, the AUC was 0.572,

Table 1: Demographic profile and biomarkers in SIRS without infection and sepsis groups

	Group I (no sepsis) N = 194	*Group II (sepsis) N = 88*	*p-value*
Age (mean)*	43 (18–94)	45 (18–92)	0.0001 (Z score = 3.890)
Sex (M/F)*	103/22	22/66	0.0001 (Z score = 3.890)
PCT[º]	0.4 (0.4–10)	2 (0.4–10)	0.0002 (Z score = 3.719)
TLC	7.4 (1.51–58.6)	10.89 (1.69–29.16)	0.00143 (Z score = 3.188)
Neutrophil	79.5 (20–97)	83.5 (41–98)	<.00001 (Z score = 4.417)
NLR	5.7 (0.28–97)	8.4 (0.82–97)	0.01108 (Z score = 2.540)

*Chi-squared test; [º]Mann–Whitney *U* test

Table 2: Table showing the correlation of PCT with other markers of sepsis

	Sepsis	*Without sepsis*
PCT and WBC	*rs* = 0.2025, *p* (2-tailed) = 0.0559)	*rs* = 0.2425, *p* (2-tailed) = 0.0006
PCT and neutrophil	*rs* = 0.2175, *p* (2-tailed) = 0.01428	*rs* = 0.2710, *p* (2-tailed) = 0.0001
PCT and N/L ratio	*rs* = 0.2515, *p* (2-tailed) = 0.0183)	*rs* = 0.2762, *p* (2-tailed) = 0.0003

To determine the cutoff values for the parameters PCT, TLC, neutrophil count, and NLR in the diagnosis of SIRS, a study of the area under receiver operating characteristic curves (AU-ROC) was conducted. Statistical significance was defined as values of $p < 0.05$

Table 3: Table showing the cutoff value, sensitivity and specificity of all the four biomarkers of sepsis

Diagnostic test	*Cutoff value*	*AUC*	*95% CI*	*p-value*	*Sensitivity*	*Specificity*
PCT	6.00	0.638	0.565–0.711	0.000	44.3%	82%
TLC	7.35	0.618	0.546–0.691	0.001	70.5%	50%
Neutrophil	72.50	0.572	0.497–0.648	0.062	73.9%	26%
NLR	6.48	0.615	0.543–0.687	0.002	64.8%	56%

$p < 0.05$

with an interval from 0.497 to 0.648, and a 95% significance obtained a cutoff of 72.50. It was 0.615, with an interval from 0.543 to 0.687, and 6.4800, respectively, for NLR. Sensitivity and specificity of each test in predicting sepsis were calculated.

PCT had moderate sensitivity and high specificity, TLC and NLR had moderate sensitivity and specificity, and neutrophil count had moderate sensitivity and poor specificity to detect sepsis (Table 3).

Discussion

Our study, along with numerous others,[9–12] revealed that procalcitonin, WBC, neutrophil, and NLR values were considerably greater in patients with sepsis. However, one study hypothesized that PCT alone could be a good indicator of sepsis. Numerous studies have indicated that WBC counts are a poor predictor of sepsis and show little correlation with sepsis status, particularly in the elderly.[13–15] Aging-related reductions in phagocytosis and cell regeneration capacity may be the cause of this.[16,17] In our investigation, there was a strong correlation between NLR and sepsis, or culture positivity. While the results were similar to many studies that identified a substantial correlation between NLR and sepsis,[18,19] they differed from the few studies that found no significant association.[20,21] The observed contradictory outcomes may be ascribed to differences in the research population, sample volume, or technique. These biomarkers are especially significant as treatment initiation at arrival may have a role in lowering the yield of culture positivity.

In correlation analysis, an insignificant correlation was found between PCT and TLC count in sepsis, which was similar to a few studies.[19,22] It was in contrast to one study where a significant correlation between the two was observed.[23] One such study revealed an insignificant correlation between PCT and all three markers.[24] This particular study found that there was a significant correlation ($p < 0.001$) between PCT and WBC, CRP, and NLR, with respective values of 0.2332, 0.2245, and 0.2582.

Klebsiella pneumoniae was the second most frequently isolated organism in culture, after another gram-negative infection, *Escherichia coli*. This was comparable to numerous other reports.[25] Our study has shown that PCT was the best parameter to diagnose sepsis and was even better than NLR. This outcome is different from a prior study, which found NLR to be superior to PCT.[26] The timing of the appearance of PCT, lymphocytes, and neutrophils in the bloodstream may be one reason for this. It takes many hours for neutrophils to proliferate and appear in the blood once the endotoxin is released by microorganisms,[27] whereas PCT levels rise rapidly following 2 hours of stimulation, peak after 12–42 hours, and then gradually decline over the next 42 hours.[28] We found that TLC or NLR has the ability to predict sepsis, which is comparable to PCT, whereas neutrophil count has poor specificity. According to one study, NLR can predict the severity of sepsis ten times better than the absolute neutrophil count.[29] In a physiologically normal state, the NLR ratio is <5. NLR is elevated and useful for clinical assessment in pathological conditions like infection or systemic inflammation. Systemic inflammation or sepsis can lead to neutrophilia because of factors such as growth factors (G-CSF) that stimulate stem cells, demarginate neutrophils, and delay neutrophil apoptosis.[30] As a result, neutrophils in inflammation live longer and emit harmful chemicals. We found a relatively high cutoff value of PCT at 6 ng/mL to detect sepsis. According to one study, a PCT cutoff point of 2.89 might predict severe sepsis with 98.2% sensitivity and 75% specificity.[31] The value of PCT >2 ng/mL was reported to be the most specific and sensitive in detecting sepsis, with 80 and 87% accuracy respectively, in another study of this type conducted on surgical ICU patients.[32] One study indicated that an NLR cutoff point of 9.05 can distinguish between patients with sepsis and critical sepsis based on ROC analysis, but the specificity was just 50.0%, and the sensitivity was only 59.6%.[31] According to a different Dutch study, NLR >10 can predict bacteremia with 77.2% sensitivity and 63% specificity.[33] As per our research, an NLR cutoff of 6.48 might also be used as a predictor of sepsis, similar to a study that showed NLR >7 was associated with a fatal outcome in sepsis patients and that it can be employed as a prognostic marker in patients with sepsis.[25]

Due to its high sensitivity and specificity in predicting sepsis, PCT fared better on ROC curve analysis than the other three biomarkers, particularly the neutrophil count. In lieu of PCT for the diagnosis of sepsis, TLC and NLR have been shown to have intermediate sensitivity and specificity in predicting sepsis.

Limitation of the Study

This is a hospital-based study, so the true prevalence of SIRS in the community cannot be known. False negative values of the inflammatory markers or culture can occur due to technical or procedural errors or when the infection remains confined to a tissue or organ with no systemic manifestations. False positive tests can be present in certain conditions that could not be ruled out in those patients.

Conclusion

PCT is the best biomarker to predict sepsis and it correlated significantly with TLC, neutrophil count, and NLR in SIRS without infection, and with neutrophil count and NLR in sepsis in our study. Secondly, TLC and NLR are also good predictors of sepsis and can diagnose sepsis in resource-poor settings.

References

1. Chakraborty RK, Burns B. Systemic Inflammatory Response Syndrome. [Updated 2021 Jul 28]. In: Stat Pearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547669/)
2. Spoto S, Lupoi DM, Valeriani E, et al. Diagnostic accuracy and prognostic value of neutrophil-to-

lymphocyte and platelet-to-lymphocyte ratios in septic patients outside the intensive care unit. Medicina (Kaunas) 2021;57(8):811.
3. Nakata A. Psychosocial job stress and immunity: a systematic review. Methods Mol Biol 2012;934:39–75.
4. Chandra S, Tripathi AK, Mishra S, et al. Physiological changes in hematological parameters during pregnancy. Indian J Hematol Blood 2012;28:144–146.
5. Agnello L, Giglio RV, Bivona G, et al. The value of a complete blood count (CBC) for sepsis diagnosis and prognosis. Diagnostics 2021;11(10):1881.
6. Dursun A, Ozsoylu S, Akyildiz BN. Neutrophil-to-lymphocyte ratio and mean platelet volume can be useful markers to predict sepsis in children. Pak J Med Sci 2018;34:918–922.
7. Velissaris D, Pantzaris ND, Bountouris P, et al. Correlation between neutrophil-to-lymphocyte ratio and severity scores in septic patients upon hospital admission. A series of 50 patients. Rom J Intern Med 2018;56:153–157.
8. Huang Z, Fu Z, Huang W, et al. Prognostic value of neutrophil-to lymphocyte ratio in sepsis: a meta-analysis. Am J Emerg Med 2020;38:641–647.
9. Ding S, Ma J, Song X, et al. Diagnostic accuracy of procalcitonin, neutrophil-to-lymphocyte ratio, and C-reactive protein in detection of bacterial infections and prediction of outcome in nonneutropenic febrile patients with lung malignancy. J Oncol 2020;2020:2192378.
10. Trippella G, Galli L, De Martino M, et al. Procalcitonin performance in detecting serious and invasive bacterial infections in children with fever without apparent source: a systematic review and meta-analysis. Expert Rev Anti Infect Ther 2017;15:1041–1057.
11. Honda T, Uehara T, Matsumoto G, et al. Neutrophil left shift and white blood cell count as markers of bacterial infection. Clin Chim Acta 2016;457:46–53.
12. George S, Thomas M, Rafiqui S, et al. Procalcitonin and other inflammatory markers in patients with sepsis and septic shock: a single-centre experience. Ibnosina J Med Biomed Sci 2019;11:176–180.
13. Jang JY, Yoo G, Lee T, et al. Identification of the robust predictor for sepsis based on clustering analysis. Sci Rep 2022;12:2336.
14. Aminzadeh Z, Parsa E. Relationship between age and peripheral white blood cell count in patients with sepsis. Int J Prev Med 2011;2:238–242.
15. Caterino JM, Scheatzle MD, Forbes ML, et al. Bacteremic elder emergency department patients: procalcitonin and white count. Acad Emerg Med 2004;11:393–396.
16. Butcher S, Chahel H, Lord JM. Review article: ageing and the neutrophil: no appetite for killing? Immunology 2000;100:411–416.
17. Weiskopf D, Weinberger B, Grubeck-Loebenstein B. The aging of the immune system. Transpl Int 2009;22(11):1041–1050.
18. Kaushik R, Gupta M, Sharma M, et al. Diagnostic and prognostic role of neutrophil-to-lymphocyte ratio in early and late phase of sepsis. Indian J Crit Care Med 2018;22:660–663.
19. Liu X, Shen Y, Wang H, et al. Prognostic significance of neutrophil-to-lymphocyte ratio in patients with sepsis: a prospective observational study. Mediators Inflamm 2016;2016:8191254.
20. Rehman FU, Khan A, Aziz A, et al. Neutrophils to lymphocyte ratio: earliest and efficacious markers of sepsis. Cureus 2020;12(10):e10851.
21. Loonen AJ, de Jager CP, Tosserams J, et al. Biomarkers and molecular analysis to improve bloodstream infection diagnostics in an emergency care unit. PLoS One 2014;9:e87315.
22. Menka K, Tanu R, Gupta GN, et al. C reactive and procalcitonin correlation with WBC counts in culture positive patients of sepsis. Med J Clin Trials Case Stud 2019;3(3).
23. Magrini L, Gagliano G, Travaglino F, et al. Comparison between white blood cell count, procalcitonin and C reactive protein as diagnostic and prognostic biomarkers of infection or sepsis in patients presenting to emergency department. Clin Chem Lab Med 2014;52(10):1465–1472.
24. Çil E, Karadeniz G, Yenigün S, et al. Evaluation of the relationships between procalcitonin and neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in patients with pneumonia. Eur Rev Med Pharmacol Sci 2022;26:3200–3205.
25. Sugimoto K, Adomi S, Koike H, et al. Procalcitonin as an indicator of urosepsis. Res Rep Urol 2013;5:77–80.
26. Ljungström LL, Karlsson D, Pernestig A, et al. Neutrophil to lymphocyte count ratio performs better than procalcitonin as a biomarker for bacteremia and severe sepsis in the emergency department. Crit Care 2015;19:66–66.
27. Fischbach FT, Dunning MB. Blood studies: hematology and coagulation. In: Fischbach FT, Dunning MB, editors. A manual of laboratory and diagnostic tests. 8th ed. Philadelphia: Lippincott Williams and Wilkins; 2009. pp. 74-85.
28. Khoshdel A, Mahmoudzadeh M, Kheiri S, et al. Sensitivity and specificity of procalcitonin in diagnosis of neonatal sepsis. Iran J Pathol 2008;3:203–207.
29. Nugroho A, Suwarman A, Nawawi M. Relationship between neutrophil lymphocyte ratio and Sequential Organ Failure Assessment score in intensive care unit patients. J Anestesi Perioperatif 2013;3:189–196.
30. Zahorec R. Ratio of neutrophil to lymphocyte counts–rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy 2001;102(1):5–14.
31. Syafri KA, Andi BSR, Sitti W. Comparison of neutrophils-lymphocytes ratio and procalcitonin parameters in sepsis patient treated in intensive care unit Dr. Wahidin Hospital, Makassar, Indonesia. J Med Sci 2017;17(1):17–21.
32. Carr JA. Procalcitonin-guided antibiotic therapy for septic patients in the surgical intensive care unit. J Intensive Care 2015;3(1):36.
33. de Jager CP, van Wijk PT, Mathoera RB, et al. Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit. Crit Care 2010;14(5):R192.

ORIGINAL ARTICLE

Estimation of Predictors of Mortality in Patients with Acute Respiratory Failure Secondary to Chronic Obstructive Pulmonary Disease Admitted in Tertiary Care Center

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Abstract

Introduction: Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation and an increased chronic inflammatory response in the airways to noxious particles and gases. More than 10 million individuals in the United States (US) are affected with COPD, the fourth largest cause of mortality. Globally 250 million individuals are affected by COPD. D-dimer, C-reactive protein (CRP), acute physiology and chronic health evaluation (APACHE) II score, and hypoalbuminemia have significant correlation with morbidity, mortality, and risk stratification of hospitalized COPD patients with acute respiratory failure (ARF). The purpose of this study is to assess how well D-dimer, CRP, APACHE II score, and hypoalbuminemia predict death in COPD with ARF.

Materials and methods: A hospital-based prospective research (observational study) was conducted in a tertiary care center. The research was carried out from 1st February 2021, until 1st November 2022. The patients (sample size = 60; 35 survived and 25 died) were taken for detailed personal history, occupational history, chest X-ray, arterial blood gas (ABG) analysis, and thorough clinical examination to identify evidence of COPD. Our study included D-dimer, CRP, APACHE II score, and hypoalbuminemia in hospitalized COPD patients.

Results: In our study, the median D-dimer levels for patients who lived and died were 1,012.34 and 7,222.64, respectively, with a *p*-value < 0.001. Patients who survived had a mean CRP of 3.56, whereas those who were dead had a value of 12.62. The mean serum albumin levels among survived and dead patients were 3.23 and 2.22, respectively. The mean APACHE II score in survived and dead patients were 9.91 and 28.48, respectively. The APACHE II score has sensitivity and specificity of 96 and 91.4%, respectively, with a critical cutoff of >19. Hypoalbuminemia has sensitivity and specificity of 96 and 65.7%, with a critical cutoff of <3.

Conclusion: High levels of CRP, an elevated APACHE II score, elevated levels of D-dimer, and lower levels of serum albumin are all independently related to an increased risk of in-hospital mortality.

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by progressive, long-lasting airflow limitation brought on by an augmented chronic inflammatory response in the airways to smoking, combustion products, and biomass fuels. It includes: **emphysema**—**d**estruction of lung alveoli with airspace dilatation, chronic bronchitis—**c**hronic cough with sputum production for >3 months for at least 2 years, and small airway disease—narrowing and reduction in the number of bronchioles.

Chronic obstructive pulmonary disease may be caused by faulty lung growth in those who are genetically prone to the disease. Even in the absence of chronic airway limitation, patients with a history of cigarette smoking may develop chronic bronchitis, emphysema, and dyspnea. Patients in this category may have a comparable disease process to those with COPD, but they are not included in the traditional definition of COPD. Individuals with airflow restriction below the typical population limits established by spirometry may nonetheless exhibit respiratory symptoms and other signs of COPD.[1]

Chronic obstructive pulmonary disease is the fourth leading cause of death in the United States (US). COPD is the second greatest cause of death from noncommunicable diseases (NCDs) and disability-adjusted life years (DALYs) in India.[2] Prevalence varies widely across nations and rises with age; however, it is estimated that around 10% of people aged 40 and over have COPD. Due to its high incidence and persistence, COPD leads to substantial usage of healthcare resources, including visits to the doctor's office, hospitalizations for acute exacerbations, and ongoing treatment in the form of supplemental oxygen.[3] So, we need mortality prediction markers as well as prognostic markers like D-dimer, C-reactive protein (CRP), hypoalbuminemia, and acute physiology and chronic health evaluation (APACHE) II score so that we can segregate patients who are very sick and need special ICU care from stable patients.

As potential indicators of mortality in COPD, age, sex, body mass index, comorbidities, and the first-second forced expiratory volume have all been studied. However, consensus on its use in multivariate prognostic models has not been reached. Moreover, this study had discriminative ability of the multicomponent prognostic model for mortality.[4]

Materials and Methods

This is a prospective study conducted at a tertiary care teaching hospital in the field of general medicine. The study was conducted from 1st February 2021 to 1st November 2022, with a sample size of 60 patients (35 survived and 25 died). We included patients aged 18–80 years who presented with 72 hours of shortness of breath, which was proved to be a COPD exacerbation, and patients with an established diagnosis of COPD with respiratory failure (type I/II). Patients under the age of 18, women who were pregnant or breastfeeding, and those with preexisting conditions such as asthma, pneumonia, bronchiectasis, interstitial lung disease (ILD), occupational lung disease (OLD), pulmonary edema (both cardiac and noncardiogenic), acute coronary syndrome (ACS), and COPD without respiratory failure were not included. Our study included D-dimer, CRP, serum albumin, APACHE II score, and PCT. Other variables included hemoglobin, total leukocyte count, hematocrit, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), partial pressure of carbon dioxide (pCO_2), partial pressure of oxygen (pO_2), and platelet count. For the analysis of continuous variables, the

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Student's *t*-test was employed, and for the analysis of ordinal variables, Fisher's exact test was used. Parameters measured at baseline that were significant at $p < 0.001$ in univariate analysis were considered to be possible predictors.

Observations and Results

In our study, the mean of D-dimer levels among survived and dead patients was 1012.34 and 7222.64, respectively, with a *p*-value < 0.001. The mean of CRP among survived and dead patients was 3.56 and 12.62, respectively. The mean of serum albumin levels among survived and dead patients was 3.23 and 2.22, respectively. The mean of APACHE II score in survived and dead patients was 9.91 and 28.48, respectively. APACHE II score has sensitivity and specificity of 96 and 91.4%, respectively, with a critical cutoff of >19. Hypoalbuminemia has sensitivity and specificity of 96 and 65.7%, with a critical cutoff of <3 (Table 1).

Receiver operating characteristic (ROC) curve is constructed for APACHE II score that reveals maximum sensitivity and specificity; they are 96 and 91.4%, respectively (Fig. 1).

Receiver Operating Characteristic Curve for APACHE II Score for Predicting Mortality

The maximum sensitivity and specificity of an ROC curve for hypoalbuminemia are calculated to be 96 and 65.7%, respectively (Fig. 2).

Receiver Operating Characteristic Curve for Albumin for Predicting Mortality

Apart from these four, other significant variables included in our study are as follows:

Mean of pCO_2 among patients who survived and those who died was 61.03 and 99.96, respectively, with a *p*-value < 0.001. Mean of pO_2 among patients who survived and those who died was 54.16 and 60.02, respectively, with a *p*-value of 0.1. Mean of hemoglobin among survived and dead patients was 11.24 and 10.99, respectively, with a *p*-value of 0.718. Mean of total leukocyte count among survived and dead patients was 17.9 and 19.25, respectively. Mean of platelet count among survived and dead patients was 1.70 and 1.96, respectively, with a *p*-value of 0.624. Mean of hematocrit among survived and dead patients was 35.29 and 34.23, respectively, with a *p*-value of 0.624. Mean of SGOT among survived and dead patients was 58.26 and 1996.84, respectively, with a *p*-value < 0.001. Mean of SGPT among survived and dead patients was 57.49 and 2127.96, respectively, with a *p*-value < 0.001. The median total bilirubin levels of those who lived and those who perished were 2.20 and 1.26, respectively ($p < 0.001$). Mean of serum procalcitonin among survived and dead patients was 0.07 and 2.26, respectively, with a *p*-value < 0.001.

Percentage of survived and dead patients having central cyanosis are 8.6 and 96%, respectively. Percentage of survived and dead patients without cyanosis are 91.4 and 4%, respectively (*p*-value < 0.001). Percentage of survived and dead among intubated patients was 5.7 and 92%, respectively. Percentage of survived and dead among nonintubated patients was 94.3 and 8%, respectively. Percentage of survived and dead patients who were in need of BiPAP therapy was 25.7 and 96%, respectively. Percentage of survived and dead patients who didn't need BiPAP therapy was 74 and 4%. Patients diagnosed with cor pulmonale had a 2.9% survival rate and a 96% mortality rate, respectively. Patients without cor pulmonale had a 97.1% survival rate and a 4% mortality rate.

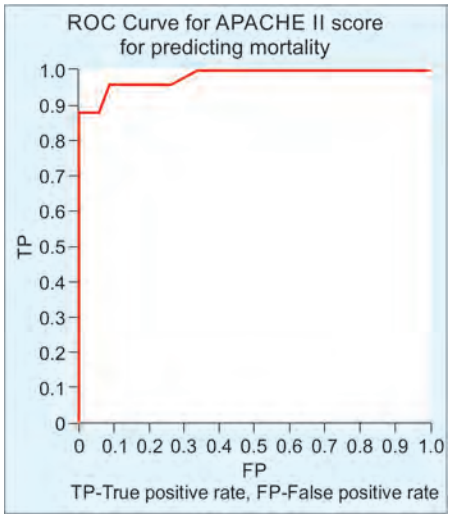

Fig. 1: APACHE II score has sensitivity and specificity of 96 and 91.4%, respectively, with critical cutoff more than 19. Its *p*-value is <0.001. AUC (95% CI) = 0.982 (0.955–1.00)

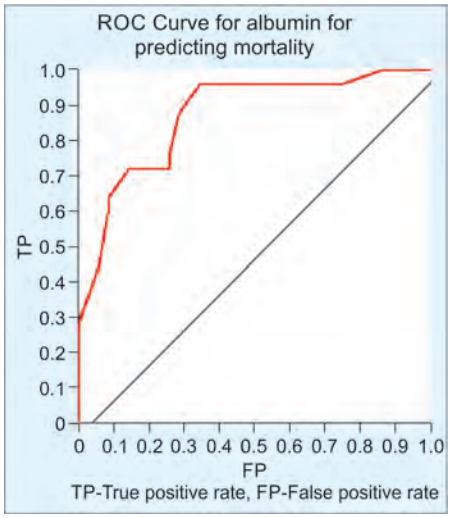

Fig. 2: Hypoalbuminemia has sensitivity and specificity of 96 and 65.7% with critical cutoff of <3. Its *p*-value <0.001. AUC (95% CI) = 0.871 (0.780–0.962)

Table 1: Comparison of results in both groups

Material	*Mean of survived patients*	*Mean of dead patients*	*p-value*
D-dimer (ng/mL)	1012.3	7222.6	<0.001
CRP (ng/mL)	3.56	12.6	<0.001
APACHE II score	9.91	28.4	<0.001
Serum PCT (ng/mL)	0.07	2.26	<0.001
Serum albumin (mg/dL)	3.23	2.22	<0.001
pCO_2 (mm Hg)	61.3	99.6	<0.001

Discussion

According to Fruchter et al. study, "Elevated D-dimer as a predictive biomarker for death in acute exacerbation of COPD (AECOPD)," which was conducted in 61 patients with AECOPD, a D-dimer of >1520 had a sensitivity of 100% and specificity of 63%. The median survival time for patients with D-dimer levels exceeding 1.52 mg/L was 9.6 months after discharge, whereas the median survival time for individuals with levels below 1.52 mg/L was 62.6 months. According to this study, higher D-dimer levels were a reliable indicator of both short- and long-term survival in patients with AECOPD who were admitted.[5] Similar results were seen in our research, with a *p*-value of 0.001 indicating that a mean D-dimer of 7222.6 was related to increased in-hospital mortality compared to a mean D-dimer of 1012.34 among survivors.

Butler et al. conducted a study with the working title "CRP testing to guide antibiotic prescribing for COPD exacerbations." When CRP-guided antibiotic prescribing for COPD exacerbations in primary care clinics was employed, fewer patients reported using antibiotics and receiving antibiotic

prescriptions from doctors without any evidence of damage.[6] Comparatively, increased inpatient mortality in our sample was related to a mean CRP of 12.7, while the mean CRP among patients who survived was 3.56 ng/dL with a *p*-value of <0.001.

Ahmed et al. conducted a study titled "Effectiveness of APACHE II and SAPS II scoring models in predicting the outcome of critically ill COPD patients." In this investigation, an APACHE II score of >20 and a SAPS II score of >48 both predicted survival or death (34.6% of patients did not survive, whereas 65.4% did). Researchers discovered that although the former was slightly favored, APACHE II and SAPS II scores were practically comparable in their capacity to predict mortality among COPD patients.[7] In our research, we found that an APACHE II score of 28.4 predicted a high risk of death in the hospital, whereas a score of 9.91 predicted survival, with a *p*-value of <0.001. Furthermore, an APACHE II score with a critical cutoff of >19 had sensitivity and specificity of 96 and 91.4%, respectively.

A research titled "Severe hypoalbuminemia is a strong independent risk factor for acute respiratory failure (ARF) in COPD" was conducted by Chen et al. The researchers found that 12.43% of the 42,732 COPD patients with hypoalbuminemia who were followed for 6 years ended up with ARF. Low albumin levels are a significant independent risk factor for respiratory failure in COPD patients, according to the study's findings.[8] Additionally, hypoalbuminemia with a critical cutoff of <3 had sensitivity and specificity of 96 and 65.7%, respectively. This is similar to our research, which found that a serum albumin level of 3.23 mg/dL was associated with higher survival rates among those who survived, and a serum albumin level of 2.2 mg/dL was related to increased in-hospital mortality.

Gong et al. conducted a study titled "Effect of procalcitonin on prognosis of COPD patients." PCT 0.1 ng/mL (PCT negative) was found in 55 of the participants in the present study. Another 55 people tested positive for PCT (PCT >0.1 ng/mL). The PCT-positive group had higher CRP, ESR, TLC, and hospitalization expenditures as compared to the PCT-negative group. The authors of the research speculate that patients with acute exacerbations of COPD may have PCT levels that reflect the severity of the condition and may be used as a reference value for prognostic risk assessment. Hospital stay length and financial burden may be predicted with serum PCT levels.[9] Similar to previous research, we found that a PCT mean of 2.26 was related to increased in-hospital mortality, whereas a PCT mean <0.07 ng/mL was found in the group that ultimately survived.

Park et al. conducted the study "Hemoglobin and mortality in patients with COPD: a countrywide population-based cohort study." In this study, 7,114 individuals with COPD were diagnosed. Anemia was present in 469 people. In comparison to the control group, anemia was linked to a death rate of 46.5% as opposed to 32.1% ($p < 0.001$).[10] The study came to the conclusion that anemia increased the long-term mortality risk of COPD patients. Similarly, in our study, the mean hemoglobin levels among survived and deceased patients were 11.24 and 10.99, respectively, with a *p*-value of 0.718.

Researchers Koo et al. looked at "Systemic WBC count as a biomarker associated with severity of COPD." A total of 1,227 patients with COPD and 8,679 individuals over the age of 40 without COPD had their WBC levels compared in this research. There was an inverse correlation between WBC count and FEV1, %FVC predicted. The study's findings indicate that WBC count is related to the severity of COPD, a risk factor for having impaired lung function, and a measure of life quality.[11] In our investigation, the median WBC count for patients who survived and those who died was 17.9 and 19.25, respectively.

The study by Fawzy et al. was titled "Association of platelet count with all-cause mortality and risk of cardiovascular and respiratory morbidity in stable COPD." According to this study, a greater platelet count (>3 L/mm^3) was linked to a 66% higher death rate than a lower platelet count (1.5 L/mm^3). In those with mild COPD and CV disease, there is a U-shaped relationship between platelet count and all-cause death.[12] Comparatively, in our study, the mean platelet count among survived and dead patients was 1.96 and 1.70, respectively, with $p = 0.624$.

Macdonald et al. conducted a study titled "Serum bilirubin and COPD: a systematic review." We discovered a weak association between bilirubin and both all-cause and COPD-related mortality in this research. Higher serum bilirubin was associated with decreased mortality in the largest trial, although the overall body of data lacked clarity and consistency.[13] Comparatively, in our study, the mean total bilirubin among survived and dead patients was 2.20 and 1.26, respectively, with a *p*-value < 0.001.

"Oxygen therapy and inpatient mortality in COPD exacerbation" by Echevarria et al. showed the adjusted mortality rates for the groups with 93–100% survival against the 88–92% group were 1.98 and 2.97, respectively. Those with a score between 88 and 92% had the lowest in-hospital death rates.[14] Comparatively, in our study, the mean pO_2 among patients who survived and died was 54.16 and 60.02, respectively, with a *p*-value of 0.1.

A research titled "Hypo and hypercapnia predict mortality in oxygen-dependent COPD: a population-based prospective study" was done by Ahmadi et al. The research found that the "mortality association was U-shaped," with the lowest mortality at pCO_2 6.5 kPa and higher mortality at pCO_2 5 kPa and >7 kPa.[15] Comparatively, in our study, the mean pCO_2 among patients who survived and died was 61.03 and 99.96, respectively, with a *p*-value < 0.001.

Limitations of the Study

In our study, the number of cases of COPD was small. We didn't compare the different stages of COPD. We didn't include healthy controls; instead, stable COPD patients were taken as controls.

Conclusion

Increased risk of mortality while hospitalized is seen in patients with elevated CRP, elevated APACHE II score, low blood albumin, and elevated D-dimer levels. Independent predictors of survival in COPD patients, these measures of systemic inflammation are low-cost, reliable, and noninvasive.

References

1. Harrison's Principles of Internal Medicine. 21st edition. pp. 2180–2189.
2. Gudi N, Mahmood A, Roy MP, et al. Burden of COPD among population above 30 years in India: protocol for a systematic review and proposed meta-analysis. Can J Respir Ther 2021;57:14–17.
3. Han MLK, Dransfield MT, Martinez FJ. Chronic obstructive pulmonary disease: definition, clinical manifestations, diagnosis and staging, prognostic factors and comorbid conditions. 2022.
4. Owusuaa C, Dijkland SA, Nieboer D, et al. Predictors of mortality in chronic obstructive pulmonary disease: a systematic review and meta-analysis. BMC Pulm Med 2022;22:125.
5. Fruchter O, Yigla M, Kramer MR. D-dimer as a prognostic biomarker for mortality in chronic obstructive pulmonary disease exacerbation. Am J Med Sci 2015;349(1):29–35.
6. Butler CC, Gillespie D, White P, et al. C-reactive protein testing to guide antibiotic prescribing for COPD exacerbations. N Engl J Med 2019;381:111–120.
7. Ahmed Y, Adam M, Bakkar LM. Effectiveness of APACHE II and SAPS II scoring models in forseeing the outcome of critically ill COPD patients. Egypt J Bronchol 2019;13:654–659.
8. Chen CW, Chen YY, Lu CL, et al. Severe hypoalbuminemia is a strong independent risk factor for acute respiratory failure in COPD: a nationwide cohort study. Int J Chron Obstruct Pulmon Dis 2015;10:1147–1154.
9. Gong C, Yang Y, Chen M, et al. Effect of procalcitonin on the prognosis of patients with COPD. Biomed Rep 2020;12(6):313–318.

10. Park SC, Kim YS, Kang YA, et al. Haemoglobin and mortality in patients with COPD: a nationwide population-based cohort study. Int J Chron Obstruct Pulmon Dis 2018;13:1599–1605.
11. Koo HK, Kang HK, Song P, et al. Systemic white blood cell count as a biomarker associated with severity of chronic obstructive lung disease. Tuberc Respir Dis (Seoul) 2017;80:304–310.
12. Fawzy A, Anderson JA, Cowans NJ, et al. Association of platelet count with all-cause mortality and risk of cardiovascular and respiratory morbidity in stable COPD. Respir Res 2019;20:86.
13. MacDonald DM, Kunisaki KM, Wilt TJ, et al. Serum bilirubin and chronic obstructive pulmonary disease (COPD): a systematic review. BMC Pulm Med 2021;21:33.
14. Echevarria C, Steer J, Wason J, et al. Oxygen therapy and inpatient mortality in COPD exacerbation. Emerg Med J 2021;38:170–177.
15. Ahmadi Z, Bornefalk-Hermansson A, Franklin KA, et al. Hypo- and hypercapnia predict mortality in oxygen-dependent chronic obstructive pulmonary disease: a population-based prospective study. Respir Res 2014;15(1):30.

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ORIGINAL ARTICLE

Safety and Efficacy of Biosimilar Insulin Glargine (Basaglar) in Indian Patients with Type 2 Diabetes Mellitus: Results from a Multicenter, Open-Label, Single-Arm, Phase 4 Trial (ABEX)

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Abstract

Background: Basaglar®, a biosimilar of glargine, was approved in India for the treatment of diabetes in patients aged >2 years. The efficacy and safety of biosimilar insulin glargine (Basaglar) have been previously established in Phase 3 clinical trials, ELEMENT-1, -2, and -5. This study assessed the safety and efficacy of Basaglar in Indian patients with type 2 diabetes mellitus (T2DM).

Materials and methods: This multicenter, open-label, single-arm, phase 4 trial included Indian patients with insulin-naïve T2DM with glycated hemoglobin A1c (HbA1c) ≥7.0 to <11.0% who were receiving ≥2 oral antihyperglycemic drugs and/or a glucagon-like peptide-1-receptor agonist. Patients received Basaglar once daily for 24 weeks, excluding 4 weeks of safety follow-up. The primary endpoint was the incidence of total hypoglycemic events [blood glucose (BG) ≤54 mg/dL (≤3.0 mmol/L)] at week 24.

Results: Of the 259 patients enrolled, 64.1% were males, had mean [standard deviation (SD)] age 52.1 (11.38) years, and had diabetes for mean (SD) 6.75 (5.16) years. The mean HbA1c (SD) levels significantly improved from baseline to week 24 [−1.03 (1.554); p <0.0001] and Basaglar titration doubled from baseline. Total hypoglycemic events were reported in 10 (3.86%), 7 (2.70%), and 4 (1.54%) patients during weeks 0–24, 0–12, and 12–24, respectively. Ten patients (3.90%) reported 12 adverse events (AE; 11 mild and moderate, one severe). One death, unrelated to Basaglar, was reported.

Conclusion: Basaglar was well tolerated with few hypoglycemic events and significantly reduced HbA1c and BG from baseline in Indian insulin-naïve patients with T2DM.

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Introduction

Diabetes and its comorbidities present major health challenges.[1,2] As per the International Diabetes Federation (IDF), India has the world's second-highest population of patients with diabetes. In 2021, 74.2 million individuals of Indian origin were diagnosed with diabetes.[3] The IDF projects 124.9 million Indians to be affected by type 2 diabetes mellitus (T2DM) by 2045.[3] Patients with T2DM often do not achieve the targeted glycemic levels with the initial combinations of oral antihyperglycemic medications (OAMs).[4,5] The 2022 Consensus Statement by the American Diabetes Association and European Association for the Study of Diabetes recommends the addition of a basal insulin like glargine to OAMs in people with T2DM who do not achieve glycemic goals.[6]

Basaglar®, a long-acting insulin glargine, received approval from both the United States Food and Drug Administration (FDA) in 2015 and the European Medicines Agency in 2014. In India, it was approved for the treatment of diabetes in patients aged >2 years (the FDA has approved insulin glargine injection (Toujeo, Sanofi) 300 units/mL in pediatric patients, ≥6 years of age).[7] Basaglar demonstrated its efficacy and safety in patients with type 1 diabetes mellitus and T2DM in the global ELEMENT-1 and ELEMENT-2 trials.[8–11] It received approval in India in 2017 as a biosimilar of glargine for the treatment of diabetes in people above two years of age. A subpopulation analysis was conducted in 100 Indian patients as part of the Phase 3 ELEMENT-5 trial. The results showed an efficacy and safety profile as reported for Basaglar in patients with T2DM in the total population of the trial.[12] As a condition for marketing approval, the Drug Controller General of India (DCGI) recommended that Basaglar should be studied in a total of 300 local individuals, in accordance with the Biosimilar Guidelines of India. Basaglar was studied in at least 300 individuals, with 100 individuals included in the ELEMENT-5 trial and over 200 individuals in this study.[12]

In this report, we present safety and efficacy data of Basaglar in an unexplored cohort of Indian patients with T2DM. This Phase 4 trial enrolled insulin-naïve individuals with T2DM who were unable to meet glycemic targets despite taking OAMs and/or glucagon-like peptide 1 receptor agonist (GLP-1 RA) and required treatment with Basaglar. As its primary objective, the trial evaluated the risk of hypoglycemia in adult Indian individuals with T2DM who received Basaglar, with the secondary objective of assessing adverse events (AEs) and other safety parameters. Efficacy of Basaglar and patient-reported outcomes (PROs) were other secondary objectives.

Materials and Methods

Study Patients and Design

I4L-IN-ABEX (NCT04153981) was a phase 4, multicenter, open-label, single-arm trial that was designed to evaluate the safety and efficacy of Basaglar in Indian patients with T2DM. The study included male and nonpregnant females aged between 18 and 75 years with T2DM lasting at least 6 months prior to screening and with HbA1c levels from ≥7.0 to <11.0%. Patients who received stable doses of at least two OAMs and/or GLP-1 RA for 90 days prior to visit 1 (screening) were also eligible. Patients were excluded from the study if they had been treated with insulin for >14 days for acute conditions, had a history of comorbidities including unstable angina, stage III or IV cardiac failure (New York Heart Association guidelines), renal failure

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(estimated glomerular filtration rate <30 mL/minute/m^2), and human immunodeficiency virus infection or hepatitis B and C (Table S1).

The study had 2-week screening and 24-week treatment phases, with a safety follow-up at week 28. The treatment phase included a titration phase from week 0 to week 12 and a maintenance phase from week 12 to week 24 (Fig. 1). Supplementary Table 2 guided dose titrations during the trial. The study was conducted following the recommendations from the DCGI and Good Clinical Practice guidelines. All patients signed an informed consent before study enrolment and agreed that data may be used for future research.

Outcomes

Table 1 lists the primary and secondary objectives of this study.

Statistical Analysis

Patients from the full analysis set (FAS, who were administered ≥1 dose of study treatment) were evaluated for the outcomes. All tests were conducted as two-sided tests at the 0.05 alpha level. The primary analysis was the calculation of the estimate and 95% confidence interval for the incidence of total hypoglycemic events [symptomatic or asymptomatic, blood glucose (BG) level ≤54 mg/dL (3.0 mmol/L)] at week 24. It was expressed as the number and percentage of patients with at least one event during the study. HbA1c at baseline, week 12, week 24, and change in HbA1c from baseline to week 12 and week 24 were presented descriptively. The analysis used nonmissing values and last observation carried forward imputed values. The association between baseline HbA1c (covariate) and change in HbA1c in FAS (dependent variable) was analyzed using a general linear model. Hypoglycemic events (*n*) per patient, the rate of hypoglycemic events per 30 days and year (assuming 365.25 days in a year) were analyzed using a negative binomial model. The binomial model used baseline HbA1c as a covariate and the log of the study treatment exposure time as an offset variable. Adverse events (AEs) were described as per Medical Dictionary for Regulatory Activities (MedDRA) coding and were defined as events reported after signing the informed consent form. Treatment-emergent adverse events (TEAEs) included either new reported events or worsening of an event after the first study drug treatment.

The analyses of other continuous secondary efficacy and safety measurements and continuous laboratory measures used the general linear model for the FAS population with the baseline value of the response variable as a covariate. Additionally, the per protocol (PP) population was analyzed, which included patients from FAS who had no violations of eligibility criteria, continued in the study until week 24, did not receive off-study medication for more than 14 consecutive days during the treatment phase, and did not receive chronic systemic glucocorticoid therapy (excluding topical, intra-articular, intraocular, and inhaled preparations).

All analyses reported are on the FAS population unless otherwise mentioned. All analyses included in this report were performed in the software package SAS V9.4 (The SAS Institute, Cary, NC).

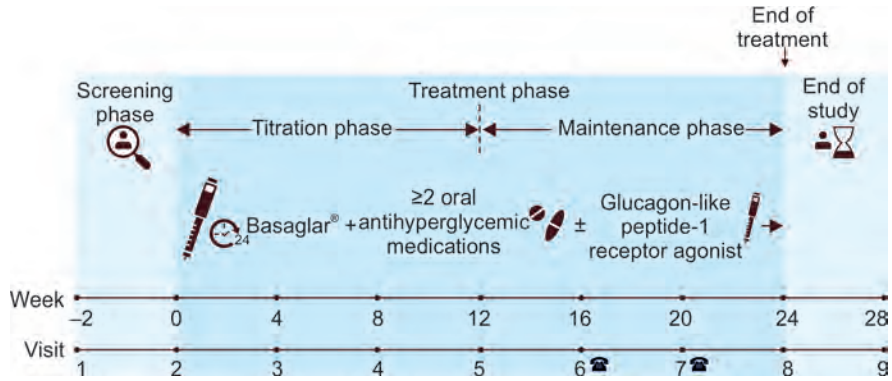


Fig. 1: Study design

Table 1: Study objectives

Objectives	*Endpoints*
Primary	
To assess the risk of hypoglycemia in adult patients with T2DM in India who were administered Basaglar	• Incidence of total [symptomatic or asymptomatic with BG level of ≤54 mg/dL (≤3.0 mmol/L)] hypoglycemic events at week 24
Secondary	
To assess AEs and other safety parameters in adult patients with T2DM in India	• SAEs and TEAEs • Rates per 30 days and per subject year of total (symptomatic or asymptomatic) hypoglycemic events • Incidence and rates per 30 days and per subject year of nocturnal, severe, documented symptomatic, and asymptomatic hypoglycemic events • Basal insulin dose (U/day and U/kg/day) • Change in weight and BMI at week 24 from baseline
To assess the efficacy of Basaglar in adult patients with T2DM in India	• Change in HbA1c at weeks 12 and 24 • Percentage of patients reaching HbA1c targets ≤6.5 or < 7% • Change in BG levels at weeks 4, 8, and 12 from baseline • Self-monitored 7-point SMBG levels at weeks 4, 8, 12, and 24 from baseline • Change in 7-point SMBG levels at weeks 4, 8, 12, and 24 from baseline • Intrasubject variability, as measured by SD of 7-point SMBG levels
To assess outcomes reported by adult patients with T2DM in India	• Change in ITSQ scores at week 24 from week 4

AE, adverse event; BG, blood glucose; BMI, body-mass index; ITSQ, Insulin Treatment Satisfaction Questionnaire; HbA1c, glycated hemoglobin; SAE, serious adverse events; SD, standard deviation; SMBG, self-monitored blood glucose; TEAE, treatment-emergent adverse event; T2DM, type 2 diabetes mellitus; Note: The ITSQ had 22 items to assess treatment satisfaction and was classified into five domains: (1) inconvenience of regimen (IR—5 items), (2) lifestyle flexibility (LF—3 items), (3) glycemic control (GC—3 items), (4) hypoglycemic control (HC—5 items), and (5) insulin delivery device (DD—6 items)

Results

The planned sample size for screening was 295 patients. However, due to the Coronavirus disease 2019 pandemic in India, 365 patients were screened, as many screened patients could not start due to lockdown measures. Among the 304 patients enrolled, 259 eligible patients were treated with at least one dose of Basaglar, and 218 patients completed the study. The predominant reasons for early withdrawal included the patient's decision [*n* = 14 (5.4%)] and other reasons including COVID-19-related issues [*n* = 26 (10.0%)]. Most patients were males (64.1%), had a mean [standard deviation (SD)] age of 52.1 (11.38) years, and a mean (SD) body mass index (BMI) of 26.7 (4.2) kg/m^2. The mean (SD) baseline level of HbA1c was 9.03% (1.02%), and approximately 64% of patients had an HbA1c level of ≥8.5%. The mean (SD) duration of diabetes was 6.75 (5.16) years. More than 25% received at least two concomitant antihyperglycemic medications, with oral BG-lowering drug combinations (53.7%), biguanides (46.7%), sulfonylureas (42.1%), dipeptidyl peptidase-4 inhibitors (40.2%), and alpha-glucosidase inhibitors (33.2%) being the most common. Metformin (98.1%), sulfonylurea (89.2%), and dipeptidyl peptidase-4 inhibitors (55.2%) were the most commonly used concomitant antihyperglycemic medications. The most commonly reported comorbidities in the medical history were hypertension (44.0%) and dyslipidemia (17.4%). The demographic and clinical characteristics for FAS and PP populations at baseline are reported in Table 2. The overall mean duration of exposure to the study treatment was 157.8 days, and the overall compliance with the administration of the study medication was 99% (see Table S3).

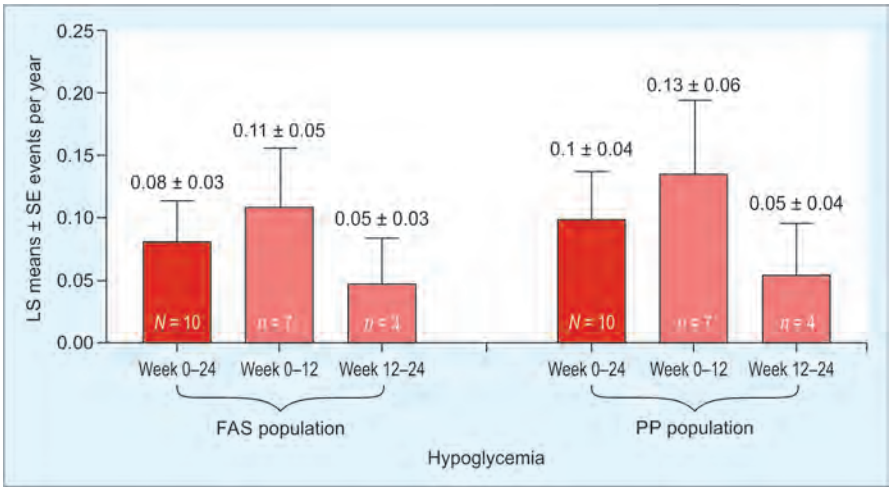


Fig. 2: Incidence of hypoglycemic events per year by study population; FAS, full analysis set; LS, least squares; *n*, number of subjects with data; *N*, total number of subjects in the relevant population; PP, per protocol; SE, standard error

Table 2: Baseline demographics and disease characteristics

Parameter	*Basaglar—full analysis set (N = 259)*	*Basaglar—per protocol (N = 207)*
Age, mean (SD), years	52.10 (11.38)	51.70 (11.44)
Median	53.0	53.0
Range, minimum; maximum	21; 74	21; 73
Sex, *n* (%)		
Male	166 (64.10)	133 (64.30)
Female	93 (35.90)	74 (35.70)
BMI, mean (SD), kg/m^2	26.73 (4.19)	26.73 (4.34)
Duration of diabetes, mean (SD), years	6.75 (5.16)	6.26 (4.85)
Median	5.00	5.00
Range, minimum; maximum	1.0; 33.0	1.0; 22.0
Baseline HbA1c, mean (SD) %	9.03 (1.02)	8.96 (1.00)
Baseline HbA1c categories, *n* (%)		
7.0–8.4%	93.00 (35.90)	77.00 (37.20)
≥8.5%	166.00 (64.10)	130.00 (62.80)
Concomitant antihyperglycemic medications, *n* (%)		
Metformin	254.00 (98.10)	203.00 (98.10)
Sulfonylureas	231.00 (89.20)	182.00 (87.90)
SGLT2 inhibitors	40.00 (15.40)	29.00 (14.00)
Dipeptidyl peptidase-4 inhibitors	143.00 (55.20)	113
Alpha-glucosidase inhibitors	101.00 (39.00)	83.00 (40.10)
Thiazolidinediones	73.00 (28.20)	60.00 (29.00)
Dual PPAR alpha/gamma agonist	1.00 (0.40)	1.00 (0.50)

FAS, full analysis set; LS, least square; *n*, number of subjects with data; *N*, total number of subjects in the relevant population; PP, per protocol; SE, standard error

Incidence of Total Hypoglycemic Events

In the FAS, the incidence of total hypoglycemic events was 10 (3.86%), 7 (2.70%), and 4 (1.54%) during weeks 0–24, 0–12, and 12–24, respectively. The incidence and rates of nocturnal, documented symptomatic, and documented asymptomatic hypoglycemic events from week 0 to week 24 are shown in Supplementary Figure 1. There was no incidence of severe hypoglycemia (an event requiring the assistance of another person to actively administer carbohydrates or glucagon or take other corrective actions). The mean (SD) total hypoglycemic events per participant were 1.2 (0.63), 1.1 (0.38), and 1.0 (0) during weeks 0–24, 0–12, and 12–24, respectively. The corresponding outcomes per 30 days and per year are listed in Supplementary Table 4. Figure 2 presents the incidence of hypoglycemic events per year for the FAS and PP populations.

Adverse Events

In the FAS population, 10 patients (3.9%) reported a total of 12 AEs, of which 11 were mild and moderate, and one was severe. None of the reported AEs were considered treatment-related or led to treatment discontinuation. Among these patients, 8 (3.1%) reported a total of 10 TEAEs, with anemia as the most commonly reported TEAE (Table 3). None of these TEAEs were considered related to the study treatment or led to early withdrawal.

The overview of AEs in the PP population is shown in Table 4, and there were no reports of any AE leading to study discontinuation or any drug-related AE. One serious adverse event (SAE) was reported in a 67-year-old male with AEs of mild pyrexia and mild cough, and

Table 3: Overview of TEAEs

Preferred term	*Basaglar—full analysis set (N=259)*				*Basaglar—per protocol (N=207)*			
	Incidence n (%)	*Mean ± SD events per patient*	*LS means ± SE events per 30 days*	*LS means ± SE events per year*	*Incidence n (%)*	*Mean ± SD events per patient*	*LS means ± SE events per 30 days*	*LS means ± SE events per year*
Number of patients who reported at least 1 TEAE	8 (3.1)	1.3 ± 0.71	0.0071 ± 0.0031	0.0868 ± 0.0380	7 (3.4)	1.0 ± 0.00	0.0054 ± 0.0022	0.0660 ± 0.0272
Anemia	5 (1.9)	1.0 ± 0.0	0.0029 ± 0.0016	0.0351 ± 0.0194	5 (2.4)	1.0 ± 0.00	0.0031 ± 0.0018	0.0383 ± 0.0221
Death	1 (0.4)	1.0 ± NE	0.0006 ± 0.0011	0.0071 ± 0.0148	0 (0.0)	0.0	0.0	0.0
Pyrexia	1 (0.4)	1.0 ± NE	0.0006 ± 0.0011	0.0071 ± 0.0148	0 (0.0)	0.0	0.0	0.0
Urinary tract infection	1 (0.4)	1.0 ± NE	0.0003 ± 0.0006	0.0037 ± 0.0070	1 (0.5)	1.0 ± NE	0.0003 ± 0.0006	0.0037 ± 0.0075
Hyperglycemia	1 (0.4)	1.0 ± NE	0.0000 ± 0.0000	0.0000 ± 0.0000	1 (0.5)	1.0 ± NE	0.0000 ± 0.0000	0.0000 ± 0.0000
Cough	1 (0.4)	1.0 ± NE	0.0006 ± 0.0011	0.0071 ± 0.0148	0 (0.0)	0.0	0.0	0.0

LS, least squares; *n*, number of subjects with data; *N*, total number of subjects in the relevant population; NE, not estimable; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse event

Table 4: Overview of AEs reported in PP and safety population

Description	*Basaglar—per protocol (N = 207)*			*Basaglar—safety population (N = 259)*		
	Incidence n (%)	*Mean ± SD events per patient*	*LSM ± SE events per year*	*Incidence n (%)*	*Mean ± SD events per patient*	*LSM ± SE events per year*
Any adverse event	9 (4.3)	1.0 ± 0.0	0.0821 ± 0.0307	10 (3.9)	1.2 ± 0.63	0.0996 ± 0.0375
Mild	7 (3.4)	1.0 ± 0.0	0.0539 ± 0.0262	8 (3.1)	1.1 ± 0.35	0.0643 ± 0.0284
Moderate	2 (1.0)	1.0 ± 0.0	0.0193 ± 0.0146	2 (0.8)	1.0 ± 0.0	0.0162 ± 0.0126
Severe	0 (0.0)	0.0	0.0	1 (0.4)	1.0 ± NE	0.0071 ± 0.0148

AE, adverse events; LSM, least square mean; *n*, number of subjects with data; *N*, total number of subjects in the relevant population; NE, not estimable; PP, per protocol; SD, standard deviation; SE, standard error

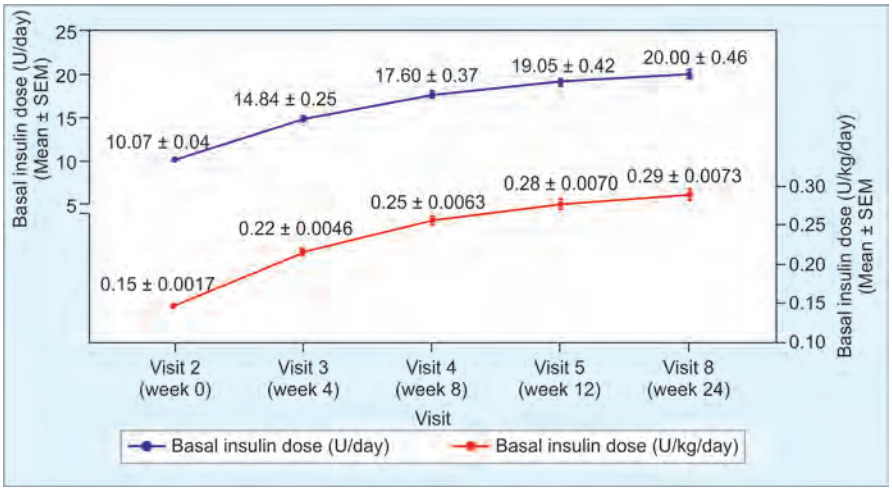


Fig. 3: Biosimilar insulin glargine (Basaglar) dose (U/day and U/kg/day) by visit in full analysis set (FAS); SEM, standard error of mean

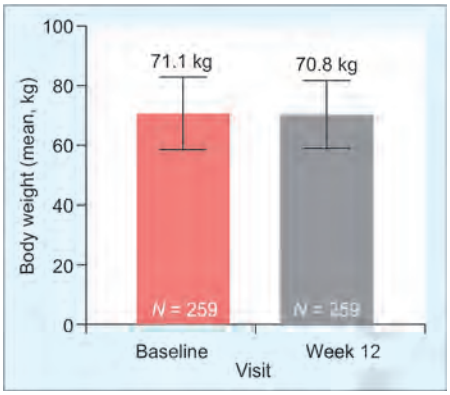


Fig. 4: Mean body weight at baseline and week 24 in FAS set population; FAS, full analysis set; *N*, total number of subjects in the relevant population

he experienced anxiety a few days prior to demise. The cause of death was reported as unknown. The investigator assessed the event of death as not related to the treatment with Basaglar.

Basaglar Dose and Body Weight

The mean Basaglar dose increased each week after baseline. A significant increase in Basaglar dose from baseline to week 24 ($p < 0.001$) was observed at all visits, as indicated in Figure 3.

Although the insulin dose was doubled from baseline to week 24, the mean weight showed a significant reduction from baseline to week 24 (71.1 ± 12.25 kg to 70.8 ± 11.53 kg; $p = 0.0006$) (Fig. 4). A significant improvement in mean BMI from baseline to week 24 (26.7 kg/m^2 to 26.5 kg/m^2; $p = 0.011$) was also observed.

Changes in Glycated Hemoglobin A1c

The mean HbA1c levels improved at weeks 12 and 24 from baseline. The mean change from baseline was significant at these visits (Fig. 5).

Percentage of Subjects Reaching Glycated Hemoglobin A1c Targets ≤6.5 or <7%

At week 12, 6.9 and 15.1% of patients achieved HbA1c ≤6.5 and <7%, respectively. At week 24, 15.1 and 23.6% of the patients were reported to have achieved HbA1c ≤6.5 and <7%, respectively.

Change in Fasting Blood Glucose Levels from Baseline

The mean fasting blood glucose (FBG) levels improved at each week after baseline.

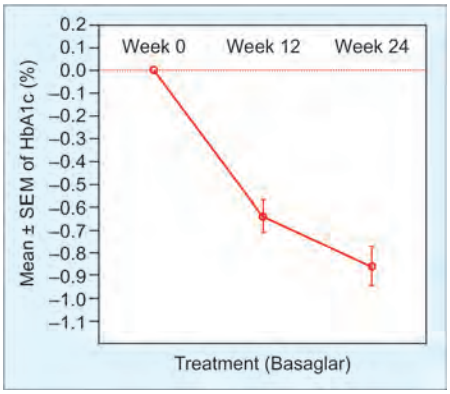


Fig. 5: HbA1c (%) change from baseline LSM in FAS population; FAS, full analysis set; HbA1c, glycated hemoglobin; LSM, least squares means; SEM, standard error of mean

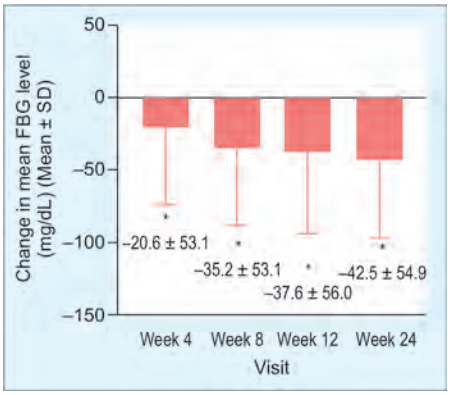


Fig. 6: Change in mean FBG until week 24; FBG, fasting blood glucose; SD, standard deviation; $p < 0.0001$ for change from baseline

The change from baseline was significant ($p < 0.0001$) at all the visits. In the FAS, the mean change in FBG was −20.6, −35.2, −37.6, and −42.5 at weeks 4, 8, 12, and 24, respectively (Fig. 6).

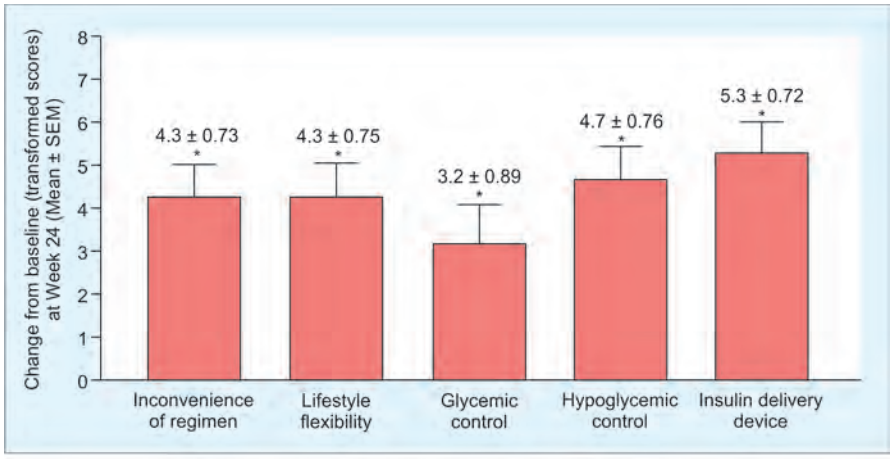
Patient-reported Outcomes

The patient-reported outcomes (PROs) were assessed using the least square means (LSM) scores of the insulin treatment satisfaction questionnaire (ITSQ) at week 24. There was a significant improvement ($p < 0.0001$) in the ITSQ score from week 4 to week 24 (Fig. 7 and Table S5).

Changes in 7-point Self-monitored Blood Glucose

The patients were evaluated using a 7-point self-monitored blood glucose (SMBG) scale before breakfast, before and 2 hours after morning, midday, and evening meals, and at 3 AM. At all the time points, there were statistically significant improvements in BG levels from baseline for all visits except at week 4 before the midday meal. At week 4, the BG level decreased from baseline, but the change was not significant (Fig. 8). Based on the SD values of 7-point SMBG levels, the change from baseline was significant at all the visits.

Overall, vital signs, physical examination, and clinical laboratory assessments were stable throughout the study.



	Inconvenience of regimen	Lifestyle flexibility	Glycemic control	Hypoglycemic control	Insulin delivery device
Raw scores (Meani ± SEM)	−0.3 ± 0.04	−0.3 ± 0.05	0.2 ± 0.05	−0.3 ± 0.05	−0.3 ± 0.04
Transformed scores (MeansS ± EM)	4.3 ± 0.73	4.3 ± 0.75	3.2 ± 0.89	4.7 ± 0.76	5.3 ± 0.72

Fig. 7: Change in ITSQ from baseline to week 24; ITSQ, insulin treatment satisfaction questionnaire; SEM, standard error of mean; $p < 0.0001$ for change from baseline; Note: Individual raw and transformed scores: Raw score was calculated as the mean of the items for that subject and is on a scale of 1 to 7. The raw scores were then transformed on a scale from 0 to 100, where a higher score indicates better treatment satisfaction (formula used: transformed score = 100 * (7 – raw score) / 6)

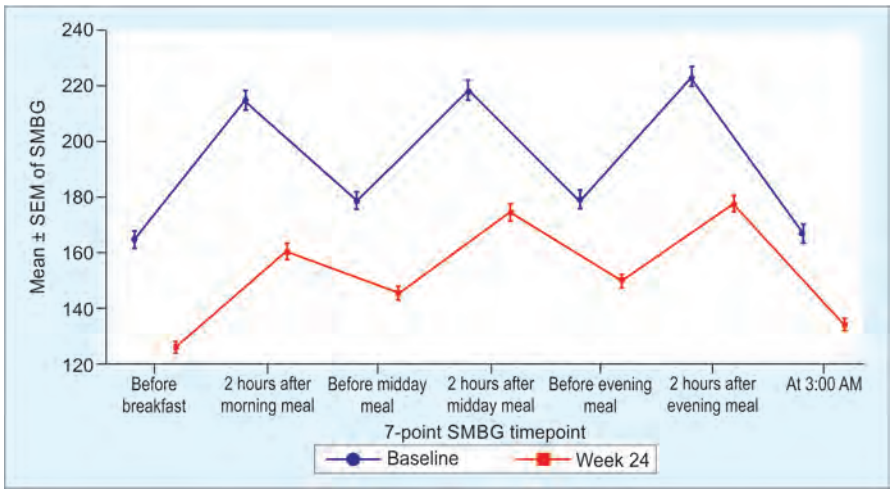


Fig. 8: SMBG at baseline and at week 24; SEM, standard error of mean; SMBG, self-monitored blood glucose

Discussion

We assessed the safety and efficacy outcomes of Basaglar in Indian patients in addition to the evaluation performed in the Indian subpopulation in the ELEMENT-5 trial.[12,13] These findings are important as they represent the first evaluation of the safety and efficacy of Basaglar in Indian patients with T2DM who received two OAMs and/or GLP-1 RA and were insulin-naïve with inadequate glycemic control.

The results from this study reported total hypoglycemia (symptomatic and asymptomatic) in 10 patients. The incidence of total hypoglycemic events per year observed in this study was 0.08 (LSM), whereas in the ELEMENT-5 trial, total hypoglycemia [BG ≤70 mg/dL (≤3.9 mmol/L)] rate was 17.0 (mean) in the global population and 2.38 (mean) in the Indian subpopulation.[12,13] The TEAEs reported

in this trial were numerically lesser than those reported in the Indian subpopulation of the ELEMENT-5 trial. Overall, Basaglar was well tolerated in Indian patients. The findings reported in our study are consistent with the findings reported in the total population in the ELEMENT-5 trial. At each visit up to week 24, we observed an improvement in SMBG levels compared to baseline, except for a slightly lower value at week 4 before the midday meal. The efficacy profile at week 24 was similar to that reported in the ELEMENT-5 trial. Basal titration was doubled from baseline to mean HbA1c levels significantly improved from baseline to week 24.

This study has some limitations. The open-label and noncontrolled study design could have influenced patient or investigator-initiated actions and increased the likelihood of selection bias. We have previously reported an improvement in ITSQ from baseline. Thus, such positive and negative perceptions could potentially affect the more subjective patient-reported outcomes.[12,13] No adjustment for type 1 error was done for the secondary efficacy endpoints. Also, the 24-week study duration may not be sufficient to address any questions on the long-term immunogenicity of Basaglar.

Conclusion

The Indian patients in the ABEX trial showed that Basaglar was well tolerated with few hypoglycemic events. Basaglar, when combined with GLP-1 RA or at least two OAMs, significantly reduced HbA1c and BG levels from baseline in patients with T2DM. The safety and efficacy profile of Basaglar in the phase 4 ABEX trial was consistent with that reported in previous phase 3 trials, ELEMENT-2 and ELEMENT-5.

Acknowledgments

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Funding: Eli Lilly and Company (Pharmaceutical company).

Ethics approval and consent to participate: The study was conducted in accordance with the principles of the Declaration of Helsinki (2000), the International Conference on Harmonization, and the E6 Guideline for Good Clinical Practice. Institutional review board approval and written informed consent from all subjects were obtained before the conduct of any evaluations or study procedures.

Disclosures: Banshi Saboo and Parag Shah have no conflicts of interest to declare. Deepak Khandelwal, Keyur Brahme, and Paramesh Shamanna have received investigator grants from Eli Lilly and Company. Piyush Desai has received speaker honoraria from Boehringer Ingelheim, Cipla, USV Private Limited, Novo Nordisk, and Sanofi. Indranil Bhattacharya and Rohit Arora are employees of Eli Lilly India Pvt. Ltd. and hold shares of Eli Lilly and Company. Erik Spaepen is an external contractor (Statistician) for Eli Lilly and Company.

Author contributions: All authors have made substantial contributions to all the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. All authors contributed equally.

Consent for publication: All authors have given their consent and approval of the final version to be submitted and published.

Clinical trial registration number: NCT04153981.

Supplementary Information

Enrollment

As a clause toward marketing approval, the Central Drugs Standard Control Organization for India recommended that Basaglar be studied in a minimum of 200 additional local subjects. Assuming a 15% screen failure rate, approximately 295 subjects were planned to be screened, so that 250 subjects could have been enrolled. Assuming a dropout rate of 20%, the target was to have a minimum of 200 subjects completing the present study. In case of hypoglycemia, the dose can be reduced by four units. It was recommended that the doses of antidiabetic medications taken by the subjects be stable for 90 days prior to enrolling them. However, the investigator can recommend that these doses be optimized to the maximum tolerated dose during 2 weeks of the screening period.\

References

1. Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–1053.
2. Nanditha A, Ma RCW, Ramachandran A, et al. Diabetes in Asia and the Pacific: Implications for the Global Epidemic. Diabetes Care 2016;39:472–485.
3. IDF. Diabetes Atlas Tenth edition 2021. (Accessed on 18 April 23). Retrieved from https://diabetesatlas.org/atlas/tenth-edition/.
4. Lin SD, Tsai ST, Tu ST, et al. Glycosylated hemoglobin level and number of oral antidiabetic drugs predict whether or not glycemic target is achieved in insulin-requiring type 2 diabetes. Prim Care Diabetes 2015;9:135–141.
5. Wangnoo SK, Maji D, Das AK, et al. Barriers and solutions to diabetes management: an Indian perspective. Indian J Endocrinol Metab 2013;17:594–601.
6. Davies MJ, Aroda VR, Collins BS, et al. Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2022;45:2753–2786.
7. Pharmacy times. Pharmacy times. (2019, 27 November). FDA Approves Insulin Glargine Injection for Pediatric Patients with Diabetes. Retrieved from https://www.pharmacytimes.com/view/fda-approves-insulin-glargina-injection-for-pediatric-patients-with-diabetes.
8. US Food and Drug Administration. (2015, December). BASAGLAR (insulin glargine injection), for subcutaneous use Initial U.S. Approval: 2000. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205692lbl.pdf. 2015 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205692Orig1s000TOC.cfm. Accessed on 18 April 2023.
9. European Medicine Agency- Abasaglar (previously Abrasia). (2014, 14 October). Retrieved from https://www.ema.europa.eu/en/medicines/human/EPAR/abasaglar-previously-abasria.
10. Blevins TC, Dahl D, Rosenstock J, et al. Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus®) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study. Diabetes Obes Metab 2015;17:726–733.
11. Rosenstock J, Hollander P, Bhargava A, et al. Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus®) in patients with type 2 diabetes who were insulin-naïve or previously treated with insulin glargine: a randomized, double-blind controlled trial (the ELEMENT 2 study). Diabetes Obes Metab 2015;17:734–741.
12. Mohan V, Ahn KJ, Cho YM, et al. Lilly Insulin Glargine Versus Lantus® in Type 2 Diabetes Mellitus Patients: India and East Asia Subpopulation Analyses of the ELEMENT 5 Study. Clin Drug Investig 2019;39:745–756.
13. Pollom RK, Ilag LL, Lacaya LB, et al. Lilly Insulin Glargine Versus Lantus(®) in Insulin-Naïve and Insulin-Treated Adults with Type 2 Diabetes: A Randomized, Controlled Trial (ELEMENT 5). Diabetes Ther 2019;10:189–203.

Table S1: List of complete inclusion and exclusion criteria for the study

Inclusion criteria

- Patients with T2DM based on the disease diagnostic criteria from the World Health Organization classification for at least 6 months before screening
- Men or nonpregnant women older than 18 years and younger than 75 years at the time of screening
- Patients receiving ≥2 OAMs ± GLP-1 RAs at stable doses for 90 days prior to screening
- Patients with HbA1c level ≥ 7.0% and < 11.0%
- Patients with no prior treatment with insulins except for short-term treatment of acute conditions up to a maximum of 14 days

Exclusion criteria

- Patients with any form of diabetes other than T2DM
- Patients with hypersensitivity to the active substance of LY2963016 or any of the excipients
- Patients who had any clinically significant disorder, other than T2DM, in the investigator's opinion
- Patients who preclude participation in the trial
- Patients receiving systemic glucocorticosteroid therapy or had excessive insulin resistance (total insulin dose >2 U/kg)
- Patients with a history or diagnosis of human immunodeficiency virus infection, hepatitis B, and C
- Patients with comorbidities of unstable angina, cardiac failure (Stage III or IV as per New York Heart Association guidelines), or renal failure (estimated glomerular filtration rate < 30 mL/minute/m^2)
- Patients who participated within 30 days of the clinical trial involving an investigational product other than LY2963016. If the previous investigational product had a long half-life, 3 months or 5 half-lives (whichever was longer) should have passed
- Patients who previously completed or withdrawn from this study or any other study investigating LY2963016. This exclusion criterion did not apply to participants who were rescreened prior to the baseline visit
- Patients enrolled in any other clinical study involving an investigational product or any other type of medical research who were judged not to be scientifically or medically compatible with this study and were unwilling or unable to comply with the use of a glucometer

GLP-1 RA, glucagon-like peptide 1 receptor agonist; HbA1c, glycated hemoglobin; OAMs, oral antihyperglycemic medications; T2DM, type 2 diabetes mellitus

Table S2: Recommendations for dose titrations

Fasting blood glucose (mg/dL)	*Fasting blood glucose (mmol/L)*	*Dose adjustments (units)*
<80	<4.4	−2
80–100	4.4–5.6	0
101–130	5.6–7.2	+2
131–160	7.3–8.9	+4
161–190	8.9–10.6	+6
>190	>10.6	+8

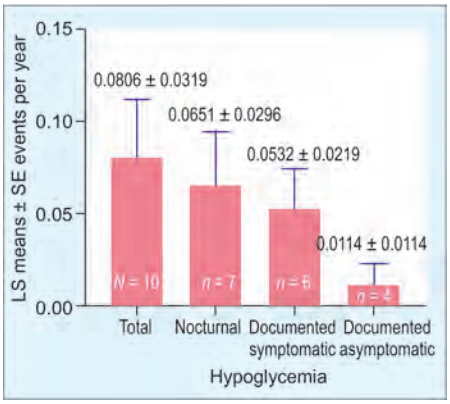

Fig. S1: Incidence of hypoglycemic events (weeks 0–24); LS, least squares; *n*, number of subjects with data; *N*, total number of subjects in the relevant population; SE, standard error

Table S3: Overall exposure to study treatment and compliance

	Basaglar—full analysis set (N = 259)	*Basaglar—per protocol (N = 207)*
Duration of exposure, days		
n (%)	259 (100.00)	207 (100.00)
Mean (SD)	157.8 (34.83)	170.4 (7.87)
IMP compliance %		
n (%)	259 (100.00)	207 (100.00)
Mean (SD)	99.9 (0.35)	100.0 (0.30)
Number of missed dose		
n (%)	259 (100.00)	207 (100.00)
Mean (SD)	0.1 (0.55)	0.1 (0.53)
Compliant patients		
n (%)	259 (100.00)	207 (100.00)

IMP, investigational medicinal product; *n*, number of subjects with data; *N*, total number of subjects in the relevant population; SD, standard deviation

Table S4: Incidences and rates of total hypoglycemic events

Total hypoglycemic events	*Basaglar—full analysis set (N = 259)*	*Basaglar—per protocol (N = 207)*
LSM ± SE per 30 days (95% CI)		
Weeks 0–24	0.0066 ± 0.00262 (0.0030, 0.0144)	0.0080 ± 0.00310 (0.0038, 0.0171)
Weeks 0–12	0.0088 ± 0.00398 (0.0036, 0.0213)	0.0111 ± 0.00486 (0.0047, 0.0262)
Weeks 12–24	0.0038 ± 0.00294 (0.0009, 0.0172)	0.0045 ± 0.00329 (0.0011, 0.0189)
LSM ± SE per year (95% CI)		
Weeks 0–24	0.0806 ± 0.03195 (0.0371, 0.1753)	0.0979 ± 0.03776 (0.0460, 0.2085)
Weeks 0–12	0.1072 ± 0.04843 (0.0442, 0.2599)	0.1346 ± 0.05920 (0.0568, 0.3187)
Weeks 12–24	0.0469 ± 0.03583 (0.0105, 0.2097)	0.0544 ± 0.04010 (0.0128, 0.2307)

CI, confidence interval; LSM, least squares mean; *N*, total number of subjects in the relevant population SE, standard error

Table S5: Insulin treatment satisfaction questionnaire scores indicating the change from baseline to week 24

	Basaglar—full analysis set (N = 259)	*Basaglar—per protocol (N = 207)*
Raw inconvenience of regimen		
LSM on LOCF imputed values, mean ± SE (95% CI)	−0.3 ± 0.04 (−0.3, −0.2)	−0.3 ± 0.05 (−0.4, −0.2)
p-value	<0.0001	<0.0001
Raw lifestyle flexibility		
LSM on LOCF imputed values, mean ± SE (95% CI)	−0.3 ± 0.05 (−0.3, −0.2)	−0.3 ± 0.05 (−0.4, −0.2)
p-value	<0.0001	<0.0001
Raw glycemic control		
LSM on LOCF imputed values, mean ± SE (95% CI)	−0.2 ± 0.05 (−0.3, −0.1)	−0.2 ± 0.06 (−0.3, −0.1)
p-value	0.0003	0.0008
Raw hypoglycemic control		
LSM on LOCF imputed values, mean ± SE (95% CI)	−0.3 ± 0.05 (−0.4, −0.2)	−0.3 ± 0.05 (−0.4, −0.2)
p-value	<0.0001	<0.0001
Raw insulin delivery device		
LSM on LOCF imputed values, mean ± SE (95% CI)	−0.3 ± 0.04 (−0.4, −0.2)	−0.4 ± 0.05 (−0.5, −0.3)
p-value	<0.0001	<0.0001
Transformed inconvenience of regimen		
LSM on LOCF imputed values, mean ± SE (95% CI)	4.3 ± 0.73 (2.9, 5.7)	4.8 ± 0.85 (3.1, 6.5)
p-value	<0.0001	<0.0001
Transformed lifestyle flexibility		
LSM on LOCF imputed values, mean ± SE (95% CI)	4.3 ± 0.75 (2.8, 5.7)	4.7 ± 0.86 (3.0, 6.4)
p-value	<0.0001	<0.0001
Transformed glycemic control		
LSM on LOCF imputed values, mean ± SE (95% CI)	3.2 ± 0.89 (1.5, 5.0)	3.5 ± 1.04 (1.5, 5.6)
p-value	0.0003	0.0008
Transformed hypoglycemic control		
LSM on LOCF imputed values, mean ± SE (95% CI)	4.7 ± 0.76 (3.2, 6.2)	5.4 ± 0.88 (3.7, 7.2)
p-value	<0.0001	<0.0001
Transformed insulin delivery device		
LSM on LOCF imputed values, mean ± SE (95% CI)	5.3 ± 0.72 (3.9, 6.7)	6.1 ± 0.84 (4.4, 7.7)
p-value	<0.0001	<0.0001

CI, confidence interval; LOCF, last-observation-carried-forward; LSM, least squares mean; *N*, total number of subjects in the relevant population; SE, standard error

ORIGINAL ARTICLE

Hospital-acquired Infections in the Adult Intensive Care Unit: Epidemiology, Resistance Patterns, and Risk Factors

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Abstract

Introduction: Hospital-acquired infections (HAIs) are defined as infections that develop in the patient after being admitted to the hospital. The overall burden of HAIs is known to be higher in developing countries. The most common HAIs include ventilator-associated pneumonia (VAP), catheter-associated urinary tract infection (CAUTI), surgical site infection (SSI), and catheter-related bloodstream infections (CRBSI).

Objectives: Due to limited recent literature, we aimed to evaluate the incidence rates and causative organisms of intensive care unit (ICU)-acquired infections at our tertiary care center and to determine the factors associated with mortality in patients with ICU-acquired infections.

Methods: Single-center prospective, observational study.

Results: The incidence rates in our study were: VAP incidence rate: 105/2681 = 39.1/1000 ventilator days, CRBSI incidence rate: 38/4871 = 7.8/1000 central venous catheter (CVC) days, CAUTI incidence rate: 54/11201 = 4.8/1000 urinary catheter days. *Acinetobacter baumannii* accounted for 41% of the infections in patients with VAP and 21% in patients with CRBSI. *E. coli* was the most common causative organism in the CAUTI group, accounting for 33% of the infections. Age >50 years, presence of hypotension on presentation, medical diagnosis, multiple ICU-acquired infections, and higher APACHE-II score on admission are the statistically significant determinants of the incidence of mortality in the overall group (*p*-value >0.05 for all).

Conclusion: Age >50 years, presence of hypotension on presentation, medical diagnosis, multiple ICU-acquired infections, and higher APACHE-II score on admission must be kept in mind as determinants of the incidence of mortality in HAIs.

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Introduction

Hospital-acquired infections (HAIs) are defined as those infections that develop in the patient after admission to the hospital. Infections that develop 48 hours or more after a patient has been admitted to the hospital are considered hospital-acquired. HAIs are known to be the most common adverse events in hospitalized patients, as per the World Health Organization (WHO).[1] The WHO estimates that these infections affect 7–12% of hospitalized patients around the globe.[2–4] A survey conducted in 55 hospitals from 14 countries demonstrated that 8.7% of the hospitalized patients had HAIs.[2] The overall burden of HAIs tends to be greater in developing countries.[5] Additionally, the prevalence of HAIs is highest among the patients admitted to intensive care units (ICUs).[2] Recent literature shows that about 2.5 million episodes of HAIs are reported in Europe every year, with over 90,000 deaths.[6] A prospective surveillance was conducted in 2007 by the International Infection Control Consortium (INICC) in 7 different Indian cities to determine the rate of HAIs, bacterial resistance, length of stay (LOS), and mortality outcomes in 12 ICUs in these hospitals.[7] In this study, a total of 10,835 patients were hospitalized for a period of 52,518 days, and these patients acquired 476 HAIs. The surveillance reported an overall incidence rate of healthcare-associated infections (HAIs) of 4.4%, equating to 9.06 infections per 1,000 ICU-days.[7]

HAIs contribute majorly to the mortality, length of stay (LOS) in the hospital and ICUs, emotional suffering, as well as the economic burden among hospitalized patients.[3,8] In a survey conducted by INICC across developing countries, including India, the crude mortality rate ranged from 35.2 to 44.9%.[9] There are a number of factors that add to the cost in these patients. The financial burden of HAIs is compounded by factors such as prolonged length of stay (LOS), increased use of expensive antibiotics and other drugs, additional laboratory tests, and the loss of work.

Ventilator-associated pneumonia (VAP), catheter-related bloodstream infections (CRBSI), catheter-associated urinary tract infection (CAUTI), and surgical site infection (SSI) are the most common HAIs. HAIs can be caused by various organisms depending on the healthcare settings, patient populations, and countries. Common Gram-positive organisms associated with HAIs are: *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), and enterococci, while Gram-negative organisms include *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Escherichia coli*.[2,10–15]

Due to limited recent literature, we aimed to evaluate the incidence rates and causative organisms of these ICU-acquired infections at our own tertiary care center and to determine the factors associated with mortality in patients with ICU-acquired infections.

Methods

A single-center prospective, observational study was conducted by us over a period of 18 months at our tertiary care center. Data for this study were collected from June 2021 to December 2022. Patients who were admitted to the ICU during the mentioned study period for >48 hours and diagnosed with one of the following infections: VAP, CAUTI, CRBSI, and

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CAUTI were included. We excluded patients <18 years of age, with an index ICU stay of <48 hours, or those who were readmitted to the ICU within the same hospitalization.

An informed and signed consent was obtained from all the patients before the data were collected from them. An Institutional Ethics Committee approval was obtained prior to the study.

Statistical Analysis

For categorical variables, the data are presented as the number of cases along with the percentage of total cases. For continuous variables, the data are displayed as the mean with the standard deviation (SD). The intergroup statistical comparison of the distribution of categorical variables was performed using the Chi-squared test or Fisher's exact probability test when >20% of cells had an expected frequency of <5. Multivariate logistic regression analysis with a backward stepwise procedure was employed to identify the independent statistically significant determinants of the incidence of mortality. In this study, a *p*-value of <0.05 was considered statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 24.0, IBM Corporation, United States) for MS Windows.

Acinetobacter baumannii accounted for 41% of the infections in patients with VAP and 21% in patients with CRBSI. The second most common organism in both of these groups was *Klebsiella pneumoniae*, accounting for 26% of the patients in the VAP group and 16% of the patients in the CRBSI group. *E. coli* was the most common causative organism in the CAUTI group, accounting for 33% of the infections, followed by *Klebsiella pneumoniae* (26%) (Figs 1A to C). Table 1 shows the distribution of drug resistance/sensitivity patterns in each type of infection.

Out of 105 cases with VAP, 23 cases (21.9%) died. Out of 38 cases with CRBSI infection, 9 cases (23.7%) died. Out of 54 cases with CAUTI infection, 14 cases (25.9%) died (Table 2). Univariate statistical analysis suggested that age-group (higher age-group, i.e., age >50 years), hypotension on presentation, diagnosis due to medical reasons, multiple ICU-acquired infections, and high APACHE-II score during admission are the statistically significant determinants of the incidence of mortality in the overall group (*p*-value <0.05 for all) (Table 3).

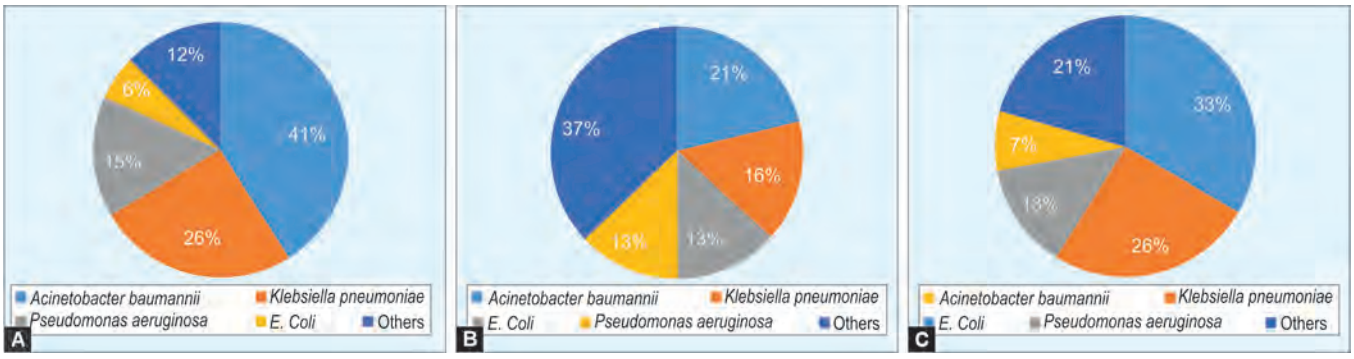
Multivariate statistical analysis revealed that the following factors were statistically significant and independent determinants of mortality incidence in the overall group: age-group (specifically those over 50 years), hypotension during presentation, diagnosis due to medical reasons, and higher APACHE-II score during admission (all with *p*-values <0.05) (Table 4). Figures 2A to D show the

Table 1: Distribution of drug resistance/sensitive pattern in each type of infection

Resistance rates for gram-negative organisms				
	MDR	*XDR*	*PDR*	*Carbapenem resistance*
Acinetobacter baumanii	85	7	–	89
Klebsiella pneumoniae/oxytoca	89	6	–	80
Pseudomonas aeruginosa	68	7	–	68
E. coli	82	–	–	71
Proteus mirabilis	100	–	–	100
Proteus vulgaris	100	–	–	100
Providentia rettgeri	66	33	–	100
Serratia marscencens	50	–	–	50
Morganella morganii	66	33		100
Resistance rates for gram-positive organisms				
	Methicillin resistant	*Vancomycin resistant*		*Linezolid resistant*
Staph. aureus (*n* = 3)	33	–		–
CoNs	100	–		
E. fecalis n = 3	NA	–		–
E. faecium n = 2	NA	50		50

Table 2: Incidence of mortality according to different types of infection

	Survived		*Death*		*Total*	
Infection	*n*	*%*	*n*	*%*	*n*	*%*
VAP	82	78.1	23	21.9	105	100.0
CRBSI	29	76.3	9	23.7	38	100.0
CAUTI	40	74.1	14	25.9	54	100.0



Figs 1A to C: Distribution of etiological agents of each type of infection. (A) Distribution of patients with VAP infection based on the etiological agents; (B) Distribution of patients with CRBSI infection based on the etiological agents; (C) Distribution of patients with CAUTI infection based on the etiological agents

Table 3: Univariate statistical analysis showing the determinants of mortality (overall group)

		Survived		*Death*		*Total*		*p-value*
Variable		*n*	*%*	*n*	*%*	*n*	*%*	
Age-group	≤50 years	57	89.1	7	10.9	64	100.0	0.010**
	>50 years	67	72.0	26	28.0	93	100.0	
Sex	Male	90	78.3	25	21.7	115	100.0	0.714^{NS}
	Female	34	81.0	8	19.0	42	100.0	
Hypotension on presentation	Yes	37	60.7	24	39.3	61	100.0	0.001***
	No	87	90.6	9	9.4	96	100.0	
Diagnosis	Medical	62	70.5	26	29.5	88	100.0	0.003**
	Surgical	62	89.9	7	10.1	69	100.0	
Comorbidity	Hypertension	50	75.8	16	24.2	66	100.0	0.399^{NS}
	Diabetes mellitus	35	74.5	12	25.5	47	100.0	0.364^{NS}
	Ischemic heart disease	9	81.8	2	18.2	11	100.0	0.999^{NS}
	Chronic kidney disease	6	66.7	3	33.3	9	100.0	0.398^{NS}
	Chronic liver disease	3	100.0	0	0.0	3	100.0	0.999^{NS}
	Cerebrovascular accident	1	50.0	1	50.0	2	100.0	0.377^{NS}
	Hypothyroid/hyperthyroid	1	100.0	0	0.0	1	100.0	0.999^{NS}
Type of infection	Single infection	100	82.6	21	17.4	121	100.0	0.039*
	Multiple infections	24	66.7	12	33.3	36	100.0	
Use of steroids	Yes	1	50.0	1	50.0	2	100.0	0.377^{NS}
	No	123	79.4	32	20.6	155	100.0	
APACHE II score	Group 1 (21–30)	13	52.0	12	48.0	25	100.0	0.001***
	Group 2 (11–20)	75	79.8	19	20.2	94	100.0	
	Group 3 (3–10)	36	94.7	2	5.3	38	100.0	
ICU stay	≤20 days	64	78.0	18	22.0	82	100.0	0.764^{NS}
	>20 days	60	80.0	15	20.0	75	100.0	

Odds ratio = 1: reference category; dependent variable: mortality; *p-value < 0.05; **p-value < 0.01; ***p-value < 0.001; NS, statistically nonsignificant; The variables entered in the model: Age, sex, comorbidity (hypertension, diabetes mellitus, IHD, CKD, CLD, CVA, hyperthyroidism/hypothyroidism), hypotension on presentation, diagnosis, steroid treatment, APACHE-II score on presentation, duration of ICU stay

percentage sensitivity of predominant Gram-negative bacilli.

Discussion

Our study found that the rates of VAP, CRBSI, and CAUTI were 39.1 per 1,000 ventilator days, 7.8 per 1,000 central venous catheter (CVC) days, and 4.8 per 1,000 urinary catheter days, respectively (Table 5). This incidence was found to be higher than that observed in a few studies. A study by Kwak et al. found the incidence rates of VAP, CRBSI, and CAUTI to be 1.89/1,000 mechanical ventilator days, 2.23/1,000 central line days, and 3.87/1,000 urinary catheter days, respectively.[16] However, a study from Morocco by Madani et al. noted a much higher incidence of these infections. In their study, rates of VAP, CRBSI, and CAUTI were 43.2 per 1,000 ventilator days, 15.7 per 1,000 CVC days, and 11.7 per 1,000 urinary catheter days, respectively.[17]

In our study, *Acinetobacter baumannii* was found to be the commonest organism causing VAP, followed by *Klebsiella pneumoniae*. The findings were similar for the cases with CRBSI. The type of organism responsible for causing VAP depends on the duration of mechanical ventilation. Organisms causing early-onset VAP are typically *Haemophilus influenzae*, *Streptococcus pneumoniae*, methicillin-sensitive *Staphylococcus aureus* (MSSA), *Escherichia coli*, **Enterobacter* species, *Klebsiella pneumoniae*, *Proteus* species, and

Table 4: Multivariate logistic regression analysis showing the independent determinants of incidence of mortality (backward stepwise procedure)

Risk factors (variables in the model)			*Odds ratio (OR)*	*95% CI for odds Ratio*	*p-value*
Overall group	Age-group	≤50 years	1.00	–	–
		>50 years	2.986	1.053–8.471	0.040*
	Hypotension	Absent	1.00	–	–
		Present	6.410	2.454–16.742	0.001***
	Diagnosis	Surgical	1.00	–	–
		Medical	3.270	1.141–9.368	0.027*
	APACHE- II score	Group 3 (3–10)	1.00	–	–
		Group 2 (11–20)	3.438	0.688–17.188	0.133^{NS}
		Group 1 (21–30)	17.851	2.946–108.163	0.002**
VAP group	Hypotension	Absent	1.00	–	–
		Present	15.251	3.987–58.337	0.001***
	Diagnosis	Surgical	1.00	–	–
		Medical	4.905	1.477–16.291	0.009**
CRBSI group	NA				
CAUTI group	Age-group	≤50 years	1.00	–	–
		>50 years	20.456	1.946–109.333	0.019*
	IHD	Absent	1.00	–	–
		Present	28.211	1.694–259.378	0.026*
	APACHE- II score	Group 3 (3–10)	1.00	–	–
		Group 2 (11–20)	0.199	0.013–3.101	0.249^{NS}
		Group 1 (21–30)	11.685	0.358–281.924	0.167^{NS}

Odds ratio = 1: reference category; dependent variable: mortality; *p-value < 0.05; **p-value < 0.01; ***p-value < 0.001; NS, statistically nonsignificant; The variables entered in the model: Age, sex, comorbidity (hypertension, diabetes mellitus, IHD, CKD, CLD, CVA, hyperthyroidism/hypothyroidism), hypotension on presentation, diagnosis, steroid treatment, APACHE-II score on presentation, duration of ICU stay

Serratia marcescens. Late-onset VAP is usually caused by *Acinetobacter*, methicillin-resistant *S. aureus* (MRSA), *Pseudomonas aeruginosa*, and extended-spectrum beta-lactamase producing bacteria (ESBL).[18] The causative agent is important, as the cost of therapy and outcomes can vary significantly.

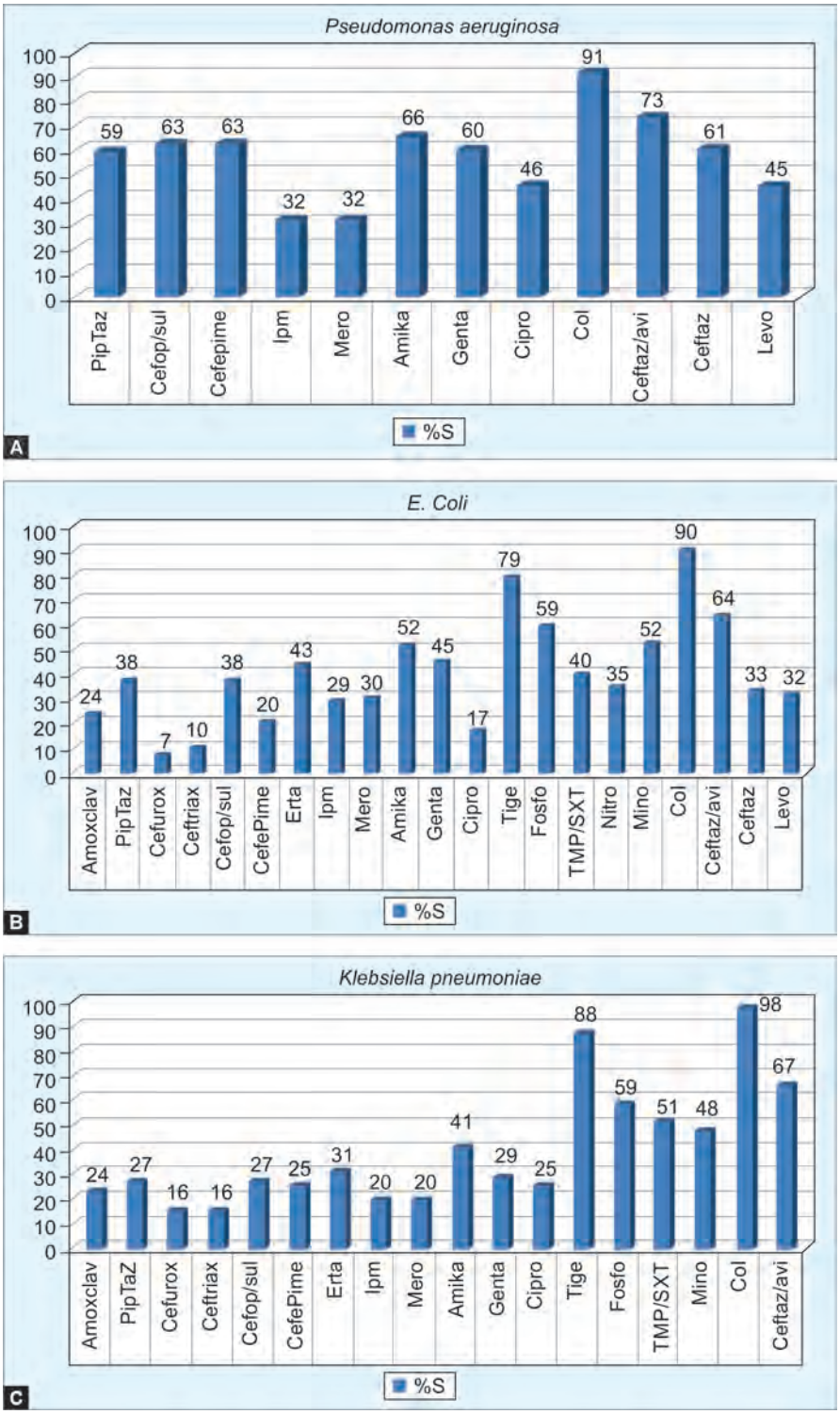
As shown in Table 2, the resistance rates in our settings are high. A report published by the Antimicrobial Resistance Research and Surveillance Network (AMRSN) stated that the incidence of carbapenem resistance was extremely high in *Acinetobacter baumannii* in India in the year 2021.[19] These high rates of resistance can leave very few treatment options for these infections and make the management of HAIs very challenging in India. This can also increase the cost of therapy. Such high resistance rates make it difficult for the treating physicians to choose empiric therapy.

As shown in Table 3, these infections were associated with significant crude mortality rates in our settings. In a study by Papazian et al.,[20] it was demonstrated that, on controlling the confounding factors, VAP did not increase the overall mortality in patients admitted to the ICU. Another systematic analysis by Safdar et al.[21] found results contradictory to the above findings. It was concluded that VAP is significantly associated with substantial morbidity and a twofold increase in the overall mortality rate. A meta-analysis conducted in 2009 derived the conclusion that the presence of CRBSI is associated with a significantly higher mortality in critically ill patients.[22] A study by Blot et al.[23] showed results that were contradictory to the above, demonstrating that the presence of CRBSI does not lead to an increased mortality rate in ICU patients. However, the authors also stated that the infection must be prevented due to the economic burden that it may impose.[23] With regard to CAUTI, Clec'h et al. demonstrated that CAUTI was not associated with an increase in the mortality rate in the ICU.[24]

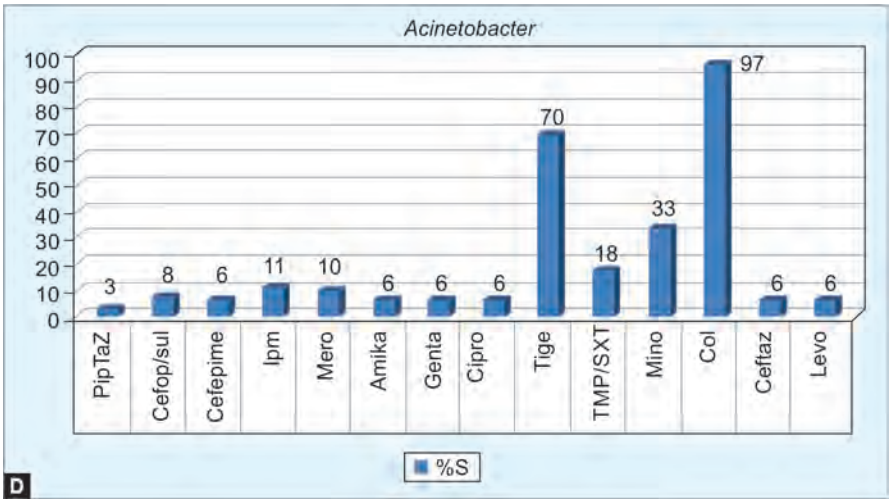
Our study showed that a higher age-group and a higher APACHE II score on admission are associated with an increased overall mortality in patients with HAIs in the ICU. Similar to the results of our study, a study by Nielsson et al. concluded that advanced age is associated with an increase in the mortality rate in patients admitted to the ICU.[25] Contradictory to this, Edipoglu et al. found that age was not significantly associated with mortality in ICU patients. However, they also demonstrated that a higher APACHE II scoring system is valuable in assessing overall mortality.[26] A study by Gursel and Demirtas, conducted prospectively on patients with VAP, concluded that the APACHE II score determined at the time of diagnosis of

Table 5: Incidence rates of three HAIs

	Infection status							
	Present		*Absent*		*Total*		*Per 1,000 days*	
Type	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
VAP	105	3.92	2576	96.08	2681	100.0	1000	39.1
CRBSI	38	0.78	4833	99.21	4871	100.0	1000	7.8
CAUTI	54	0.48	11147	99.52	11201	100.0	1000	4.8



Figs 2A to D: Percentage sensitivity of predominant gram-negative bacilli *(Contd...)*



Figs 2A to D: *Contd...*

VAP is valuable in predicting the mortality in ICU patients.[27] A recent study by Sadaka et al. also demonstrated that the APACHE II scoring system, applied in septic patients, is a strong predictor of overall mortality.[28]

Conclusion

In our setting, VAP was found to have the highest incidence rate with regard to the HAIs. *Acinetobacter baumannii* was the most common causative organism in patients with VAP and CRBSI admitted to the ICU. The second most common organism in these groups was *Klebsiella pneumoniae*. However, the most common causative organism in the CAUTI group was found to be *E. coli*. In our study, the statistically significant factors influencing the incidence of mortality in the overall group included age (with higher mortality in patients older than 50 years), presence of hypotension at presentation, medical diagnosis, multiple ICU-acquired infections, and a higher APACHE-II score upon admission.

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References

1. WHO. Report on the Burden of Endemic Health Care-Associated. Infection Worldwide Clean Care is Safer Care. 2011:1–40. Available at: https://apps.who.int/iris/bitstream/handle/10665/80135/9789241501507_eng.pdf;sequence=1. Accessed February 18, 2020.
2. WHO 2002.Prevention of hospital acquired infections. A practical guide. 2nd Edition. [Online]. Available from: URL: http://www.who.int/csr/resources/publications/whocdscsreph200212.pdf
3. Patel DA, Patel KB, Bhatt SK, et al. Surveillance of hospital acquired infection in surgical wards in tertiary care centre Ahmedabad, Gujarat. Nat J Commun Med 2011;2(3):340.
4. Ahmad I, Saleem M,Vaish AK, et al. Prevalence of nosocomial infections in surgical wards of tertiary care hospital at Lucknow. Ind J Sci Res 2012;3(2):79–84.
5. Allegranzi B, Bagheri Nejad S, Combescure C, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. Lancet 2011;377(9761):228.
6. Cassini A, Plachouras D, Eckmanns T, et al. Burden of six healthcare-associated infections on European population health: estimating incidence-based disabilityadjusted life years through a population prevalence-based modelling study. PLoS Med 2016;13:1.
7. Mehta A, Rosenthal VD, Mehta Y, et al. Device-associated nosocomial infection rates in intensive care units of seven Indian cities. Findings of the International Nosocomial Infection Control Consortium (INICC). J Hosp Infect 2007;67(2):168.
8. Chugh TD. Hospital Infection Control – Are we serious? Medical update 2012. [Online] Available from: URL: http://www.apiindia.org/pdf/medicine_update_2012/infectious_disease_14.pdf
9. Rosenthal VD, Maki DG, Salomao R, et al. International Nosocomial Infection Control Consortium. Device-associated nosocomial infections in 55 intensive care units of 8 developing countries. Ann Intern Med 2006;145(8):582–591.
10. Kamat U, Ferreira A, Savio R, et al. Antimicrobial resistance among nosocomial isolates in a teaching hospital in Goa. Indian J Community Med 2008;33(2):89–92.
11. Safdar N, Maki DG. Risk of catheter-related bloodstream infection with peripherally inserted central venous catheters used in hospitalized patients. Chest 2005;128(2):489.
12. Singh S, Pandya Y, Patel R, et al. Surveillance of device-associated infections at a teaching hospital in rural Gujarat-India. Ind J Med Microbiol 2010;28(4):342.
13. Ghadiri H, Vaez H, Khosravi S, et al. The antibiotic resistance profiles of bacterial strains isolated from patients with hospital-acquired bloodstream and urinary tract infections. Crit Care Res Pract 2012;2012:890797.
14. Chawla R. Epidemiology, etiology, and diagnosis of hospital-acquired pneumonia and ventilator-associated pneumonia in Asian countries. Am J Infect Control 2008;36(4 Suppl):S93–S100.
15. Mathai E, Kaufmann ME, Richard VS, et al. Typing of Acinetobacter baumannii isolated from hospital-acquired respiratory infections in a tertiary care centre in southern India. J Hosp Infect 2001;47(2):159.
16. Kwak YG, Lee SO, Kim HY, et al. Risk factors for device-associated infection related to organisational characteristics of intensive care units: findings from the Korean Nosocomial Infections Surveillance System. J Hosp Infect 2010;75(3):195.
17. Madani N, Rosenthal VD, Dendane T, et al. Health-care associated infections rates, length of stay, and bacterial resistance in an intensive care unit of Morocco: findings of the International Nosocomial Infection Control Consortium (INICC). Int Arch Med 2009;2(1):1–7.
18. Hunter JD. Ventilator associated pneumonia. BMJ 2012;344:e3325.
19. Annual report (January 2021 to December 2021) of the Antimicrobial Resistance Research & Surveillance Network (AMRSN), Division of epidemiology and communicable diseases, Indian Council of Medical Research; 2021:6.
20. Papazian L, Bregeon F, Thirion X, et al. Effect of ventilator-associated pneumonia on mortality and morbidity. Am J Respir Crit Care Med 1996;154(1):91.
21. Safdar N, Dezfulian C, Collard HR, et al. Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. Crit Care Med 2005;33(10):2184.
22. Siempos II, Kopterides P, Tsangaris I, et al. Impact of catheter-related bloodstream infections on the mortality of critically ill patients: a meta-analysis. Crit Care Med 2009;37(7):2283.
23. Blot SI, Depuydt P, Annemans L, et al. Clinical and economic outcomes in critically ill patients with nosocomial catheter-related bloodstream infections. Clin Infect Dis 2005;41(11):1591.
24. Clec'h C, Schwebel C, Français A, et al. Does catheter-associated urinary tract infection increase mortality in critically ill patients? Infect Control Hosp Epidemiol 2007;28(12):1367.
25. Nielsson MS, Christiansen CF, Johansen MB, et al. Mortality in elderly ICU patients: a cohort study. Acta Anaesthesiol Scand 2014;58(1):19.
26. Edipoglu IS, Dogruel B, Dizi S, et al. The association between the APACHE-II scores and age groups for predicting mortality in an intensive care unit: a retrospective study. Rom J Anaesth Intensive Care 2019;26(1):53.
27. Gursel G, Demirtas S. Value of APACHE II, SOFA and CPIS scores in predicting prognosis in patients with ventilator-associated pneumonia. Respiration 2006;73(4):503.
28. Sadaka F, EthmaneAbouElMaali C, Cytron MA, et al. Predicting mortality of patients with sepsis: a comparison of APACHE II and APACHE III scoring systems. J Clin Med Res 2017;9(11):907.

REVIEW ARTICLE

Biomarkers of Gestational Diabetes Mellitus: Mechanisms, Advances, and Clinical Utility

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Abstract

Gestational diabetes mellitus (GDM) continues to pose a significant challenge to maternal and fetal health, driving the need for advanced diagnostic and therapeutic strategies. Biomarker discovery has proven essential for early detection, mechanistic insights, and targeted interventions. This review provides an in-depth examination of biomarkers related to GDM, focusing on glucose metabolism, insulin resistance, inflammatory signaling, adipokines, oxidative stress markers, and genetic/epigenetic determinants. We also evaluate novel biomarkers emerging from omics technologies and their translational potential in clinical practice. Additionally, we explore the role of microRNAs and extracellular vesicles as emerging biomarkers that could offer new perspectives on GDM pathophysiology. Integration of these biomarkers into predictive models holds the potential to improve risk assessment and patient health outcomes.

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Introduction

Gestational diabetes mellitus (GDM), identified as glucose intolerance that arises or is first detected during pregnancy, impacts approximately 13% of pregnancies worldwide.[1,2] This definition overlooks the distinction that GDM does not include women previously diagnosed with type 1 or type 2 diabetes mellitus (T1D or T2D) prior to pregnancy, which is called "diabetes in pregnancy" (DIP), and this group is linked to higher rates of maternal and fetal complications.[3] FIGO recommends using the term "hyperglycemia in pregnancy" (HIP) to encompass both GDM and preexisting DIP.[4] In India, this prevalence is estimated to be between 15 and 18%, reflecting a growing public health challenge.[5–8] In Russia, GDM is also very frequent, with 13.6% of pregnant women estimated to have GDM.[9] GDM contributes significantly to adverse maternal and fetal outcomes.[10–12] GDM poses risks such as preeclampsia, fetal macrosomia, and long-term metabolic disturbances, including an increased predisposition to T2D in mothers.[12–15] Moreover, children of mothers with GDM are at a higher risk of developing obesity, T2D, and cardiovascular diseases (CVD) as they grow older.[16,17]

Addressing this issue effectively requires targeted interventions and best management strategies to reduce these risks and improve outcomes for both mothers and their children.

Several studies, such as the TOBOGM (Treatment of Booking Diabetes Mellitus) study,[18] the WINGS (Women in India with GDM Strategy) study,[19,20] and the STRIDE (STratification of Risk of Diabetes in Early pregnancy) study,[21] have provided valuable insights into screening, risk stratification, and management of GDM in India. The WINGS study demonstrates the effectiveness of structured screening programs and follow-up care in improving maternal and fetal outcomes, advocating for widespread implementation of GDM screening guidelines.[22] Additionally, the STRIDE study has been instrumental in providing a threshold for early pregnancy screening using HbA1c and routinely collected maternal data to identify a subgroup of women, in early pregnancy, who are at the highest risk of developing GDM. This has the potential to offer intervention to this subgroup for prevention.[21]

While these studies have enhanced screening and glycemic management strategies, there is still a need for more personalized approaches to treatment. The identification of reliable biomarkers is essential in addressing this gap, as these contribute to a better understanding of the pathophysiology of GDM and present opportunities for more focused therapeutic interventions.[23,24] An ideal biomarker for GDM would offer two primary benefits: it could significantly reduce unnecessary testing by efficiently identifying women at low risk, simplifying the prenatal care process. Additionally, it enables the early identification of women at higher risk, facilitating prompt intervention and targeted preventive measures. This review aims to consolidate current and emerging biomarkers of GDM (Table 1), emphasizing their mechanistic roles and clinical relevance, with a particular focus on their implications in the Indian and Russian context.

Glucose Metabolism Markers

Fasting Plasma Glucose

Fasting plasma glucose (FPG) is a key component in diagnosing GDM, defining a threshold of ≥92 mg/dL for diagnosis, indicating impaired glucose homeostasis.[25,26] Elevated FPG levels, reflecting hepatic insulin resistance and increased glucose production, are central to the pathophysiology of GDM.[27] However, various studies suggest that the optimal FPG cut point may vary. For instance, the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study identified increased risks of adverse outcomes at lower FPG cut points, leading to recommendations for a threshold of ≥95 mg/dL.[12] Additionally, multiple studies found that different cut points, such as ≥90 mg/dL and ≥100 mg/dL, were linked with varying risks of complications,[28,29] underscoring the need

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Table 1: Biomarkers for GDM—timing, significance, and limitations

Biomarker	*Timing for test in GDM*	*Significance in GDM*	*Limitations*
Preconception or early pregnancy			
Genetic variants	Preconception or early pregnancy (genetic testing)	Can identify risk variants associated with GDM	Genetic predisposition alone does not predict GDM development; complex interaction with environment
Epigenetic modifications	Preconception or early pregnancy	Can show heritable changes in gene expression related to GDM	Experimental; not yet applicable in routine clinical practice
Early pregnancy			
Adiponectin	Early pregnancy	Low levels are associated with insulin resistance and GDM	Limited availability of assays; influenced by obesity and other metabolic conditions
Metabolomics	Early pregnancy	Profiles metabolic changes that may indicate risk for GDM	High cost; complex interpretation; still in research phase
Proteomics	Early pregnancy	Identifies protein markers that could predict GDM risk	Expensive; complex data analysis; not yet used in clinical practice
MicroRNAs	Early pregnancy	Potential biomarkers For GDM diagnosis and prognosis	Limited clinical use; requires further validation and standardization
Ficolin-3	Early pregnancy	A novel biomarker that may be linked to inflammation and insulin resistance in GDM	Early research; not validated for clinical use in GDM diagnosis or management
F2-isoprostanes	Early pregnancy	Sensitive marker of oxidative stress, may be elevated in GDM	High cost; difficult to standardize; nonspecific to GDM
Early to mid-pregnancy			
Insulin and C-peptide levels	Early to mid-pregnancy	Reflects insulin secretion and pancreatic beta-cell function	Variability in assays; not routinely used for diagnosis; limited by fasting and circadian changes
C-reactive protein	Early to mid-pregnancy	Marker of inflammation, which is elevated in GDM	Nonspecific marker of inflammation; elevated in other conditions
Leptin	Early to mid-pregnancy	Associated with insulin resistance and obesity, common in GDM	Influenced by body mass index and other metabolic conditions
Nesfatin-1	Early to mid-pregnancy	May regulate glucose metabolism and insulin sensitivity in GDM	Limited studies; unclear clinical utility in routine diagnosis
Fasting plasma glucose	Early pregnancy or at 24–28 weeks	Indicator of baseline glucose metabolism; commonly used for GDM diagnosis	May miss postprandial hyperglycemia; poor sensitivity in early GDM diagnosis
Mid-pregnancy			
Oral glucose tolerance test	24–28 weeks	Gold standard for diagnosing GDM based on glucose levels after a glucose challenge	Time-consuming; requires fasting; patient discomfort
Any time in pregnancy			
HOMA-IR	Any time in pregnancy	Assesses insulin resistance, which increases in GDM	Requires fasting insulin and glucose measurements; not routinely used in clinical practice
Malondialdehyde	Throughout pregnancy	Marker of oxidative stress, elevated in GDM	Not widely available; oxidative stress markers can be nonspecific
1,5-anhydroglucitol	Throughout pregnancy	Reflects short-term postprandial hyperglycemia; low levels indicate poor glucose control	Not commonly used in routine GDM diagnosis; expensive; not always correlated with other measures

for a multiparametric diagnostic approach. Integrating FPG with other measures, like the 75 gm oral glucose tolerance test (OGTT), enhances diagnostic accuracy and risk prediction for adverse maternal and fetal outcomes, including macrosomia and preeclampsia.[30] Therefore, a comprehensive approach that incorporates FPG alongside additional metabolic parameters ensures a more accurate assessment of glucose intolerance and informs effective intervention strategies.

Oral Glucose Tolerance Test

This is a diagnostic test that involves a 1-hour (≥180 mg/dL) and 2-hour (≥153 mg/dL) postglucose values rather than a biomarker, used for assessing specific health conditions.[25] The OGTT is still considered the gold standard for GDM diagnosis, as it effectively evaluates both insulin secretion and glucose metabolism over time. By assessing glucose levels at fasting, as well as 1-hour and 2-hour intervals following a 75 gm glucose load, the dynamic interplay between fasting and postprandial glucose excursions provides insights into beta-cell responsiveness and resistance to insulin in peripheral tissues. The glucose challenge-induced hyperglycemia reveals underlying impaired beta-cell function and insulin

resistance in the liver.[31] However, despite its utility, the OGTT has several drawbacks. One major limitation is the variability in glucose thresholds across different populations, complicating the establishment of a universal diagnostic standard.[32,33] Additionally, the test requires significant time (2–3 hours) and can cause discomfort due to nausea and vomiting, leading to poor patient compliance. Factors such as stress or illness can influence glucose readings, increasing the risk of false positives or negatives.[34]

Glycated Hemoglobin

In the context of GDM, HbA1c has been explored for both diagnostic and prognostic purposes. Mechanistically, HbA1c formation is driven by the nonenzymatic glycation of hemoglobin, with higher glucose concentrations leading to increased glycation.

Despite the dynamic shifts in glucose metabolism during pregnancy, HbA1c is not typically utilized for the diagnosis of GDM. Recent advances have highlighted its potential utility in identifying women at risk of adverse pregnancy outcomes, such as preeclampsia and macrosomia.[35] A recent study revealed that early pregnancy HbA1c levels, either alone or in combination with factors such as age, BMI, and family history, were strongly linked to the risk of developing GDM between 24 and 28 weeks. The adjusted risk ratios were 1.60 (95% CI 1.19–2.16) in India, 3.49 (95% CI 2.80–4.34) in Kenya, and 4.72 (95% CI 3.82–5.82) in the UK. Using a composite risk score model could potentially decrease the reliance on OGTTs by 50–64%. The HbA1c thresholds for diagnosing or ruling out GDM varied across regions, with rule-in and rule-out values of 5.4 and 4.9% in India, 6.0 and 5.2% in Kenya, and 5.6 and 5.2% in the UK.[21]

Clinically, HbA1c offers a practical advantage as it does not require fasting, making it a convenient marker for follow-up assessments in GDM management.[36] However, its sensitivity in predicting GDM remains lower compared to traditional oral glucose tolerance tests.[37,38] Certain conditions, like hemoglobinopathies (e.g., thalassemias, Hb variants) and iron-deficiency anemia, can interfere with accurate HbA1c measurement, which is more prevalent in regions like India.[39] Further research is required to confirm its role in early pregnancy screening and risk assessment.

Insulin Sensitivity and Secretion Markers

Homeostasis Model Assessment of Insulin Resistance

Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) is a commonly used method for estimating insulin resistance by integrating fasting insulin and glucose concentrations, providing a surrogate marker for hepatic insulin sensitivity. In the context of GDM, elevated HOMA-IR values are indicative of significant insulin resistance, a hallmark of the disorder. This increase in insulin resistance reflects impaired insulin signaling, specifically to the insulin receptor and its downstream signaling pathways, including the AKT/PKB cascade, which is critical for glucose uptake and glycogen synthesis.[40] Research has demonstrated that in women with GDM, HOMA-IR levels are significantly elevated compared to those in normoglycemic pregnancies, highlighting the disruption in insulin receptor function and its downstream metabolic effects.[41] This impairment is further exacerbated by pregnancy-induced hormonal changes, including elevated placental hormones such as human placental lactogen (hPL) and progesterone, which impair insulin resistance during pregnancy.[42] Research also suggests that HOMA-IR may predict not only the severity of GDM but also the likelihood of postpartum metabolic complications.[43] Given its noninvasive and cost-effective nature, HOMA-IR is a valuable tool for assessing insulin resistance in GDM at any time during pregnancy, although its limitations, such as reliance on fasting measures alone, necessitate careful interpretation in clinical settings.

Insulin and C-Peptide Concentrations in Gestational Diabetes Mellitus

Elevated insulin and C-peptide levels in individuals with GDM reflect a compensatory response of the pancreatic beta cells to increased insulin resistance, a defining characteristic of GDM. Normally, insulin and C-peptide are released together from pancreatic beta cells in equal amounts, but C-peptide is considered a more reliable marker of endogenous insulin secretion because it has a longer half-life.[44] In GDM, insulin resistance rises significantly during the second and third trimesters, largely due to placental hormones like human placental lactogen (hPL), progesterone, and cortisol, which interfere with insulin's effects on target tissues.[45] As insulin resistance worsens, beta cells initially respond by ramping up insulin production to compensate, leading to elevated insulin and C-peptide concentrations in circulation.[46] However, in late pregnancy, the disproportionate rise in C-peptide compared to insulin suggests potential alterations in insulin clearance or changes in the kinetics of insulin secretion.[47] This variation might be attributed to enhanced hepatic insulin clearance, leading to elevated levels of circulating C-peptide in comparison to insulin. Furthermore, elevated C-peptide levels are often seen as a marker of beta-cell stress, indicating that while beta cells are compensating for insulin resistance, they are also under considerable strain, potentially leading to beta-cell dysfunction if this compensatory mechanism fails. From a pathophysiological perspective, the persistence of elevated C-peptide and insulin levels in GDM individuals suggests that while there is compensatory hyperinsulinemia, it is not always sufficient to address the insulin resistance, particularly in the postprandial state. This disruption in glucose regulation leads to hyperglycemia and increases the risk of negative maternal and fetal outcomes, such as macrosomia and neonatal hypoglycemia.[48] Moreover, understanding these shifts in insulin and C-peptide dynamics is critical for evaluating beta-cell reserve and functional capacity in GDM, which can have implications for long-term metabolic health. Monitoring both insulin and C-peptide levels, therefore, provides important insight into the underlying pathophysiology of GDM and its potential progression to future metabolic disorders.

Sex Hormone Binding Globulin

Sex hormone binding globulin (SHBG) has gained recognition as an early biomarker for GDM.[49] Low levels of SHBG in early pregnancy have consistently been linked to a higher risk of developing GDM during the 24–28-week gestational period. This association suggests that SHBG could serve as an early marker for GDM risk.[50] SHBG is crucial in regulating insulin sensitivity and glucose metabolism, with reduced levels reflecting insulin resistance, a defining characteristic of GDM.[51] Various studies have shown that combining early pregnancy SHBG measurements with other risk factors improves the prediction of GDM.[52] This composite risk scoring model can significantly reduce the need for OGTTs, especially in resource-limited settings, by stratifying women into risk categories. SHBG thresholds for diagnosing GDM vary across populations, and its sensitivity adds to its limitation,[53] but its inclusion in screening strategies provides a simple, reproducible, and efficient method for identifying women at high risk, enabling earlier interventions to enhance both maternal and fetal outcomes.

Quantitative Insulin Sensitivity Check Index

Quantitative insulin sensitivity check index (QUICKI) serves as an important indicator for evaluating insulin sensitivity in the context of GDM. QUICKI is calculated from fasting insulin and glucose levels and offers a dependable measure of insulin sensitivity,

which is frequently diminished in women with GDM.[54] Research indicates that lower QUICKI values during early pregnancy are predictive of GDM onset, as they signify underlying insulin resistance, a central factor in the pathophysiology of GDM.[41] When used alongside insulin secretion markers such as fasting insulin and C-peptide, QUICKI can improve the identification of women at high risk for developing GDM.[55] Its simplicity and efficiency make it a useful tool for early screening, especially in low-resource settings, reducing the dependence on more burdensome tests like the OGTT. Incorporating QUICKI into a composite risk score can also improve the prediction of adverse pregnancy outcomes related to GDM.

Urinary Markers

Urinary L-Tryptophan

Urinary L-tryptophan excretion has gained attention in the context of metabolic disorders, including GDM.[56] The urinary excretion of L-tryptophan and its metabolites, such as kynurenine, reflects disturbances in tryptophan metabolism, which are often linked to inflammatory and oxidative stress pathways.[57] In GDM, altered tryptophan metabolism could play a role in the development of insulin resistance and disrupted glucose regulation, with increased excretion potentially indicating a dysregulation in the kynurenine pathway.[58] This dysregulation can enhance oxidative stress and immune activation, further exacerbating the metabolic disturbances observed in GDM. Through targeted and untargeted metabolomic analysis, the integration of both plasma and urine metabolites enhanced the accuracy of GDM prediction, with an AUC of 0.99.[59] Monitoring urinary L-tryptophan and its metabolites could thus serve as a noninvasive biomarker for assessing metabolic stress and insulin resistance in pregnant women.

L-Urobilinogen

L-urobilinogen, a bile pigment derivative formed from the breakdown of hemoglobin, has been explored as a potential indicator in numerous metabolic disorders, including GDM. Its presence in urine reflects liver function and gut microbial activity, both of which can be affected by metabolic changes during pregnancy.[59] In GDM, altered glucose metabolism may influence liver function, potentially leading to elevated levels of L-urobilinogen.[60] Additionally, the dysbiosis of gut microbiota, commonly observed in GDM, could impact urobilinogen metabolism.[61] Increased urinary L-urobilinogen levels may thus serve as an indicator of hepatic or gut-related metabolic disturbances in GDM, presenting a possible noninvasive biomarker for the early diagnosis and monitoring of the disease. Additional research is needed to explore its precise role and diagnostic significance in the pathology of GDM.

Ceramides

Ceramides, a class of bioactive sphingolipids, have been implicated in insulin resistance and inflammation,[62] both of which are key features of GDM. Recent studies suggest that urinary ceramide levels may reflect underlying metabolic disturbances in GDM, as ceramides play a crucial role in lipid metabolism, cell signaling, and apoptosis. Elevated urinary ceramide levels in GDM individuals may indicate disrupted lipid homeostasis and play a role in the development of insulin resistance, a common feature of GDM.[59] Additionally, ceramides are linked to oxidative stress and inflammation, which further exacerbate glucose intolerance during pregnancy.[63] Measuring ceramide levels in urine may serve as a noninvasive biomarker for the early identification and progression of GDM, providing perspectives into the pathophysiology of the disease and prospective treatment targets for managing metabolic dysfunction in pregnant women. Further investigations are necessary to validate the diagnostic utility of urinary ceramides in GDM.

21-Deoxycortisol

21-deoxycortisol, a steroid intermediate in the biosynthesis of cortisol, has been studied in various metabolic and endocrine disorders.[64] In GDM, the hormonal and metabolic environment is significantly altered, often leading to disruptions in the hypothalamic-pituitary-adrenal (HPA) axis.[65] This disruption may result in abnormal levels of steroid intermediates like 21-deoxycortisol. Elevated levels of 21-deoxycortisol could indicate impaired steroidogenesis or dysregulation of adrenal function, both of which are relevant to the insulin resistance and glucose intolerance seen in GDM.[66] A recent study revealed that women who later developed GDM had elevated levels of 21-deoxycortisol during the first trimester, compared to those who did not develop the condition. The study's GDM prediction model, which incorporated multiple variables including 21-deoxycortisol, demonstrated a high specificity of 96.6% and sensitivity of 97.5%, indicating that early risk estimation based on these markers could provide an effective tool for preventing and managing GDM.[67] As a biomarker, 21-deoxycortisol in urine or plasma may provide insight into the hormonal imbalance characteristic of GDM, potentially offering a tool for early detection and risk stratification. Additional research is required to establish the significance of 21-deoxycortisol in the pathophysiology of GDM and its clinical utility as a diagnostic marker.

Cucurbitacin-C and Aspartame

Cucurbitacin-C is recommended during pregnancy due to its medicinal properties, and aspartame, a nonnutritive sweetener, has also been noted in dietary patterns. As urine composition is largely affected by dietary intake, analyzing maternal urine can help detect shifts in dietary patterns. A study found that aspartame and cucurbitacin-C were among the metabolites dysregulated in the urine of pregnant women with GDM.[59] However, these markers are not highly specific, and additional research is required to gain a more comprehensive understanding of the implications of these results.

Inflammatory Markers

C-Reactive Protein

C-reactive protein (CRP), a widely recognized systemic marker of inflammation, has garnered significant attention for its role in the development of GDM. Increased CRP levels are frequently observed in individuals diagnosed with GDM, reflecting subclinical inflammation that parallels the metabolic and hormonal changes occurring during pregnancy. This inflammatory state is not just a consequence of metabolic dysfunction but may actively contribute to it, creating a feedback loop that increases insulin resistance, a hallmark feature of GDM.[68] The relationship between CRP and GDM involves multiple complex mechanisms, particularly at the molecular level. CRP serves as an indicator of heightened immune activation, signifying systemic inflammation that impacts vascular function. A major pathway involved in this process is the activation of nuclear factor-kappa B (NF-κB), an essential transcription factor that controls the expression of various pro-inflammatory cytokines.[69] In GDM, NF-κB activation triggers the release of inflammatory mediators like tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β), all of which contribute to insulin resistance and endothelial dysfunction.[70,47] CRP, through its interaction with endothelial cells, promotes vascular inflammation, oxidative stress, and dysregulation of insulin signaling pathways. This pro-inflammatory environment enhances insulin resistance, making glucose regulation more challenging for the mother and increasing the risk of

adverse pregnancy outcomes. The risk of unfavorable pregnancy outcomes may increase for the mother.[71] However, the specificity of CRP as a diagnostic tool is limited, as it reflects generalized inflammation and is elevated in various conditions.[72] Nonetheless, its role in the inflammatory cascade central to GDM underscores the importance of targeting inflammation in therapeutic interventions.

Interleukin-6 and Tumor Necrosis Factor-Alpha

The pro-inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are critical contributors to the impairment of insulin signaling in GDM. These cytokines promote insulin resistance by inducing serine phosphorylation of insulin receptor substrates (IRS), particularly IRS-1, which impairs the downstream signaling necessary for insulin action.[27,73] This disruption of insulin pathways is a core feature of GDM and exacerbates glucose intolerance. Increased levels of these cytokines in GDM point to a chronic low-grade inflammatory condition, often referred to as "meta-inflammation."[74] This inflammation also impairs adipose tissue function, which leads to the elevated release of free fatty acids, altered adipokine secretion, and lipotoxicity—all contributing to further insulin resistance and metabolic dysregulation. The dysfunction of adipose tissue further perpetuates the inflammatory cycle, exacerbating metabolic impairment.[75] This chronic inflammatory state not only worsens insulin resistance during pregnancy but may also have lasting implications, increasing the likelihood of cardiovascular complications in both the mother and her offspring.[71] Early interventions targeting inflammatory pathways could potentially mitigate these risks, leading to improved outcomes for women with GDM and their children. These interventions may also contribute to reducing the long-term metabolic consequences associated with GDM, such as the risk of developing type 2 diabetes in the mother.

Adipokines

Leptin

Leptin, an adipokine primarily produced by adipose tissue, plays a crucial role in regulating body weight by controlling appetite and energy expenditure through its central actions on the hypothalamus. However, its influence extends far beyond appetite regulation.[76] In GDM, elevated leptin levels are often observed, but they are typically accompanied by a diminished physiological response, a condition known as leptin resistance. This resistance impairs the hypothalamic regulation of energy balance, resulting in increased food consumption and decreased energy expenditure, both of which can exacerbate insulin resistance.[77] Leptin's role in glucose metabolism is also significant. It directly influences insulin sensitivity in peripheral tissues such as skeletal muscle, liver, and adipose tissue, enhancing glucose uptake and utilization. However, in leptin resistance, these beneficial actions are reduced, leading to increased blood glucose levels and insulin resistance.[78] Moreover, leptin has an impact on the hypothalamic-pituitary axis, which regulates hormones involved in glucose homeostasis. Leptin resistance disrupts this delicate hormonal balance, further impairing glucose metabolism and contributing to the development of GDM.[79] Given leptin's multifaceted role in energy homeostasis and glucose regulation, it is a critical factor in the metabolic disturbances observed in GDM. Leptin's involvement in both central and peripheral processes affecting insulin sensitivity and glucose metabolism underscores its potential as a target for therapeutic interventions in GDM. Continued research is necessary to explore leptin's role further, as understanding its exact mechanisms and therapeutic potential could offer new approaches to managing GDM and reducing the risk of its long-term complications.[80]

Nesfatin-1

Nesfatin-1, a novel adipokine, has gained significant attention for its diverse metabolic functions, particularly its role in regulating energy balance, maintaining glucose homeostasis, and enhancing insulin sensitivity. Initially discovered in the hypothalamus as a key regulator of satiety, nesfatin-1 has since been found to be expressed in several peripheral tissues, including adipose tissue, the pancreas, and the gastrointestinal tract.[81] This broader expression suggests that nesfatin-1 has systemic effects on metabolism, beyond just controlling hunger. In the context of GDM, emerging research indicates that nesfatin-1 plays a critical role in glucose metabolism.[82] Studies have shown that nesfatin-1 improves insulin sensitivity and enhances glucose uptake in peripheral tissues, which is essential for maintaining glucose balance.[83] Recent reports[84–86] have found that circulating nesfatin-1 levels are significantly lower in women with GDM, correlating with increased insulin resistance and dysregulated glucose metabolism. This pattern suggests that nesfatin-1 may be an important marker or even a potential therapeutic target in GDM management. Our recent study on nesfatin-1 demonstrated similar findings, where reduced levels of nesfatin-1 were associated with insulin resistance in GDM. This further underscores the role of nesfatin-1 in regulating glucose metabolism during pregnancy. Given its ability to modulate insulin sensitivity and glucose uptake, nesfatin-1 could hold promise not only as a biomarker for early detection of GDM but also as a potential therapeutic agent to improve glucose regulation and insulin sensitivity in affected women. These findings highlight the need for further investigation into the precise mechanisms by which nesfatin-1 influences metabolic processes in GDM, and how its modulation could offer new avenues for managing the condition.[84]

Additionally, nesfatin-1 has demonstrated anti-inflammatory properties, which may help mitigate the chronic low-grade inflammation characteristic of GDM.[87] These results indicate that nesfatin-1 could be a potential biomarker and therapeutic target for the management of GDM, warranting further investigation into its mechanistic pathways and clinical implications.

Adiponectin

Adiponectin, a key adipokine secreted by adipocytes, plays an essential role in modulating insulin sensitivity and exerting anti-inflammatory effects.[88,89] In GDM, low adiponectin levels are frequently observed, reflecting impaired adipocyte function and reduced insulin sensitization.[90] This reduction in adiponectin is particularly concerning given its metabolic benefits, such as enhancing glucose uptake and fatty acid oxidation, as well as inhibiting hepatic gluconeogenesis, which collectively help maintain metabolic balance.[91] Multiple studies have indicated that reduced adiponectin levels in GDM are linked to higher insulin resistance and a greater likelihood of progressing to T2D after pregnancy.[92,93] Research also suggests that the reduction in adiponectin levels in GDM may be linked to hypertrophied adipocytes, which become dysfunctional in the setting of obesity and insulin resistance. These hypertrophied adipocytes exhibit a dysregulated secretion of adiponectin, further exacerbating insulin resistance and contributing to metabolic imbalances.[27] A study conducted by Retnakaran et al.[94] revealed that women with GDM exhibited significantly reduced levels of circulating adiponectin when compared to healthy pregnant women, and this was linked with impaired glucose tolerance and elevated insulin resistance. Another study by Pheiffer et al.[95] highlighted that adiponectin levels in mid-pregnancy could help predict the onset of GDM, underscoring its role as an early biomarker for metabolic disturbances

in pregnancy. Adiponectin are inflammatory markers which may increase due to proinflammatory state. They gain importance only if they have predictive ability in early/prepregnancy singly or in combination. Thus, adiponectin serves as a valuable marker for assessing metabolic health in GDM and could offer potential avenues for early diagnosis and therapeutic intervention to improve maternal and fetal outcomes.

Resistin

Resistin, an adipokine primarily secreted by adipose tissue, has garnered growing attention for its potential role in the pathophysiology of GDM.[96] It is recognized as a contributor to insulin resistance, a defining characteristic of GDM. Research has shown that pregnant women with GDM exhibit significantly elevated levels of HOMA-IR, resistin, IL-6, and TNF-alpha, while adiponectin levels are notably reduced compared to those in healthy pregnant women.[97] Elevated resistin levels during the first trimester (hyperresistinemia) were strongly linked to a higher likelihood of developing GDM later in pregnancy.[98] Resistin demonstrated a high predictive value for GDM, with an AUC of 0.836, indicating its potential as a reliable early marker for identifying women at risk of developing the condition. However, the precise mechanisms connecting resistin to GDM are still not well understood, and additional research is required to clarify its exact function and potential as a biomarker or therapeutic target in managing GDM.

Visfatin, Omentin-1, and Ghrelin

Visfatin, omentin-1, and ghrelin are increasingly being recognized as important biomarkers in the context of GDM.[99,100] Visfatin, produced by visceral adipose tissue, is believed to affect glucose metabolism by exerting insulin-like effects. Increased levels in GDM have been associated with greater insulin resistance and metabolic dysregulation.[101] A meta-analysis revealed that omentin-1, an adipokine with anti-inflammatory and insulin-sensitizing effects, is generally decreased in individuals with GDM. Its reduced levels are linked to impaired glucose regulation, increased insulin resistance, and chronic inflammation, all of which play a role in the development of GDM.[102] Ghrelin, commonly known as the "hunger hormone," regulates appetite and energy homeostasis, and its levels tend to be dysregulated in GDM.[103] A study found that pregnant women with GDM and T2D exhibited significantly reduced ghrelin levels in comparison to healthy women ($p < 0.001$). Additionally, maternal proinsulin levels were lower in those with GDM ($p < 0.001$).[104] Preterm births in GDM showed higher maternal ghrelin ($p = 0.031$) and lower neonatal proinsulin ($p = 0.033$). These adipokines collectively reflect the intricate metabolic and hormonal alterations that occur in GDM, and their combined measurement may offer enhanced predictive value, enabling earlier intervention and better management strategies to improve maternal and fetal outcomes.

Oxidative Stress Markers

Malondialdehyde

Malondialdehyde (MDA) is a by-product of lipid peroxidation, commonly used as a marker for oxidative stress.[105] Elevated MDA levels have been observed in GDM, highlighting the critical role that oxidative stress plays in the development of this condition.[106] Increased oxidative damage not only contributes to the interruption of normal insulin signal transduction pathways but also worsens insulin resistance in critical metabolic tissues like the liver and skeletal muscle. The accumulation of MDA indicates heightened lipid peroxidation, which is linked to cellular stress and damage, further worsening the metabolic imbalances seen in GDM.[107] Studies have shown that oxidative stress impairs mitochondrial function in insulin-sensitive tissues, reducing their capacity for efficient glucose uptake and energy production.[108] Mitochondrial dysfunction disrupts the balance between reactive oxygen species (ROS) generation and the body's antioxidant defenses, triggering pro-inflammatory pathways that exacerbate insulin signaling impairment. The detrimental cycle of oxidative stress, mitochondrial dysfunction, and insulin resistance is a key contributor to the progression of GDM.[109] Lappas et al.[110] demonstrated that women with GDM exhibited significantly higher levels of MDA compared to healthy pregnant women, indicating that oxidative stress may play a key role in the metabolic dysfunction associated with pregnancy. As a result, addressing oxidative stress and mitochondrial dysfunction could present promising therapeutic strategies for enhancing insulin sensitivity and alleviating the negative metabolic effects of GDM.

F2-Isoprostanes

Endothelial dysfunction, mediated by oxidative stress, plays a crucial role in disrupting vascular homeostasis, which is essential for maintaining proper insulin signaling and glucose uptake.[111] The rise in F2-isoprostanes mirrors the oxidative damage to cell membranes and the resultant inflammatory responses that aggravate insulin resistance in GDM.[112] Studies have shown a strong link between increased F2-isoprostane levels and worsened insulin sensitivity, linking oxidative damage to metabolic dysfunction.[113] Furthermore, the heightened oxidative stress reflected by F2-isoprostanes is linked with increased risk in pregnancy outcomes, making them a potential biomarker for early detection and intervention in GDM.[105] By measuring F2-isoprostanes, researchers and clinicians can better understand the oxidative stress burden in GDM, offering insights into the molecular mechanisms underlying its progression and potential therapeutic strategies to mitigate its effects.

Placenta-derived Markers

Placenta-derived markers are essential for assessing both maternal and fetal health, particularly in complicated pregnancies such as those involving GDM and preeclampsia.[114] Follistatin-like 3 (FSTL3), a glycoprotein primarily expressed in the placenta, regulates several signaling pathways, including those of activin and myostatin, which are essential for placental development and function.[115] Studies have shown altered FSTL3 levels in pregnancies complicated by GDM and preeclampsia, suggesting its role in placental dysfunction.[116] Similarly, placental growth factor (PlGF) is vital for angiogenesis and vascular development in pregnancy.[117] Decreased levels of PlGF are strongly associated with placental insufficiency and are widely used as a marker for predicting preeclampsia.[118] These markers are critical for understanding the pathophysiology of pregnancy complications and can serve as potential therapeutic targets. Additionally, emerging markers such as placental exosomes, afamin, and fetuin-A provide further insight into placental biology.[119,120] Placental exosomes, which are extracellular vesicles released into the maternal circulation, play key roles in immune modulation and metabolic regulation during pregnancy.[121] Afamin, a vitamin E-binding glycoprotein, has been found to be elevated in cases of GDM, reflecting changes in metabolic and oxidative stress pathways. A meta-analysis showed that pregnant women with GDM had significantly elevated plasma afamin levels during the first trimester (SMD = 0.481, 95% CI: 0.280–0.682), but this difference was not observed in the later stages of pregnancy. In women with preeclampsia, afamin levels were elevated across all trimesters, with the highest levels observed in the second/third trimesters (SMD = 0.904, 95% CI: 0.570–1.239).[122] Fetuin-A, another glycoprotein, is involved in insulin resistance and inflammation, making it a

relevant marker in pregnancies affected by diabetes.[123] A study found that women who developed GDM had significantly reduced levels of maternal fetuin-A during the first trimester compared to those who did not (AUC = 0.337, $p = 0.013$). The optimal cutoff value for fetuin-A in predicting GDM was identified as <166 mg/dL. Additionally, a significant inverse correlation was found between fetuin-A and hs-CRP levels ($r = -0.21$, $p = 0.047$).[124] Moreover, fibroblast growth factors-21 (FGF-21) and FGF-23 are involved in metabolic processes and have been linked to altered placental function.[125] Ficolin-3, a protein involved in the innate immune response, has also been linked to the development of preeclampsia. In preeclamptic patients, plasma ficolin-2 and ficolin-3 levels were significantly lower compared to healthy pregnant (ficolin-2: 3.1 µg/mL, ficolin-3: 17.6 µg/mL) and nonpregnant women (ficolin-2: 3.7 µg/mL, ficolin-3: 18.2 µg/mL). Ficolin-2 levels showed a positive correlation with PlGF and an inverse correlation with sFlt-1, endothelial injury markers, and trophoblast debris,[126] highlighting the interplay between immune regulation and placental health. Collectively, these placenta-derived markers provide broad understanding of the multifaceted roles performed by the placenta in maintaining pregnancy and the potential disruptions caused by metabolic and vascular complications.

Emerging Biomarkers

Genetic and Epigenetic Markers

Genetic Variants

Multiple genetic variants have been strongly linked to the development of GDM. Notably, polymorphisms in the TCF7L2 (transcription factor 7-like 2) and PPARG (peroxisome proliferator-activated receptor gamma) genes are among the most studied (Fig. 1).[127] TCF7L2 is essential for regulating insulin secretion and maintaining glucose homeostasis, with gene variants frequently associated with decreased insulin secretion and an elevated risk of GDM.[128] PPARG is central to adipocyte differentiation and insulin sensitivity, and its variants have been associated with impaired insulin action, contributing to the metabolic dysregulation seen in pregnancy.[129] These findings underscore the genetic predisposition to GDM, particularly in individuals carrying risk alleles that impair beta-cell function and insulin signaling pathways. Beyond TCF7L2 and PPARG, other loci such as MTNR1B (melatonin receptor 1B), GCK (glucokinase), and IRS1 (insulin receptor substrate 1) have also been linked to GDM, further reinforcing the role of genetic predisposition in the disease.[130] Collectively, these genetic variants may interact with environmental factors such as nutrition, body mass, and physical activity levels, exacerbating the susceptibility to metabolic dysregulation during pregnancy. In three recent studies conducted by Kanthimathi et al.,[131] the genetic susceptibility to GDM was explored in a South Indian population, uncovering key associations with several gene variants. The initial study discovered two single nucleotide polymorphisms (SNPs) in the CDKAL1 gene, rs7754840 and rs7756992, which were associated with an elevated risk of developing GDM, with corresponding odds ratios of 1.34 and 1.45, respectively. The second study[132] focused on variations in the hexokinase domain containing 1 (HKDC1) gene, identifying that rs10762264 and rs4746822 were linked to a 1.24- and 1.34-fold increased risk of GDM. A third study[133] investigated gene variants associated with T2D and found that variants in HMG20A (rs7178572) and HNF4A (rs4812829), previously connected to T2D, also conferred significant risk for GDM, with risk alleles increasing susceptibility by 1.24 and 1.28 times, respectively, and up to 1.97 times when carrying two risk genotypes. These studies collectively highlight the shared genetic foundations of T2D and GDM in South Asians, providing valuable understanding into the genetic factors contributing to GDM susceptibility in this population.

In Russia, Popova et al.[134] conducted a study looking at the effect of gene-lifestyle interactions on GDM risk. They found that the association between certain lifestyle factors, such as sausage consumption, and GDM risk was influenced by genetic susceptibility loci. Specifically, they discovered an interaction between sausage consumption and the number of risk alleles in MTNR1B (rs10830963) and GCK (rs1799884), suggesting that dietary habits may differentially impact GDM risk based on genetic background. These results highlight the significance of taking both genetic and lifestyle factors into account when evaluating the risk of GDM. Identifying these genetic markers provides an opportunity for personalized risk evaluation and targeted interventions for those at elevated risk of developing GDM. Apart from studying associations of SNPs with GDM, several genome-wide association studies (GWAS) have focused specifically on exploring the genetic factors associated with GDM.[135] These studies have confirmed the associations with GDM of previously linked to T2D genes MTNR1B, TCF7L2, CDKAL1, and CDKN2A-CDKN2B, along with MTNR1B exhibiting the highest significance. Additionally, a recent study by Zhen et al. revealed 14 novel loci that were significantly associated with four commonly measured glycemic traits.[136]

Epigenetic Modifications

Epigenetic changes, especially DNA methylation and histone modifications, control the expression of crucial genes responsible for glucose metabolism, insulin sensitivity, and inflammation. DNA methylation refers to the addition of methyl groups to cytosine residues in the DNA sequence, leading to gene silencing or altered gene expression, while histone modifications affect chromatin structure and gene accessibility.[137] Environmental factors like maternal obesity, diet, and intrauterine exposures during pregnancy can trigger these epigenetic changes. Research has shown that pregnant women with GDM exhibit specific

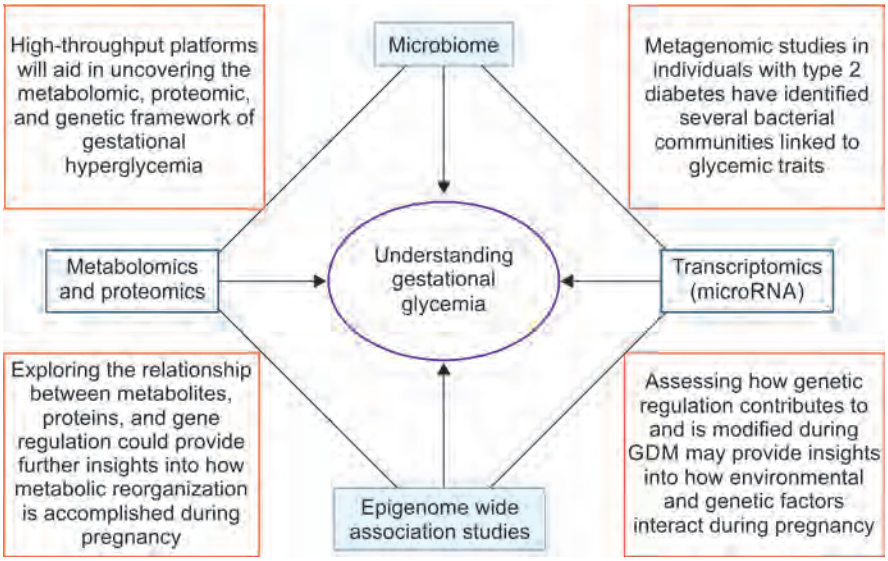

Fig. 1: Biomarkers to understand the disease biology of GDM

epigenetic profiles, with altered methylation patterns in genes associated with glucose transport (e.g., SLC2A4 encoding GLUT4) and insulin signaling (e.g., IGF2 and LEP).[138] Epigenetic changes resulting from GDM can extend well beyond pregnancy, potentially contributing to the higher likelihood of metabolic disorders in the offspring of affected mothers. This suggests that these epigenetic modifications may not only impact the mother's metabolism but also increase her children's susceptibility to conditions like insulin resistance and obesity in the future. According to a study conducted by Popova et al.,[139] examining genomic expression in the human umbilical vein endothelial cells (HUVECs) from newborns showed an elevated leptin-to-adiponectin ratio. Additionally, newborns of mothers with GDM show a reduced expression of angiopoietin-like protein 4 in their umbilical cord blood when compared to those from the control group. Achieving target glycemic levels was associated with the normalization of the elevated leptin-to-adiponectin ratio in the umbilical cord blood. In another study by the same authors,[140] a correlation between TRIB1 gene expression in HUVECs and the duration of intrauterine hyperglycemia exposure was observed. It is known that the TRIB1 gene affects plasma lipid concentrations and is associated with the risk of developing ischemic heart disease. Epigenetic alterations have the potential to function as biomarkers for the early detection of GDM and may also present novel targets for therapeutic intervention.[141] Gokulakrishnan et al.[142] presented their findings at the 60th Annual Meeting of the European Association for the Study of Diabetes (EASD), where they highlighted that DNA methylome profiling identified a set of seven CpG sites with strong predictive value for GDM in Indian women. The CpGs identified from first-trimester blood samples were found to be significantly hypermethylated in women who subsequently developed GDM compared to those who maintained normal glucose levels. The study employed machine learning classifiers to validate the predictive power of these CpGs, achieving high sensitivity (92%) and specificity (86%) in early GDM detection (unpublished data). The CpGs were also correlated with glucose levels and linked to pathways such as insulin resistance, AGE-RAGE signaling, and Th1/Th2 cell differentiation, highlighting their potential utility in GDM prevention and personalized treatment strategies. The reversibility of some epigenetic changes holds promise for interventions that could mitigate the risk of GDM and its long-term effects on offspring health, emphasizing the importance of understanding both genetic and epigenetic contributions to GDM pathophysiology.[143]

MicroRNAs

MicroRNAs (miRNAs) are short, noncoding RNA molecules that control gene expression at the posttranscriptional level and have been increasingly recognized for their role in metabolic diseases, including GDM. MicroRNA profiling in women with GDM has identified dysregulated miRNAs involved in insulin sensitivity, glucose metabolism, and inflammatory pathways.[144] For example, miRNAs like miR-29a, miR-222, and miR-330 have been found to be dysregulated in GDM, possibly influencing insulin signaling and inflammatory pathways.[145] These miRNAs may serve as upstream regulators of gene expression changes that contribute to the metabolic derangements observed in GDM. Beyond their role in disease development, miRNAs show potential as biomarkers for GDM. Their stability in bodily fluids such as blood and urine makes them attractive candidates for noninvasive testing. Targeting specific miRNAs could also represent a novel therapeutic strategy for improving insulin sensitivity and reducing inflammation in GDM.

Metabolomics

Advances in metabolomics have provided new insights into the metabolic alterations associated with GDM. Metabolomic profiling allows for an in-depth examination of small molecules and metabolites present in biological samples, offering a snapshot of metabolic changes in response to physiological states such as pregnancy. In GDM, studies have revealed disruptions in amino acid metabolism. Elevated levels of branched-chain amino acids (BCAAs), such as leucine, isoleucine, and valine, have been observed in women diagnosed with GDM.[146] These elevated levels may reflect impaired insulin sensitivity, as BCAAs have been shown to influence insulin signaling pathways. Furthermore, alterations in lipid metabolism have also been observed, with elevated levels of specific ceramides and triglycerides indicating lipid dysregulation in GDM.[147]

These metabolomic signatures not only reflect the metabolic stress of pregnancy but also suggest potential early biomarkers for GDM risk. For example, a unique metabolic profile characterized by elevated levels of acylcarnitines, fatty acids, and amino acids has been linked to a higher risk of GDM, even before clinical diagnosis.[148] This suggests that metabolomic profiling could be used for early screening and risk stratification in pregnant women, enabling preventive strategies to mitigate the progression of GDM.

Proteomics

Proteomics has emerged as a powerful tool for understanding the molecular mechanisms underlying GDM by identifying protein dysregulation in plasma and placental tissues. Proteomic analyses have uncovered significant alterations in proteins involved in insulin signaling, inflammation, and oxidative stress. For instance, proteins associated with insulin resistance, such as insulin receptor substrate 1 (IRS1) and glucose transporter type 4 (GLUT4), exhibit altered expression in GDM, providing insights into the mechanisms driving hyperglycemia in pregnancy.[149] Placental proteomics has also revealed changes in proteins involved in nutrient transport, mitochondrial function, and cellular stress responses, shedding light on how GDM affects placental function and, consequently, fetal development.[150] These proteomic discoveries enhance our knowledge of GDM pathophysiology and present promising biomarkers for early diagnosis and potential therapeutic targets.

1,5-Anhydroglucitol (1,5-AG) and Fructosamine

1,5-AG is a naturally occurring polyol that has gained recognition as a potential biomarker for short-term glycemic control.[151,152] 1,5-AG levels are typically lower due to hyperglycemia. Elevated glucose levels interfere with the renal reabsorption of 1,5-AG, resulting in greater urinary excretion,[153] particularly in the late stages of pregnancy when postprandial hyperglycemia becomes more pronounced.[154] Given its sensitivity to short-term fluctuations in glucose levels, 1,5-AG could complement traditional markers like HbA1c in providing glycemic control in women with GDM. Additionally, 1,5-AG may aid in the early detection of GDM and offer a useful tool for monitoring the effectiveness of interventions aimed at improving glycemic control during pregnancy.

Fructosamine, which reflects the nonenzymatic glycation of circulating proteins such as albumin, globulins, and lipoproteins, has become a viable alternative to HbA1c testing in cases where HbA1c may be unreliable.[155] Fructosamine levels measured in the second trimester have been shown to be an unreliable indicator of gestational glucose tolerance and postpartum glycemic outcomes.[156]

Microbiome

Dysbiosis during early pregnancy, in conjunction with the host's immune system, can impact the development of GDM later on. Numerous studies have identified differences in gut microorganisms

between pregnant women with GDM and those with normal glucose levels.[62,157,158] In women with GDM, there was an observed increase in the abundance of microbial species such as *Ruminococcus*, *Klebsiella variicola*, *Prevotella*, *Rothia*, *Desulfovibrio*, *Fusobacterium*, the *Eubacterium hallii* group, and *Blautia*. Conversely, there was a decrease in populations of *Eubacterium* spp., *Bifidobacterium* spp., *Akkermansia*, *Bacteroides*, *Parabacteroides*, *Dialister*, *Marvinbryantia*, *Faecalibacterium*, and *Anaer osporobacte*.[62,157,158] A recent study by Pinto et al. identified an altered gut microbiome and elevated levels of proinflammatory cytokines in women who later developed GDM. The researchers further validated that changes in microbial composition linked to GDM during the first trimester contributed to inflammation and insulin resistance >10 weeks prior to the GDM diagnosis. This was demonstrated through fecal microbiota transplantation (FMT) experiments. They later implemented a machine learning method to accurately predict GDM by using clinical data, microbial profiles, and inflammatory markers from the first trimester.[159] Thus, the gut microbiome seems to play a role in the development of GDM by promoting inflammation, with interleukin-6 possibly playing a role in this process. Potential markers for GDM, such as specific microbiota, could be used for early diagnosis and targeted therapy, which may help in preventing the condition.

Other Markers

In GDM, several biomarkers are crucial for diagnosis and management. Vitamin D levels are considered important as deficiencies are associated with greater risk of GDM and may impact insulin sensitivity.[160] Although, some studies provide conflicting results concerning the role of Vitamin D in GDM.[161–163] Glycosylated fibronectin helps assess placental function, with elevated levels indicating potential complications such as preterm birth or restricted fetal growth.[164] The soluble (pro) renin receptor, a component of the renin-angiotensin system, could potentially act as an early marker for gestational GDM due to its link with insulin resistance.[165,166] Ferritin levels, reflecting iron status, are crucial as both deficiency and overload can affect glucose metabolism and increase GDM risk.[167] While not primary markers, glucagon levels can influence glucose regulation, and elevated PAI-1 levels indicate insulin resistance and increased thrombotic risk.[168] Adipocyte fatty acid-binding protein (AFABP) levels can highlight metabolic stress associated with GDM.[169]

Biomarkers to Distinguish "Early Gestational Diabetes Mellitus" from "Late Gestational Diabetes Mellitus"

FPG combined with other markers in machine learning models shows some limitations in accurately identifying early GDM, as adding more predictors did not significantly improve the model's discriminant power.[170] GDM has traditionally been diagnosed between 24 and 28 weeks of pregnancy, and this is referred to as "Late GDM."

More recently, GDM is being diagnosed before 20 weeks and even before 14 weeks of gestation. This is referred to as "Early GDM."[171,172] It would be useful if biomarkers for Early GDM and Late GDM are developed, as this will lead to better identification of the two forms of GDM.

Future Perspectives

It is important to note that all of the aforementioned studies have used glucose levels from OGTT conducted after 24 weeks of gestation. A key direction for future research would be to investigate the genetic factors influencing glycemic traits in early pregnancy (before 20 weeks) and to compare the genetic profiles of early-onset GDM with those of late-onset GDM. Additionally, maternal ethnicity may contribute to heterogeneity, leading to both phenotypic and genotypic differences among women with GDM.[173] Existing GWAS studies did not include Indian and Russian women. Polygenic scores (PGSs) predominantly developed from European populations have demonstrated significantly higher accuracy in White Europeans than in South Asians.[174] Consequently, multi-ancestry GWAS data are crucial for creating ancestry-specific PGSs to help mitigate health disparities. The most impactful biomarkers should be integrated into mathematical models predicting GDM and validated on independent cohorts.

Clinical Implications

In the realm of clinical implications, there is growing potential for the practical application of specific biomarkers to detect high-risk GDM at an early stage. Biomarkers with enhanced specificity and sensitivity can significantly improve day-to-day clinical practice by empowering clinicians to make more informed decisions and implement timely interventions. Emerging biomarkers have shown promise in enhancing early risk stratification. Incorporating these biomarkers into routine screening could greatly improve personalized patient management, potentially reducing the complications associated with GDM.

Looking ahead, the development of a clinical predictive model that integrates these biomarkers with traditional risk factors—which include family history, advanced age, and higher BMI—offers a promising avenue. Such a predictive algorithm, tailored for early GDM detection, could help clinicians identify high-risk individuals well before traditional screening methods indicate abnormalities. This approach has the potential to form the basis for future research, informing new clinical guidelines and fostering more precise and effective strategies for GDM management. By integrating biomarker research into clinical practice, we can improve the early detection of GDM and tailor interventions. Biomarkers also hold potential for monitoring postpartum progression to T2D, providing a continuum of care for women at risk.

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References

1. Hod M, Kapur A, Sacks DA, et al. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: a pragmatic guide for diagnosis, management, and care. Int J Gynaecol Obstet 2015;131:S173–S211.
2. Adam S, McIntyre HD, Tsoi KY, et al. Pregnancy as an opportunity to prevent type 2 diabetes mellitus: FIGO best practice advice. Int J Gynaecol Obstet 2023;160(Suppl 1):56–67.
3. Greene MF. Screening for gestational diabetes mellitus. N Engl J Med 1997;337(22):1625.
4. World Health Organization. Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy. http://apps.who.int/iris/bitstream/10665/85975/1/WHO_NMH_MND_13.2_eng.pdf. Published 2013.
5. Swaminathan G, Swaminathan A, Corsi DJ. Prevalence of gestational diabetes in India by individual socioeconomic, demographic, and clinical factors. JAMA Netw Open 2020;3(11):e2025074.

6. Bhavadharini B, Mahalakshmi MM, Anjana RM, et al. Prevalence of gestational diabetes mellitus in urban and rural Tamil Nadu using IADPSG and WHO 1999 criteria (WINGS 6). Clin Diabetes Endocrinol 2016;2:8.
7. Seshiah V, Balaji V, Shah SN, et al. Diagnosis of gestational diabetes mellitus in the community. J Assoc Physicians India 2012;60:15–17.
8. Mantri N, Goel AD, Patel M, et al. National and regional prevalence of gestational diabetes mellitus in India: a systematic review and meta-analysis. BMC Public Health 2024;24(1):527.
9. Popova P, Tkachuk A, Dronova A, et al. Fasting glycemia at the first prenatal visit and pregnancy outcomes in Russian women. Minerva Endocrinol 2016;41(4):477–485.
10. Mahalakshmi MM, Bhavadharini B, Maheswari K, et al. Comparison of maternal and fetal outcomes among Asian Indian pregnant women with or without gestational diabetes mellitus: a situational analysis study (WINGS-3). Indian J Endocrinol Metab 2016;20(4):491–449.
11. Ye W, Luo C, Huang J, et al. Gestational diabetes mellitus and adverse pregnancy outcomes: systematic review and meta-analysis. BMJ 2022;377:e067946.
12. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358(19):1991–2002.
13. Bhavadharini B, Anjana RM, Mahalakshmi MM, et al. Glucose tolerance status of Asian Indian women with gestational diabetes at 6 weeks to 1 year postpartum (WINGS-7). Diabetes Res Clin Pract 2016;117:22–27.
14. Kc K, Shakya S, Zhang H. Gestational diabetes mellitus and macrosomia: a literature review. Ann Nutr Metab 2015;66:14–20.
15. Shivashri C, Hannah W, Deepa M, et al. Prevalence of prediabetes and type 2 diabetes mellitus in south and southeast Asian women with history of gestational diabetes mellitus: systematic review and meta-analysis. PLoS One 2024;19(5):e0304170.
16. Page KA, Luo S, Wang X, et al. Children exposed to maternal obesity or gestational diabetes mellitus during early fetal development have hypothalamic alterations that predict future weight gain. Diabetes Care 2019;42(8):1473–1480.
17. Lowe WL Jr, Scholtens DM, Kuang A, et al. Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): maternal gestational diabetes mellitus and childhood glucose metabolism. Diabetes Care 2019;42(3):372–380.
18. Simmons D, Immanuel J, Hague WM, et al. Treatment of gestational diabetes mellitus diagnosed early in pregnancy. N Engl J Med 2023;388(23):2132–2144.
19. Kayal A, Mohan V, Malanda B, et al. Women in India with Gestational Diabetes Mellitus Strategy (WINGS): methodology and development of model of care for gestational diabetes mellitus (WINGS 4). Indian J Endocrinol Metab 2016;20(5):707–715.
20. Mahalakshmi MM, Bhavadharini B, Maheswari K, et al. Current practices in the diagnosis and management of gestational diabetes mellitus in India (WINGS-5). Indian J Endocrinol Metab 2016;20(3):364–368.
21. Saravanan P, Deepa M, Ahmed Z, et al. Early pregnancy HbA1c as the first screening test for gestational diabetes: results from three prospective cohorts. Lancet Diabetes Endocrinol 2024;12(8):535–544.
22. Uma R, Bhavadharini B, Ranjani H, et al. Pregnancy outcome of gestational diabetes mellitus using a structured model of care: WINGS project (WINGS-10). J Obstet Gynaecol Res 2017;43(3):468–475.
23. Powe CE. Early pregnancy biochemical predictors of gestational diabetes mellitus. Curr Diab Rep 2017;17(2):12.
24. Bogdanet D, Reddin C, Murphy D, et al. Emerging protein biomarkers for the diagnosis or prediction of gestational diabetes-a scoping review. J Clin Med 2021;10(7):1533.
25. International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;33(3):676–682.
26. McIntyre HD, Sacks DA, Barbour LA, et al. Issues with the diagnosis and classification of hyperglycemia in early pregnancy. Diabetes Care 2016;39(1):53–54.
27. Plows JF, Stanley JL, Baker PN, et al. The pathophysiology of gestational diabetes mellitus. Int J Mol Sci 2018;19(11):3342.
28. Yan B, Yu YX, Chen YL, et al. Assessment of the optimal cutoff value of fasting plasma glucose to establish diagnosis of gestational diabetes mellitus in Chinese women. Sci Rep 2019;9(1):15998.
29. Bhattacharya S, Nagendra L, Krishnamurthy A, et al. Early gestational diabetes mellitus: diagnostic strategies and clinical implications. Med Sci (Basel) 2021;9(4):59.
30. Bidhendi Yarandi R, Vaismoradi M, Panahi MH, et al. Mild gestational diabetes and adverse pregnancy outcome: a systemic review and meta-analysis. Front Med (Lausanne) 2021;8:699412.
31. Mohan V, Mahalakshmi MM, Bhavadharini B, et al. Comparison of screening for gestational diabetes mellitus by oral glucose tolerance tests done in the non-fasting (random) and fasting states. Acta Diabetol 2014;51(6):1007–1013.
32. Behboudi-Gandevani S, Amiri M, Bidhendi Yarandi R, et al. The impact of diagnostic criteria for gestational diabetes on its prevalence: a systematic review and meta-analysis. Diabetol Metab Syndr 2019;11:11.
33. Popova P, Castorino K, Grineva EN, et al. Gestational diabetes mellitus diagnosis and treatment goals: measurement and measures. Minerva Endocrinol 2016.
34. Lachmann EH, Fox RA, Dennison RA, et al. Barriers to completing oral glucose tolerance testing in women at risk of gestational diabetes. Diabet Med 2020;37(9):1482–1489.
35. Mañé L, Navarro H, Pedro-Botet J, et al. Early HbA1c levels as a predictor of adverse obstetric outcomes: a systematic review and meta-analysis. J Clin Med 2024;13(6):1732.
36. Thakur A, Agrawal S, Chakole S, et al. A critical review of diagnostic strategies and maternal offspring complications in gestational diabetes mellitus. Cureus 2023;15(12):e51016.
37. Lai Y, Chen H, Du Z, et al. The diagnostic accuracy of HbA1c in detecting gestational diabetes mellitus among Chinese pregnant individuals. Ann Transl Med 2020;8(16):1014.
38. Thewjitcharoen Y, Jones Elizabeth A, Butadej S, et al. Performance of HbA1c versus oral glucose tolerance test (OGTT) as a screening tool to diagnose dysglycemic status in high-risk Thai patients. BMC Endocr Disord 2019;19:23.
39. Unnikrishnan R, Mohan V. Challenges in estimation of glycated hemoglobin in India. Diabetes Technol Ther 2013;15(10):897–899.
40. Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. Physiol Rev 2018;98(4):2133–2223.
41. Duo Y, Song S, Zhang Y, et al. Predictability of HOMA-IR for gestational diabetes mellitus in early pregnancy based on different first trimester BMI values. J Pers Med 2022;13(1):60.
42. Kampmann U, Knorr S, Fuglsang J, et al. Determinants of maternal insulin resistance during pregnancy: an updated overview. J Diabetes Res 2019;2019:5320156.
43. Lin J, Jin H, Chen L. Associations between insulin resistance and adverse pregnancy outcomes in women with gestational diabetes mellitus: a retrospective study. BMC Pregnancy Childbirth 2021;21(1):526.
44. Leighton E, Sainsbury CA, Jones GC. A practical review of C-peptide testing in diabetes. Diabetes Ther 2017;8(3):475–487.
45. Sonagra AD, Biradar SM, K D, et al. Normal pregnancy - a state of insulin resistance. J Clin Diagn Res 2014;8(11):CC01.
46. Cerf ME. Beta cell dysfunction and insulin resistance. Front Endocrinol (Lausanne) 2013;4:37.
47. Skajaa GO, Fuglsang J, Knorr S, et al. Changes in insulin sensitivity and insulin secretion during pregnancy and post partum in women with gestational diabetes. BMJ Open Diabetes Res Care 2020;8(2):e001728.
48. Yildiz Atar H, Baatz JE, Ryan RM. Molecular mechanisms of maternal diabetes effects on fetal and neonatal surfactant. Children (Basel) 2021;8(4):281.
49. Tawfeek MA, Alfadhli EM, Alayoubi AM, et al. Sex hormone binding globulin as a valuable biochemical marker in predicting gestational diabetes mellitus. BMC Womens Health 2017;17(1):18.
50. Li MY, Rawal S, Hinkle SN, et al. Sex hormone-binding globulin, cardiometabolic biomarkers, and gestational diabetes: a longitudinal study and meta-analysis. Matern Fetal Med 2020;2(1):2–9.
51. Bartha JL, Comino-Delgado R, Romero-Carmona R, et al. Sex hormone-binding globulin in gestational diabetes. Acta Obstet Gynecol Scand 2000;79(10):839–845.
52. Hedderson MM, Xu F, Darbinian JA, et al. Prepregnancy SHBG concentrations and risk for subsequently developing gestational diabetes mellitus. Diabetes Care 2014;37(5):1296–1303.
53. Kumru P, Arisoy R, Erdogdu E, et al. Prediction of gestational diabetes mellitus at first trimester in low-risk pregnancies. Taiwan J Obstet Gynecol 2016;55(6):815–820.
54. Muniyappa R, Madan R, Varghese RT. Assessing Insulin Sensitivity and Resistance in Humans. [Updated 2021 Aug 9]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc. 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK278954/
55. Omazić J, Viljetić B, Ivić V, et al. Early markers of gestational diabetes mellitus: what we know and which way forward? Biochem Med (Zagreb) 2021;31(3):30502.
56. Leitner M, Fragner L, Danner S, et al. Combined metabolomic analysis of plasma and urine reveals AHBA, tryptophan and serotonin metabolism as potential risk factors in gestational diabetes mellitus (GDM). Front Mol Biosci 2017;4:84.
57. Badawy AA. Kynurenine pathway of tryptophan metabolism: regulatory and functional aspects. Int J Tryptophan Res 2017;10:1178646917691938.
58. Law KP, Han TL, Mao X, et al. Tryptophan and purine metabolites are consistently upregulated in the urinary metabolome of patients diagnosed with gestational diabetes mellitus throughout pregnancy: a longitudinal metabolomics study of Chinese pregnant women part 2. Clin Chim Acta 2017;468:126–139.
59. López-Hernández Y, Herrera-Van Oostdam AS, Toro-Ortiz JC, et al. Urinary metabolites altered during the third trimester in pregnancies complicated by gestational diabetes mellitus: relationship with potential upcoming metabolic disorders. Int J Mol Sci 2019;20(5):1186.
60. Lorenzo-Almorós A, Hang T, Peiró C, et al. Predictive and diagnostic biomarkers for gestational diabetes and its associated metabolic and cardiovascular diseases. Cardiovasc Diabetol 2019;18(1):140.
61. Ionescu RF, Enache RM, Cretoiu SM, et al. Gut microbiome changes in gestational diabetes. Int J Mol Sci 2022;23(21):12839.
62. Hammad SM, Lopes-Virella MF. Circulating sphingolipids in insulin resistance, diabetes and associated complications. Int J Mol Sci 2023;24(18):14015.
63. Mustaniemi S, Keikkala E, Kajantie E, et al. Serum ceramides in early pregnancy as predictors of gestational diabetes. Sci Rep 2023;13(1):13274.
64. Ng JL, Lim EM, Zhang R, et al. Serum 21-deoxycortisol for diagnosis of nonclassic congenital adrenal hyperplasia in women with androgen excess. J Clin Endocrinol Metab 2023;108(12):e1560–e1570.
65. Krishnaveni GV, Veena SR, Jones A, et al. Exposure to maternal gestational diabetes is associated with higher cardiovascular responses to stress

in adolescent Indians. J Clin Endocrinol Metab 2015;100(3):986–993.
66. Gerszi D, Orosz G, Török M, et al. Risk estimation of gestational diabetes mellitus in the first trimester. J Clin Endocrinol Metab 2023;108(11):e1214.
67. Eberle C, Fasig T, Brüseke F, et al. Impact of maternal prenatal stress by glucocorticoids on metabolic and cardiovascular outcomes in their offspring: a systematic scoping review. PLoS One 2021;16(1):e0245386.
68. Pantham P, Aye IL, Powell TL. Inflammation in maternal obesity and gestational diabetes mellitus. Placenta 2015;36(7):709–715.
69. Lawrence T. The nuclear factor NF-kappaB pathway in inflammation. Cold Spring Harb Perspect Biol 2009;1(6):a001651.
70. Abell SK, De Courten B, Boyle JA, et al. Inflammatory and other biomarkers: role in pathophysiology and prediction of gestational diabetes mellitus. Int J Mol Sci 2015;16(6):13442–13473.
71. Sharma AK, Singh S, Singh H, et al. Deep insight of the pathophysiology of gestational diabetes mellitus. Cells 2022;11(17):2672.
72. Mouliou DS. C-reactive protein: pathophysiology, diagnosis, false test results and a novel diagnostic algorithm for clinicians. Diseases 2023;11(4):132.
73. Deepa R, Velmurugan K, Arvind K, et al. Serum levels of interleukin 6, C-reactive protein, vascular cell adhesion molecule 1, and monocyte chemotactic protein 1 in relation to insulin resistance and glucose intolerance–the Chennai Urban Rural Epidemiology Study (CURES). Metabolism 2006;55(9):1232–1238.
74. Musumeci A, McElwain CJ, Manna S, et al. Exposure to gestational diabetes mellitus increases subclinical inflammation mediated in part by obesity. Clin Exp Immunol 2024;216(3):280–292.
75. Ahmed B, Sultana R, Greene MW. Adipose tissue and insulin resistance in obese. Biomed Pharmacother 2021;137:111315.
76. Picó C, Palou M, Pomar CA, et al. Leptin as a key regulator of the adipose organ. Rev Endocr Metab Disord 2022;23(1):13–30.
77. Pérez-Pérez A, Vilariño-García T, Guadix P, et al. Leptin and nutrition in gestational diabetes. Nutrients 2020;12(7):1970.
78. Paz-Filho G, Mastronardi C, Wong ML, et al. Leptin therapy, insulin sensitivity, and glucose homeostasis. Indian J Endocrinol Metab 2012;16(Suppl 3):S549–S555.
79. Ylli D, Sidhu S, Parikh T, et al. Endocrine Changes in Obesity. [Updated 2022 Sep 6]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc. 2000.
80. D'souza AM, Neumann UH, Glavas MM, et al. The glucoregulatory actions of leptin. Mol Metab 2017;6(9):1052–1065.
81. Yang M, Zhang Z, Wang C, et al. Nesfatin-1 action in the brain increases insulin sensitivity through Akt/AMPK/TORC2 pathway in diet-induced insulin resistance. Diabetes 2012;61(8):1959–1968.
82. Ruszała M, Pilszyk A, Niebrzydowska M, et al. Novel biomolecules in the pathogenesis of gestational diabetes mellitus 2.0. Int J Mol Sci 2022;23(8):4364.
83. Bertucci JI, Blanco AM, Unniappan S. Nesfatin-1 regulates glucoregulatory genes in rainbow trout (Oncorhynchus mykiss). Comp Biochem Physiol A Mol Integr Physiol 2019;235:121–130.
84. Thirumoorthy C, Deepa M, Srikumar BN, et al. Altered levels of neurobiological biomarkers at the interface of depression and gestational diabetes mellitus in Asian Indian women. Neuropeptides 2022;93:102245.
85. Mierzyński R, Poniedziałek-Czajkowska E, Dłuski D, et al. Nesfatin-1 and vaspin as potential novel biomarkers for the prediction and early diagnosis of gestational diabetes mellitus. Int J Mol Sci 2019;20(1):159.
86. Huang K, Liang Y, Wang K, et al. Influence of circulating nesfatin-1, GSH and SOD on insulin secretion in the development of T2DM. Front Public Health 2022;10:882686.
87. Damian-Buda AC, Matei DM, Ciobanu L, et al. Nesfatin-1: a novel diagnostic and prognostic biomarker in digestive diseases. Biomedicines. 2024;12(8):1913.
88. Nguyen TMD. Adiponectin: role in physiology and pathophysiology. Int J Prev Med 2020;11:136.
89. Pandey GK, Vadivel S, Raghavan S, et al. High molecular weight adiponectin reduces glucolipotoxicity-induced inflammation and improves lipid metabolism and insulin sensitivity via APPL1-AMPK-GLUT4 regulation in 3T3-L1 adipocytes. Atherosclerosis 2019;288:67–75.
90. Moyce Gruber BL, Dolinsky VW. The role of adiponectin during pregnancy and gestational diabetes. Life (Basel) 2023;13(2):301.
91. Achari AE, Jain SK. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. Int J Mol Sci 2017;18(6):1321.
92. Lee DH, Lim JA, Kim JH, et al. Longitudinal changes of high molecular weight adiponectin are associated with postpartum development of type 2 diabetes mellitus in patients with gestational diabetes mellitus. Endocrinol Metab (Seoul) 2021;36(1):114–122.
93. Saucedo R, Zarate A, Basurto L, et al. Relationship between circulating adipokines and insulin resistance during pregnancy and postpartum in women with gestational diabetes. Arch Med Res 2011;42(4):318–323.
94. Retnakaran R, Hanley AJ, Raif N, et al. Hypoadiponectinaemia in South Asian women during pregnancy: evidence of ethnic variation in adiponectin concentration. Diabet Med 2004;21(4):388–392.
95. Pheiffer C, Dias S, Jack B, et al. Adiponectin as a potential biomarker for pregnancy disorders. Int J Mol Sci 2021;22(3):1326.
96. Kabbani N, Blüher M, Stepan H, et al. Adipokines in pregnancy: a systematic review of clinical data. Biomedicines 2023;11(5):1419.
97. Ramachandrayya SA, D'Cunha P, Rebeiro C. Maternal circulating levels of Adipocytokines and insulin resistance as predictors of gestational diabetes mellitus: preliminary findings of a longitudinal descriptive study. J Diabetes Metab Disord 2020;19(2):1447–1452.
98. Bawah AT, Seini MM, Abaka-Yawason A, et al. Leptin, resistin and visfatin as useful predictors of gestational diabetes mellitus. Lipids Health Dis 2019;18(1):221.
99. Karami M, Mousavi SH, Rafiee M, et al. Biochemical and molecular biomarkers: unraveling their role in gestational diabetes mellitus. Diabetol Metab Syndr 2023;15(1):5.
100. Kimber-Trojnar Ż, Patro-Małysza J, Skórzyńska-Dziduszko KE, et al. Ghrelin in serum and urine of post-partum women with gestational diabetes mellitus. Int J Mol Sci 2018;19(10):3001.
101. Abdalla MMI. Role of visfatin in obesity-induced insulin resistance. World J Clin Cases 2022;10(30):10840–10851.
102. Pan X, Kaminga AC, Wen SW, et al. Omentin-1 in diabetes mellitus: a systematic review and meta-analysis. PLoS One 2019;14(12):e0226292.
103. Brink HS, van der Lely AJ, Delhanty PJD, et al. Gestational diabetes mellitus and the ghrelin system. Diabetes Metab 2019;45(4):393–395.
104. Gómez-Díaz RA, Gómez-Medina MP, Ramírez-Soriano E, et al. Lower plasma ghrelin levels are found in women with diabetes-complicated pregnancies. J Clin Res Pediatr Endocrinol 2016;8(4):425–431.
105. Gaweł S, Wardas M, Niedworok E, et al. Dialdehyd malonowy (MDA) jako wskaźnik procesów peroksydacji lipidów w organizmie [Malondialdehyde (MDA) as a lipid peroxidation marker]. Wiad Lek 2004;57(9-10):453–455.
106. Grzeszczak K, Łanocha-Arendarczyk N, Malinowski W, et al. Oxidative stress in pregnancy. Biomolecules 2023;13(12):1768.
107. Saucedo R, Ortega-Camarillo C, Ferreira-Hermosillo A, et al. Role of oxidative stress and inflammation in gestational diabetes mellitus. Antioxidants (Basel) 2023;12(10):1812.
108. Kim JA, Wei Y, Sowers JR. Role of mitochondrial dysfunction in insulin resistance. Circ Res 2008;102(4):401–414.
109. Coughlan MT, Vervaart PP, Permezel M, et al. Altered placental oxidative stress status in gestational diabetes mellitus. Placenta 2004;25(1):78–84.
110. Lappas M, Hiden U, Desoye G, et al. The role of oxidative stress in the pathophysiology of gestational diabetes mellitus. Antioxid Redox Signal 2011;15(12):3061–3100.
111. Hadi HA, Suwaidi JA. Endothelial dysfunction in diabetes mellitus. Vasc Health Risk Manag 2007;3(6):853–876.
112. Miller E, Morel A, Saso L, et al. Isoprostanes and neuroprostanes as biomarkers of oxidative stress in neurodegenerative diseases. Oxid Med Cell Longev 2014;2014:572491.
113. Ferreira CS, Pinto GDA, Reis DL, et al. Placental F4-Neuroprostanes and F2-Isoprostanes are altered in gestational diabetes mellitus and maternal obesity. Prostaglandins Leukot Essent Fatty Acids 2023;189:102529.
114. Chaemsaithong P, Luewan S, Taweevisit M, et al. Placenta-derived extracellular vesicles in pregnancy complications and prospects on a liquid biopsy for Hemoglobin Bart's Disease. Int J Mol Sci 2023;24(6):5658.
115. Tian S, Xu X, Yang X, et al. Roles of follistatin-like protein 3 in human non-tumor pathophysiologies and cancers. Front Cell Dev Biol 2022;10:953551.
116. Founds SA, Ren D, Roberts JM, et al. Follistatin-like 3 across gestation in preeclampsia and uncomplicated pregnancies among lean and obese women. Reprod Sci 2015;22(4):402–409.
117. Chau K, Hennessy A, Makris A. Placental growth factor and pre-eclampsia. J Hum Hypertens 2017;31(12):782–786.
118. McLaughlin K, Snelgrove JW, Audette MC, et al. PlGF (placental growth factor) testing in clinical practice: evidence from a Canadian Tertiary Maternity Referral Center. Hypertension 2021;77(6):2057–2065.
119. Wang CY, Su MT, Cheng HL, et al. Fetuin-A inhibits placental cell growth and ciliogenesis in gestational diabetes mellitus. Int J Mol Sci 2019;20(20):5207.
120. Köninger A, Enekwe A, Mach P, et al. Afamin: an early predictor of preeclampsia. Arch Gynecol Obstet 2018;298(5):1009–1016.
121. Nakahara A, Nair S, Ormazabal V, et al. Circulating placental extracellular vesicles and their potential roles during pregnancy. Ochsner J 2020;20(4):439–445.
122. Yuan Y, He W, Fan X, et al. Serum afamin levels in predicting gestational diabetes mellitus and preeclampsia: a systematic review and meta-analysis. Front Endocrinol (Lausanne) 2023;14:1157114.
123. Wang WJ, Zhang L, Zheng T, et al. Fetuin-A and fetal growth in gestational diabetes mellitus. BMJ Open Diabetes Res Care 2020;8(1):e000864.
124. Kansu-Celik H, Ozgu-Erdinc AS, Kisa B, et al. Prediction of gestational diabetes mellitus in the first trimester: comparison of maternal fetuin-A, N-terminal proatrial natriuretic peptide, high-sensitivity C-reactive protein, and fasting glucose levels. Arch Endocrinol Metab 2020;64(1):97.
125. Vrachnis N, Argyridis S, Vrachnis D, et al. Increased Fibroblast Growth Factor 21 (FGF21) concentration in early second trimester amniotic fluid and its association with fetal growth. Metabolites 2021;11(9):581.
126. Halmos A, Rigó J Jr, Szijártó J, et al. Circulating ficolin-2 and ficolin-3 in normal pregnancy and pre-eclampsia. Clin Exp Immunol 2012;169(1):49–56.
127. Suthon S, Tangjittipokin W. Mechanisms and physiological roles of polymorphisms in gestational diabetes mellitus. Int J Mol Sci 2024;25(4):2039.
128. Pagán A, Sabater-Molina M, Olza J, et al. A gene variant in the transcription factor 7-like 2(TCF7L2) is associated with an increased risk of gestational diabetes mellitus. Eur J Obstet Gynecol Reprod Biol 2014;180:77–82.
129. Corrales P, Vidal-Puig A, Medina-Gómez G. PPARs and metabolic disorders associated with challenged adipose tissue plasticity. Int J Mol Sci 2018;19(7):2124.
130. Zhang Y, Sun CM, Hu XQ, et al. Relationship between melatonin receptor 1B and insulin receptor substrate

1 polymorphisms with gestational diabetes mellitus: a systematic review and meta-analysis. Sci Rep 2014;4:6113.
131. Kanthimathi S, Chidambaram M, Liju S, et al. Identification of genetic variants of gestational diabetes in South Indians. Diabetes Technol Ther 2015;17(7):462–467.
132. Kanthimathi S, Liju S, Laasya D, et al. Hexokinase Domain Containing 1 (HKDC1) gene variants and their association with gestational diabetes mellitus in a South Indian Population. Ann Hum Genet 2016;80(4):241–245.
133. Kanthimathi S, Chidambaram M, Bodhini D, et al. Association of recently identified type 2 diabetes gene variants with gestational diabetes in Asian Indian population. Mol Genet Genomics 2017;292(3):585–591.
134. Popova PV, Klyushina AA, Vasilyeva LB, et al. Effect of gene-lifestyle interaction on gestational diabetes risk. Oncotarget 2017;8(67):112024–112035.
135. Pervjakova N, Moen GH, Borges, et al. Multi-ancestry genome-wide association study of gestational diabetes mellitus highlights genetic links with type 2 diabetes. Hum Mol Genet 2022;31:3377–3391.
136. Zhen J, Gu Y, Wang P, et al. Genome-wide association and Mendelian randomisation analysis among 30,699 Chinese pregnant women identifies novel genetic and molecular risk factors for gestational diabetes and glycaemic traits. Diabetologia 2024;67(4):703–713.
137. Klimczak S, Śliwińska A. Epigenetic regulation of inflammation in insulin resistance. Semin Cell Dev Biol 2024;154(Pt C):185–192.
138. Ustianowski Ł, Udzik J, Szostak J, et al. Genetic and epigenetic factors in gestational diabetes mellitus pathology. Int J Mol Sci 2023;24(23):16619.
139. Popova PV,Vasilyeva L, Tkachuck A, et al. Randomised, controlled study of different glycaemic targets during gestational diabetes treatment: effect on the level of adipokines in cord blood and ANGPTL4 expression in human umbilical vein endothelial cells. Int J Endocrinol 2018;2018:6481658.
140. Popova PV,Vasileva LB, Tkachuk AS, et al. Association of tribbles homologue 1 gene expression in human umbilical vein endothelial cells with duration of intrauterine exposure to hyperglycaemia. Genet Res (Camb) 2018;100:e3.
141. Linares-Pineda T, Peña-Montero N, Fragoso-Bargas N, et al. Epigenetic marks associated with gestational diabetes mellitus across two time points during pregnancy. Clin Epigenetics 2023;15(1):110.
142. Gokulakrishnan K, Thirumoorthy C, Deepa M. et al (2024). First-trimester DNA Methylome Profiling Identifies Novel Predictors of Gestational Diabetes Mellitus in Indian Women. Abstract: 60th Annual Meeting of the European Association for the Study of Diabetes (EASD), 9th to 13th September 2024 Madrid, Spain.
143. Lehnen H, Zechner U, Haaf T. Epigenetics of gestational diabetes mellitus and offspring health: the time for action is in early stages of life. Mol Hum Reprod 2013;19(7):415–422.
144. Liu ZN, Jiang Y, Liu XQ, et al. MiRNAs in gestational diabetes mellitus: potential mechanisms and clinical applications. J Diabetes Res 2021;2021:4632745.
145. Elhag DA, Al Khodor S. Exploring the potential of microRNA as a diagnostic tool for gestational diabetes. J Transl Med 2023;21(1):392.
146. Tang N, Liu Y, Yang S, et al. Correlation between newborn weight and serum BCAAs in pregnant women with diabetes. Nutr Diabetes 2024;14:38.
147. Zhang Z, Zhou Z, Li H. The role of lipid dysregulation in gestational diabetes mellitus: early prediction and postpartum prognosis. J Diabetes Investig 2024;15(1):15–25.
148. Alesi S, Ghelani D, Rassie K, et al. Metabolomic biomarkers in gestational diabetes mellitus: a review of the evidence. Int J Mol Sci 2021;22(11):5512.
149. Roverso M, Brioschi M, Banfi C, et al. A preliminary study on human placental tissue impaired by gestational diabetes: a comparison of gel-based versus gel-free proteomics approaches. Eur J Mass Spectrom 2016;22:71–82.
150. Assi E, D'Addio F, Mandò C, et al. Placental proteome abnormalities in women with gestational diabetes and large-for-gestational-age newborns. BMJ Open Diabetes Res Care 2020;8(2):e001586.
151. Dungan KM. 1,5-anhydroglucitol (GlycoMark) as a marker of short-term glycemic control and glycemic excursions. Expert Rev Mol Diagn 2008;8(1):9–19.
152. Pramodkumar TA, Jayashri R, Gokulakrishnan K, et al. Relationship of glycemic control markers - 1,5 anhydroglucitol, fructosamine, and glycated hemoglobin among Asian Indians with different degrees of glucose intolerance. Indian J Endocrinol Metab 2016;20(5):690–695.
153. Dworacka M, Wender-Ozegowska E, Winiarska H, et al. Plasma anhydro-D-glucitol (1,5-AG) as an indicator of hyperglycaemic excursions in pregnant women with diabetes. Diabet Med 2006;23(2):171–175.
154. Pramodkumar TA, Jayashri R, Gokulakrishnan K, et al. 1,5 Anhydroglucitol in gestational diabetes mellitus. J Diabetes Complications 2019;33(3): 231–235.
155. Gounden V, Ngu M, Anastasopoulou C, et al. Fructosamine. In: StatPearls. Treasure Island (FL): StatPearls Publishing; August 14, 2023.
156. Gingras V, Rifas-Shiman SL, Switkowski KM, et al. Mid-pregnancy fructosamine measurement-predictive value for gestational diabetes and association with postpartum glycemic indices. Nutrients 2018;10(12):2003.
157. Crusell MKW, Hansen TH, Nielsen T, et al. Gestational diabetes is associated with change in the gut microbiota composition in third trimester of pregnancy and postpartum Microbiome 2018;6:89.
158. Wang J, Zheng J, Shi W, et al. Dysbiosis of maternal and neonatal microbiota associated with gestational diabetes mellitus. Gut 2018;67:1614–1625.
159. Pinto Y, Frishman S, Turjeman S, et al. Gestational diabetes is driven by microbiota-induced inflammation months before diagnosis. Gut 2023;72(5):918–928.
160. Amraei M, Mohamadpour S, Sayehmiri K, et al. Effects of vitamin D deficiency on incidence risk of gestational diabetes mellitus: a systematic review and meta-analysis. Front Endocrinol (Lausanne) 2018;9:7.
161. Tkachuk AS, Vasukova EA, Anopova AD, et al. Vitamin D status and gestational diabetes in Russian pregnant women in the period between 2012 and 2021: a nested case–control study. Nutrients 2022;14:2157.
162. Griew K, Nunn R, Fairbrother G, et al. Early pregnancy vitamin D deficiency and gestational diabetes: exploring the link. Aust J Gen Pract 2019;48:797–802.
163. Corcoy R, Mendoza LC, Simmons D, et al. The DALI vitamin D randomized controlled trial for gestational diabetes mellitus prevention: no major benefit shown besides vitamin D sufficiency. Clin Nutr 2020;39(3):976–984.
164. Huhn EA, Hoffmann I, Martinez De Tejada B, et al. Maternal serum glycosylated fibronectin as a short-term predictor of preeclampsia: a prospective cohort study. BMC Pregnancy Childbirth 2020;20(1):128.
165. Bonakdaran S, Azami G, Tara F, et al. Soluble (Pro) renin receptor is a predictor of gestational diabetes mellitus. Curr Diabetes Rev 2017;13(6):555–559.
166. Gokulakrishnan K, Maheswari K, Mahalakshmi MM, et al. Association of soluble (Pro) renin receptor with gestational diabetes mellitus. Endocr Pract 2015;21(1):7–13.
167. Kataria Y, Wu Y, Horskjær PH, et al. Iron status and gestational diabetes-a meta-analysis. Nutrients 2018;10(5):621.
168. Horie I, Haraguchi A, Ito A, et al. Impaired early-phase suppression of glucagon secretion after glucose load is associated with insulin requirement during pregnancy in gestational diabetes. J Diabetes Investig 2020;11(1):232–240.
169. Karasek D, Krystynik O, Kucerova V, et al. Adiponectin, A-FABP and FGF-19 levels in women with early diagnosed gestational diabetes. J Clin Med 2022;11(9):2417.
170. Yang MN, Zhang L, Wang WJ, et al. Prediction of gestational diabetes mellitus by multiple biomarkers at early gestation. BMC Pregnancy Childbirth 2024;24(1):601.
171. Hannah W, Pradeepa R, Anjana RM, et al. Early gestational diabetes mellitus: an update. J Assoc Physicians India 2023;71(9):101–103.
172. Mohan V, Hannah W, Anjana RM. Early gestational diabetes mellitus: an update about its current status. Int J Diabetes Dev Ctries 2024;44(Suppl 1):22–26.
173. Arora GP, Åkerlund M, Brøns C, et al. Phenotypic and genotypic differences between Indian and Scandinavian women with gestational diabetes mellitus. J Intern Med 2019;286:192–206.
174. Topriceanu CC, Chaturvedi N, Mathur R, et al. Validity of European-centric cardiometabolic polygenic scores in multi-ancestry populations. Eur J Hum Genet 2024;32(6):697–707.

REVIEW ARTICLE

Association of Physicians of India Consensus Recommendations for Vonoprazan in Management of Acid Peptic Disorders

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Abstract

The suppression of gastric acid secretion has long been the cornerstone of treatment for acid peptic disorders (APDs). Proton pump inhibitors (PPIs) have played a central role in managing these conditions, but their effectiveness can be hindered by notable limitations such as refractoriness or treatment failure due to inadequate acid suppression in some gastroesophageal reflux disease (GERD) patients, nonadherence to prescribed regimens due to the complexity of dosing, variability of response, and nocturnal acid breakthrough, etc. Vonoprazan is a first-in-class potassium-competitive acid blocker (P-CAB), recently introduced in India and also approved in several countries such as Japan, South Korea, and the USA. Extensive clinical evidence suggests that vonoprazan offers more potent acid suppression than PPIs. This consensus from the Association of Physicians of India (API) has been developed with the objective of providing key recommendations for the appropriate clinical usage of vonoprazan across various subsets of APDs, thereby optimizing the existing therapeutic options and improving the care and management of APD patients.

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Introduction

India is a land of multiple cultural practices with strong differences in foods consumed across different states and regions. Despite the lifestyle differences, acid peptic disorders (APDs) are widely prevalent across India.[1,2] Among various APDs, gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal disorders globally and in India.[3] Consensus guidelines from the Association of Physicians of India (API) and the Indian Society of Gastroenterology (ISG) identified GERD prevalence as being around <10% in most population studies.[4] Besides GERD, peptic ulcer disease (PUD) has been a significant contributor to morbidity and mortality.[5] Amidst multiple risk factors, infection with *Helicobacter pylori* has been identified as a significant contributor to APDs and gastric malignancy.[6] Among all these APDs, inhibition of gastric acid secretion has been the mainstay of treatment. The self-medication of antacids in the setting of heartburn or similar symptoms is often insufficient, as individuals tend to stop drugs with some symptomatic relief. This leads to massive under-treatment of APDs. Over the last few decades, H_2 receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs) have been the principal acid suppressants.[7] Despite their efficacy in APDs, nonresponsiveness to PPIs in GERD and *H. pylori* infection is not uncommon.[8–10] Vonoprazan is a novel potassium-competitive acid blocker (P-CAB) recently approved in India and may represent a real breakthrough in acid suppression. Considering the pharmacological limitations of PPIs, there is a strong need to understand the pharmacokinetics, pharmacodynamics, and clinical evidence pertaining to the use of vonoprazan. It is necessary, on the part of the treating physicians, to adequately and safely use this new therapeutic entity in different subsets of APD patients. At present, there is no guidance document from India available regarding the appropriate clinical usage of vonoprazan.

Need for the Consensus

In India, primary care physicians or family physicians are the first point of contact for patients with complaints related to APDs. However, inappropriate use of PPIs is widely prevalent in the Indian setting.[11,12] This is of great concern considering the suboptimal dosing, insufficient acid suppression, adverse effects, and drug interactions associated with PPIs. Owing to such practices and concerns, Indian experts have published recommendations for the rational use of PPIs.[13] Another important aspect is the under-dosing of PPIs in indications requiring twice-daily dosing of PPIs. However, this has not been observed in routine clinical practices, probably because of physician unawareness, clinical inertia in prescribing

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twice-daily dosing of PPIs, or possible fear of adverse effects.

Vonoprazan, a first-in-class P-CAB, was first approved in Japan in 2015 and subsequently approved in more than 15 countries, including Russia, South Korea, and the USA.[14] Over the period of 8 years, vonoprazan has accumulated considerable clinical evidence globally in several acid-related disorders. In 2024, regulatory approval of vonoprazan was further expanded in India.[15] In clinical studies, vonoprazan has shown effectiveness in PPI-resistant erosive esophagitis (EE), nonerosive reflux esophagitis (NERD), as well as in *H. pylori* regimens.[16–18] Although substantial clinical studies on vonoprazan have been published globally, no guidance document on its usage in Indian clinical practice has been published or is available to date. Therefore, to ensure vonoprazan's appropriate clinical usage across various subsets of APDs and to optimize the existing therapeutic options, this consensus document has been developed to provide relevant guidance to Indian physicians on the use of vonoprazan in Indian clinical settings. In this context, the expert working group of API recognized an urgent need to develop this consensus to guide physicians across India in the appropriate use of vonoprazan for managing various APDs.

Approach to the Consensus Development

Expert Panel

For this consensus development, a multidisciplinary consensus working group was formulated by the lead expert from the API. Each expert involved in the consensus had vast clinical experience in the management of APDs in India. They also had experience with prescribing Vonoprazan in different patient profiles. The experts belonged to specialties such as internal medicine, gastroenterology, otorhinolaryngology, pulmonology, cardiology, rheumatology, and nephrology.

Conesus Statements

The lead expert, in discussion with others, developed the consensus statements. While deriving the consensus statements, the criteria of answerability, effectiveness, potential for translation to clinical practice, novelty, and potential impact on the healthcare burden were considered. A total of 13 statements were initially framed for presentation in the consensus working group meeting.

Arriving at a Consensus

We utilized the Delphi method for arriving at a consensus. The Delphi method is a scientifically proven technique that assists in the organization and management of structured group discussions. Often, it aims to generate insights on situations wherein there is limited information or there is a need to address current or future challenges in given situations. It has been frequently used in medicine.[19] In this consensus development, there were two rounds of consensus working group experts. In the initial round of discussion, the lead expert presented the clinical evidence pertaining to each consensus statement, followed by the discussion among the experts. After the discussion, each expert was asked to rate their opinion on a 5-point Likert scale as strongly disagree, disagree, neutral, agree, strongly agree.[20] The voted opinion was collated from each expert and was analyzed descriptively.

Acceptance Criteria

We used a 5-point Likert scale (strongly agree, agree, neutral, disagree, and strongly disagree) for expert voting.[21] The expert voting for agree/strongly agree for a given consensus statement was considered as acceptable. To finally accept or refute the consensus, a voting percentage of 85% was considered as the cutoff for accepting the consensus statement. Figure 1 provides the key steps in developing the consensus. Table 1 summarizes all the finally accepted consensus statements.

Prevalence of Acid Peptic Disorders in India

Acid peptic disorders are widely prevalent in India. A meta-analysis of nine studies with 20,614 subjects reported a pooled GERD prevalence of 15.6%.[22] The ISG consensus on GERD in adults identified that GERD prevalence ranges between 7.6 and 30%, with most studies reporting it to be <10%.[23] In relation to GERD, EE and NERD are important contributors to symptomatology and morbidity. In EE diagnosed by upper GI (UGI) endoscopy, India ranks second in the world with a prevalence of 52% and is preceded by Indonesia (55%).[24] A multiethnic study from Malaysia involving 1000 patients reported NERD prevalence of 28.2, 32.1, and 16.8% in Malay, Indian, and Chinese ethnicities, respectively. The Indian race was also the strongest risk factor for NERD.[25] Based on the UGI endoscopy, EE is classified as grade A–D based on the size and extent of mucosal breaks (Table 2).[26] A recent study from South India involving 100 refractory GERD patients identified NERD in 33% and EE in 67% of cases. LA grade B was the most frequent EE (43%).[27] GERD has also been linked to the development of Barrett's esophagus (BE). A study from West India observed 278 patients with GERD over 2 years and reported BE in 16.54% of cases.[28] The API-ISG consensus also identifies BE prevalence in India to range from 2.6 to 9%.[4] Another important acid reflux disorder is laryngopharyngeal reflux disease (LPRD). A recent survey of 2300 individuals from India was performed to detect LPRD using the reflux symptom index (RSI). In 253 responders, RSI was >13, amounting to an 11% prevalence of LPRD with no difference in males and females (11.2 vs 10.6%, respectively).[29] The burden of *H. pylori* disease is enormous in India.[30,31] Recent global estimates indicate that the crude prevalence of *H. pylori* is 35.1%. In India, the pooled prevalence of *H. pylori* from 12 studies in adults was observed to be 59.5%.[32] *H. pylori* has been linked to the development of PUD. Over three decades (1990–2019), there has been a substantial reduction in PUD-related age-standardized mortality in India.[33] Nonetheless, the PUD burden still remains an important issue in the Indian setting.

- Consensus 1: There is a substantial presence of APDs in India [agree/strongly agree: 100%].

Limitations of Proton Pump Inhibitors

Since their introduction, PPIs have been used extensively across the globe and in India as well. Although proven effective in APDs, PPIs have notable limitations. One important limitation is the relative ineffectiveness of PPIs in GERD. Nearly 40% of patients with GERD do not respond to 8-week therapy of PPIs and are labeled as refractory GERD.[34,35] One possible reason for such inefficacy could be suboptimal

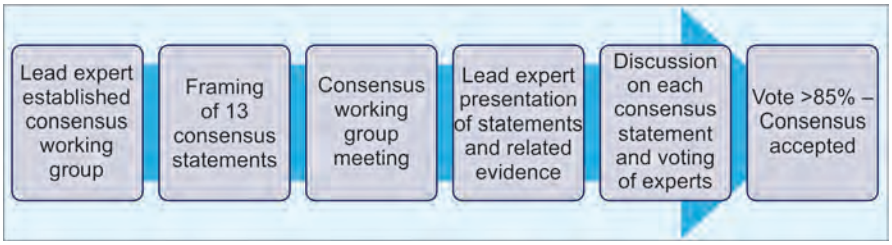

Fig. 1: Approach to the consensus development

Table 1: Consensus statements

PREVALENCE OF APDs IN INDIA
Consensus 1: There is a substantial presence of APDs in India [agree/strongly agree: 100%]
LIMITATIONS OF PPIs
Consensus 2: Currently available PPIs have certain limitations in management of GERD [agree/strongly agree: 100%]
FOOD AND PPIs ADMINISTRATION TIMING
Consensus 3: In real-world clinical practice, majority of GERD patients on PPI therapy do not comply with the advice of taking PPIs at least 30–45 minutes before meal that may lead to diminished treatment effectiveness and/or increased treatment failures [agree/strongly agree: 100%]
VONOPRAZAN PHARMACOLOGY
Consensus 4.1: In managing APDs, vonoprazan potentially overcomes the clinically relevant limitations of PPIs [agree/strongly agree: 100%]
Consensus 4.2: In managing GERD patients with predominant nocturnal acid breakthrough, vonoprazan may be considered as an alternative treatment approach to PPIs [agree/strongly agree: 100%]
Consensus 4.3: Vonoprazan can be administered irrespective of the meal timing [agree/strongly agree: 100%]
VONOPRAZAN AND REFRACTORY GERD
Consensus 5: In refractory GERD patients, switching from PPIs to vonoprazan (20 mg, once daily) is considered as the most suitable treatment approach [agree/strongly agree: 100%]
VONOPRAZAN & EROSIVE ESOPHAGITIS (EE)
Consensus 6.1: In mild EE (Los Angeles grade A and B), vonoprazan (20 mg, once daily) may be considered as an alternative to PPIs as it reduces the treatment duration by 4 weeks [agree: 91.7%/neutral:8.3%]
Consensus 6.2: Vonoprazan (20 mg, once daily) may be considered as an alternative to PPIs in mild EE (LA grade A/B) patients who are noncompliant to PPI dosing schedule [agree/strongly agree: 100%]
Consensus 7: Vonoprazan is recommended as the initial treatment approach for severe EE (LA grades C/D) [agree/strongly agree: 100%]
VONOPRAZAN & NON-EROSIVE REFLUX DISEASE (NERD)
Consensus 8.1: Vonoprazan may be considered as an alternative to PPIs in the treatment of NERD with excessive esophageal acid exposure [agree/strongly agree: 100%]
Consensus 8.2: In the long-term management of NERD, vonoprazan may be considered as an on-demand treatment approach [agree/strongly agree: 100%]
VONOPRAZAN & *H. PYLORI* ERADICATION REGIMENS
Consensus 9: In eradication regimens for *H. pylori* infection, vonoprazan is recommended in place of PPIs [agree/strongly agree: 100%]
VONOPRAZAN AND NSAID INDUCED PEPTIC ULCERS
Consensus 10: Vonoprazan can be an alternative to PPIs as a concomitant therapy in patients at a high risk of peptic ulcer with chronic use of NSAIDs [agree/strongly agree: 100%]
VONOPRAZAN & LARYNGOPHARYNGEAL REFLUX DISEASE (LPRD)
Consensus 11: Vonoprazan may be considered as an alternative to PPIs in the treatment of LPRD [agree: 100%]
VONOPRAZAN LONG TERM SAFETY
Consensus 12.1: In the maintenance therapy of GERD, vonoprazan is found to be safe (clinical evidence is up to 5 years–as per Japanese VISION trial) [agree/strongly agree: 100%]
Consensus 12.2: In patients with cardiovascular comorbidity receiving antiplatelet therapy, vonoprazan may be considered as a treatment option with careful monitoring [agree/strongly agree: 100%]
VONOPRAZAN IN HEPATIC AND RENAL IMPAIRMENT
Consensus 13.1: Vonoprazan can be considered in patients with renal impairment with careful monitoring (as per dosages suggested in Table 5) [agree/strongly agree: 100%]
Consensus 13.2 Vonoprazan can be considered in patients with hepatic impairment with careful monitoring (as per dosages suggested in Table 5) [agree/strongly agree: 100%]

Table 2: Los Angeles (LA) Grading of Erosive Esophagitis (EE)

LA grade	*UGI endoscopy finding*
A	≥1 mucosal breaks, <5 mm long, no extension between tops of 2 mucosal folds
B	≥1 mucosal breaks, >5 mm long, no extension between tops of 2 mucosal folds
C	≥1 mucosal breaks, continuous between tops of 2 or more mucosal folds, involves <75% of the esophageal circumference
D	≥1 mucosal breaks, continuous between tops of 2 or more mucosal folds, involves at least 75% of the esophageal circumference

adherence and inappropriate use of PPIs.[36] PPIs are prodrugs and provide effective acid suppression only after protonation to form disulfide bonds with cysteines of the H^+, K^+-ATPase pump. As PPIs irreversibly inhibit the active proton pump, it is necessary to administer PPIs 30–45 minutes before a meal to achieve peak concentration at gastric canaliculi.[37] This limits the PPIs administration in relation to food. In addition, the stability of the binding of PPIs to the proton pump determines the duration of pump inhibition.[37] Additionally, the short half-life of PPIs is a concern, as once- or twice-daily administration may not achieve complete acid suppression. Nearly 20% of pumps are synthesized in 24 hours, and it takes 48–73 hours for PPIs to reach the steady-state phase of acid inhibition.[37] Another limitation is nocturnal acid-breakthrough (NAB), which occurs in

40–70% of GERD patients receiving PPIs.[38,39] This can contribute to esophageal mucosal damage. Another important limitation with PPIs is drug-drug interactions involving CYP2C19 and CYP3A4 metabolism. Liver function impairment and older age impact the clearance of PPIs. Mutations in CYP2C19 also affect the metabolism of PPIs, and 15–20% of Asians are known to be rapid metabolizers, increasing the risk of side effects.[40]

- Consensus 2: Currently available PPIs have certain limitations in the management of GERD [agree/strongly agree: 100%].

Food and Proton Pump Inhibitors Administration Timing

PPIs need to be administered 30–45 minutes before a meal to achieve the inhibition of active proton pumps. A survey of 100 GERD patients who had persistent symptoms despite PPIs was conducted to identify suboptimal dosing of PPIs. Suboptimal dosing was considered when PPIs were taken >60 minutes prior to meals, after meals, as needed, and at bedtime before sleeping. About 54% of respondents were dosed suboptimally, whereas only 12% were taking PPIs in a manner that maximized acid suppression.[41] The OSCAR trial reported that the administration of PPIs 30 minutes before breakfast, compared to any other time of administration, is associated with improvement in GERD symptoms.[42] In India, studies have identified that incorrect timing of PPI administration contributes significantly to the persistence of GERD symptoms.[27] Further, studies identify a strong need for patient education and reinforcement of dosing instructions by treating physicians in relation to PPI dosing.[43]

- Consensus 3: In real-world clinical practice, the majority of GERD patients on PPI therapy do not comply with the advice of taking PPI at least 30–45 minutes before a meal, which may lead to diminished treatment effectiveness and/or increased treatment failures [agree/strongly agree: 100%].

Vonoprazan: A Potassium-competitive Acid Blocker

P-CABs are a new class of drugs that target the potassium binding sites of proton pumps to exhibit acid suppression. Vonoprazan is the first P-CAB with initial global approval in Japan (2015)[44] and has been approved in the USA.[45] In the gastric parietal cells, the H^+–K^+ ATPase pumps (proton pumps) are stored in tubulovesicles and are inactive. Once pumps are inserted in the canalicular membrane at luminal borders, the proton pumps are activated. Part of the pump that protrudes in the lumen is the extra-cytoplasmic secretory canaliculus. This section is acidic as it is exposed to the gastric lumen. PPIs, being prodrugs, are converted to sulfenamide, a step necessary for the drug to bind to cysteines on active proton pumps. The site of accumulation and activation of PPIs is therefore the extra-cytoplasmic secretory canaliculus. The binding of PPIs to cysteine residues is by covalent disulfide bonds and is irreversible. Vonoprazan, a P-CAB, is not a prodrug, and there is no need for its activation or acid dependence for proton pump binding. Vonoprazan binds to both active pumps present at the membrane of parietal cells as well as the pumps that are inactive in the tubulovesicles. The binding of vonoprazan is ionic and is thus reversible. Vonoprazan blocks the access of potassium (K^+) ions to the potassium-binding site of the pump that is necessary for the exchange of H^+ into the lumen. This results in reduced entry of H^+ ions into the gastric lumen and helps to reduce both basal and stimulated gastric acid secretion (Fig. 2).[46,47]

Pharmacodynamic Effects

Compared to PPIs, vonoprazan is shown to have rapid and potent antacid activity as measured by 24-hour gastric pH measurements. Better gastric acid suppression than lansoprazole has been reported in the US study.[47] In another randomized, cross-over study from Japan, a comparatively better acid suppressive effect of vonoprazan than either esomeprazole or rabeprazole was reported (Fig. 3). The likelihood of NAB with vonoprazan was lower as the duration of vonoprazan was 4 hours longer to maintain pH >4.[48] These studies prove that vonoprazan has a significantly rapid impact on intragastric pH and the effect is sustained for 24 hours. Based on the results of the US study, vonoprazan can be taken irrespective of fed or fasted conditions.[49] Table 3 provides a comparative assessment of PPIs vis-à-vis vonoprazan.[50]

- Consensus 4.1: In managing APDs, vonoprazan potentially overcomes the clinically relevant limitations of PPIs [agree/strongly agree: 100%].
- Consensus 4.2: In managing GERD patients with predominant NAB P, vonoprazan may be considered as an alternative treatment

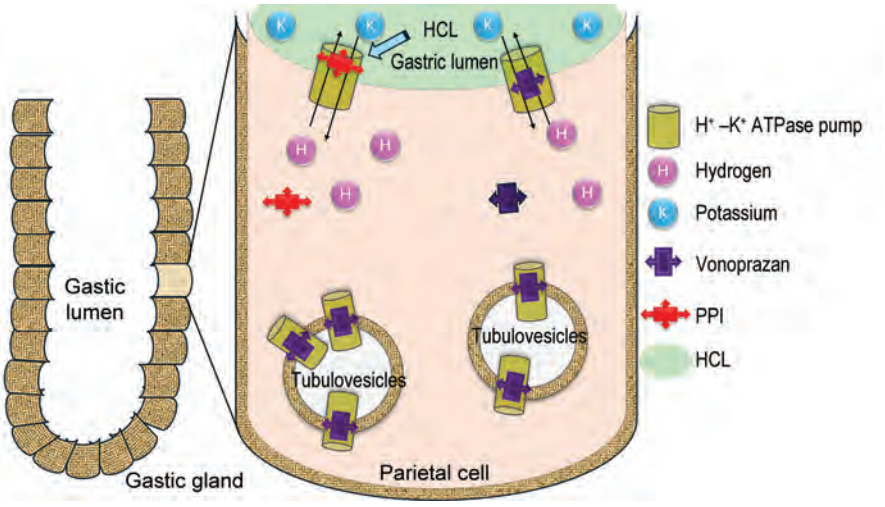

Fig. 2: Mechanism of action of vonoprazan: In the gastric parietal cells, PPI block the H^+–K^+ ATPase pump from the luminal side after their activation in the gastric acid. PPIs do not affect the resting or inactive pumps in the tubulovesicles. Vonoprazan blocks both active and inactive pumps in the parietal cells at the active site of potassium. Entry of potassium inside the cell is inhibited and hydrogen exchange fails leading to lesser hydrogen concentration in the lumen and thereby decreased acid output.

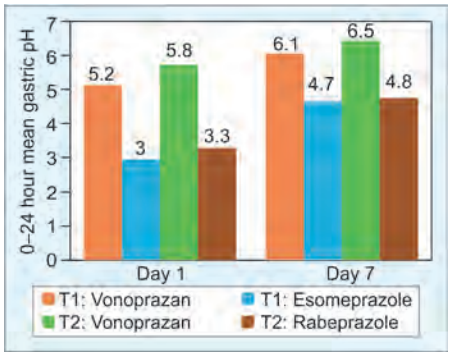

Fig. 3: 0–24 hour mean gastric pH in vonoprazan, esomeprazole and rabeprazole groups: T1—first time period of the study; T2—second time period of the study

approach to PPIs [agree/strongly agree: 100%].

- Consensus 4.3: Vonoprazan can be administered irrespective of the meal timing [agree/strongly agree: 100%].

Vonoprazan and Refractory GERD

Gastroesophageal reflux disease (GERD) is termed refractory when there are typical or atypical symptoms of GERD with no response to twice-daily PPI therapy for a minimum of 8 weeks.[27] Besides noncompliance and improper or underdosing of PPIs, residual reflux, esophageal hypersensitivity to weakly acidic reflux, chronic and persistent breach in the mucosal integrity of the esophagus, and concomitant psychological distress are the major factors identified to be contributory to refractory GERD.[35] Management of such refractory GERD is difficult. Possible approaches for the management of refractory GERD are summarized in Figure 4.

Multiple studies have shown the short-term (4–12 weeks) as well as long-term (1 year) efficacy of vonoprazan in PPI-refractory GERD.[51,52] A systematic review and meta-analysis of three observational studies reported that vonoprazan 20 mg for 4–8 weeks was associated with symptom improvement in a significant proportion of patients (86.3%) with PPI-resistant GERD.[16] These studies are further supported by the international recommendations. Guidelines from the Japanese Society of Gastroenterology (2021) advised that vonoprazan can be considered for PPI-refractory GERD. In addition, guidelines indicate that the use of prokinetics and Japanese herbal medicine can be considered.[53] The American Gastroenterology Association (AGA) clinical practice update also recommends that vonoprazan can be used in patients who have acid reflux despite twice-daily therapy with PPIs.[50]

- Consensus 5: In refractory GERD patients, switching from PPIs to vonoprazan is considered the most suitable treatment approach [agree/strongly agree: 100%].

Table 3: Pharmacokinetic and pharmacodynamic comparison between PPIs and vonoprazan

Parameter	*PPIs*	*Vonoprazan (P-CAB)*
Acid stability	Labile (enteric coating must)	Stable
Prodrugs	Yes	No
Activation in acid environment	Required	Not required
Binding to H^+–K^+ ATPase pump	Covalent, irreversible	Ionic, reversible
Proton pump inhibition	Only active	Both active and inactive
Time of administration	30–60 minutes before meal	Food independent
Half life	1–2 hours	6–9 hours
Onset of action	Delayed	Rapid
Time to maximal acid suppression	3–5 days	1 day
24-hour acid suppression	Not achieved	Achieved
Nocturnal acid breakthrough	More likely	Less likely
Duration of acid suppression	Shorter	Longer
CYP2C19 related interactions	Yes	No

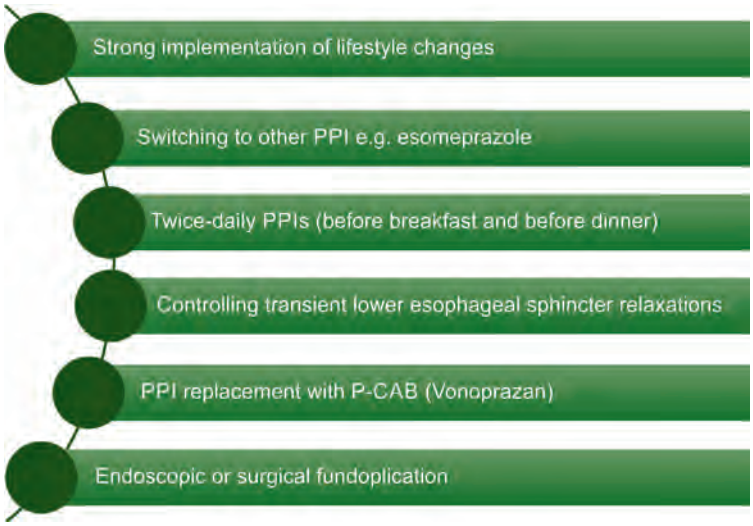

Fig. 4: Possible approaches to manage refractory GERD

Vonoprazan in Erosive Esophagitis

Mild Erosive Esophagitis (Los Angeles Grade A and B)

The 2021 Japanese Society of Gastroenterology guidelines have recommended the use of either PPI for 8 weeks or vonoprazan for 4 weeks. This suggests that vonoprazan can help reduce the treatment duration by 4 weeks. After 4 weeks, maintenance therapy with vonoprazan can be considered to prevent recurrences. Patients who do not respond to 8 weeks of standard-dose PPI therapy can be switched to vonoprazan 20 mg daily.[53] The AGA practice update also recommends that clinicians may use P-CABs in selected patients who fail therapy with twice-daily PPIs.[50] Thus, vonoprazan can be an alternative to PPIs.

- Consensus 6.1: In mild EE (Los Angeles grade A and B), vonoprazan 20 mg, once daily, may be considered an alternative to PPIs as it reduces the treatment duration by 4 weeks [agree: 91.7%/neutral: 8.3%].
- Consensus 6.2: Vonoprazan (20 mg once daily) may be considered an alternative to PPIs in mild EE (LA grade A/B) patients who are noncompliant with the PPI dosing schedule [agree/strongly agree: 100%].

Severe Erosive Esophagitis (Los Angeles Grade C and D)

In severe EE, PPIs have been standard treatment for a long time. However, nearly 15% of EE patients do not achieve complete healing even after 8 weeks of PPIs. Even with continuation of PPIs, relapse within 6 months is seen in 24–41% of EE patients with LA grade C and D.[54] With severe EE, failure of PPI calls for effective therapy. Vonoprazan has been shown to be effective in both healing and maintenance of healing in severe EE grades.[55] In another double-blind trial from

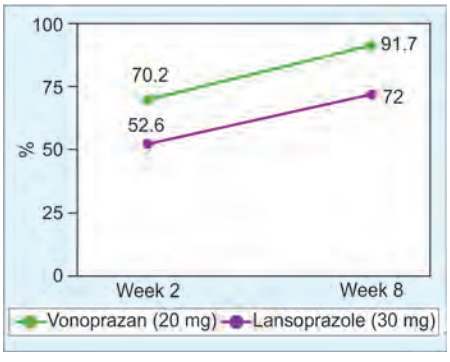

Fig. 5: Healing rates in Los Angeles grade C/D EE with vonoprazan and lansoprazole

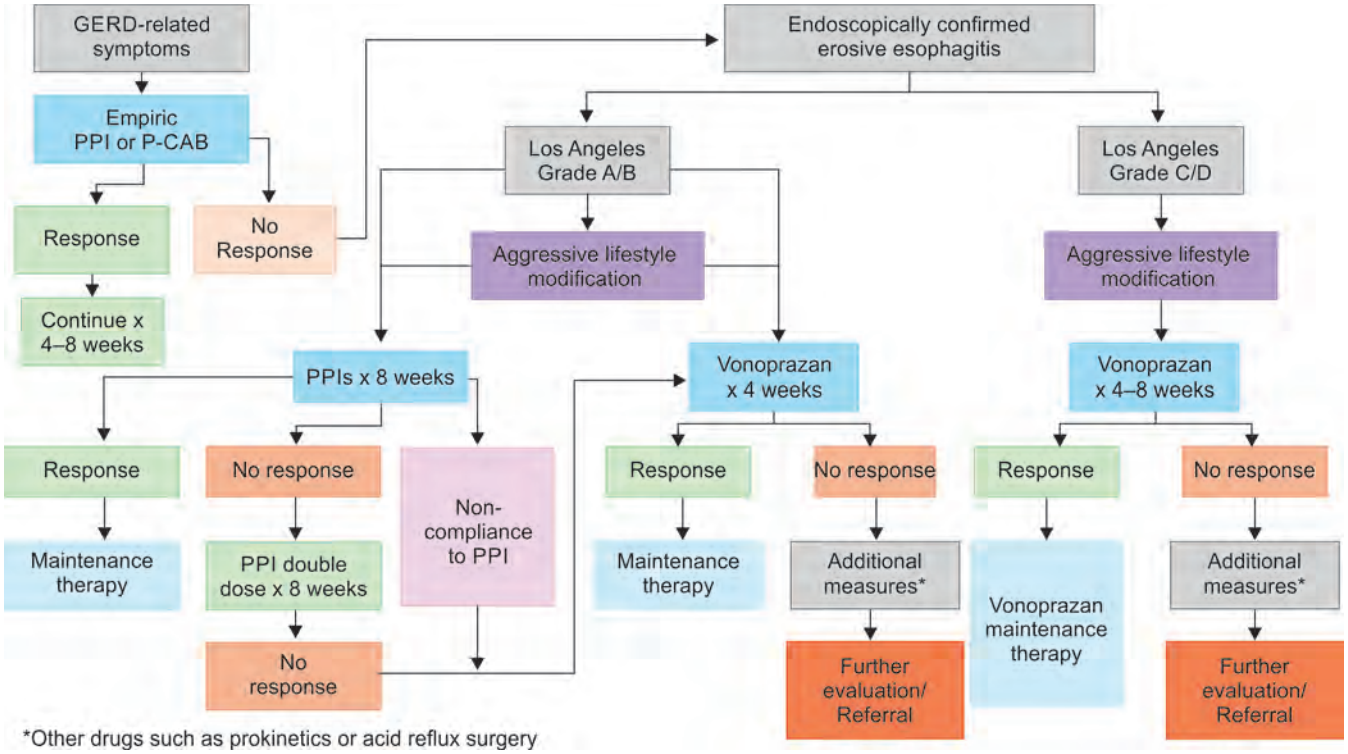

Fig. 6: Approach to the management Erosive Esophagitis (EE)

the US, Laine et al. reported greater overall EE healing rates (all grades A–D) at 8 weeks with vonoprazan than lansoprazole (92.9 vs 84.6%). Figure 5 provides healing rates for grade C/D EE in two groups. During the maintenance phase, healing rates of grade C/D EE at 24 weeks were significantly better with vonoprazan 20 mg (77.2%) and 10 mg (74.7%) than lansoprazole 15 mg (61.5%). Also, the heartburn-free days were substantially higher with both doses of vonoprazan.[56] These findings indicate that vonoprazan has substantial promise as starting therapy for severe EE. This is confirmed by the Japanese Gastroenterology Guidelines[53] as well as the AGA practice update recommendations.[50] Also, vonoprazan has been approved for this indication by the United States Food and Drug Administration (USFDA).[45] Figure 6 provides the approach to the management of EE.

- Consensus 7: Vonoprazan is recommended as the initial treatment approach for severe EE (Los Angeles grades C/D) [agree/strongly agree: 100%].

Vonoprazan in Nonerosive Reflux Disease

NERD does not involve the acidic erosion of the esophageal lining, and thus the absence of erosion on endoscopy is classified as NERD. It commonly occurs because of nonacid or weak acid reflux, causing symptoms such as heartburn. PPIs have long been used in heartburn due to NERD.[57] Vonoprazan has been evaluated in phase 2 and phase 3 trials for heartburn in NERD. A phase 2 trial involved 458 patients with NERD having heartburn for ≥6 months or during any ≥4 days of consecutive seven days in the screening period with normal endoscopic features. In a 4-week run-in period, all patients received vonoprazan 20 mg daily and were randomized at the end of 4 weeks to vonoprazan 10, 20, and 40 mg groups and placebo as "on-demand" therapy (to be taken only when heartburn occurs). After 6 weeks, complete and sustained relief was reported by 56, 60.6, and 70% of patients from the three vonoprazan dose groups, respectively. Compared to the response rate of 27.3% in the placebo group, all vonoprazan doses provided significantly better results. There were no serious adverse events related to the treatments.[58] The PHALCON-NERD-301 trial confirmed the effectiveness of vonoprazan in NERD. The trial included patients similar to the phase 2 study. Patients were randomized to vonoprazan 20 mg, 10 mg, and placebo. Patients in the placebo arm were rerandomized to either vonoprazan 10 or 20 mg. All patients continued treatment for 20 more weeks. Vonoprazan significantly improved the primary efficacy results of 24-hour heartburn-free days (Fig. 7) in NERD patients. The effect on reducing 24-hour heartburn was evident on day 1. In the extension phase, patients shifted from placebo to vonoprazan rapidly responded and joined

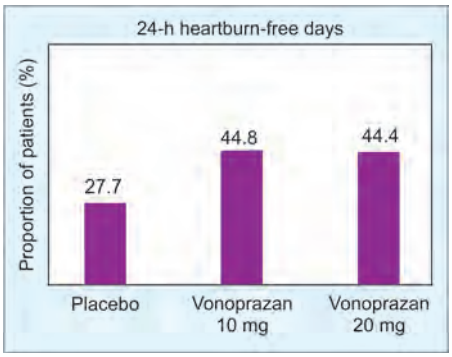

Fig. 7: Vonoprazan effect on 24-hour heartburn-free days in NERD patients in 4-week

the previously continued vonoprazan group in terms of the efficacy endpoint. The study concluded that NERD patients derived benefit in terms of relief from heartburn as early as day 1, and benefits persisted over a period of 24 weeks. Both doses of vonoprazan were effective.[59] This led to the indication approval for vonoprazan by the USFDA.[45] The Japanese guidelines also indicated that P-CABs like vonoprazan may also be effective in NERD with excessive esophageal acid exposure.[53]

- Consensus 8.1: Vonoprazan may be considered as an alternative to PPIs in the treatment of NERD with excessive esophageal acid exposure [agree/strongly agree: 100%].
- Consensus 8.2: In the long-term management of NERD, vonoprazan may

be considered as an on-demand treatment approach [agree/strongly agree: 100%].

Vonoprazan in *H. Pylori* Infection

As discussed previously, the *H. pylori* burden is substantial in India. Current management of *H. pylori* is dependent on the use of PPIs and antibiotics. It has been shown that acid suppression is of prime importance in *H. pylori* eradication. *H. pylori* has the ability to survive in an acidic environment. It has acid acclimation activity by which the bacteria are able to maintain vitality but not growth. The bacteria raise the cytoplasmic pH moderately against external acidic pH. With the rise in pH after the use of PPIs it grows in the less acidic pH in the stomach with a doubling time of 4–6 hours.[60] It is at this phase that antibiotics such as amoxicillin and clarithromycin effectively exert antibacterial activity. The current 2024 regimens recommended by the American College of Gastroenterology (ACG) are shown in Table 4.[61] The American Gastroenterological Association recommends that P-CAB (vonoprazan) should be used in place of PPIs for most patients with *H. pylori*.[50] This has also been supported by the US FDA approval of vonoprazan use in combination with clarithromycin and amoxicillin as triple therapy or with amoxicillin as double therapy for adults with *H. pylori*.[45]

One of the key problems with *H. pylori* is the recurrence of disease. Multiple recurrences are common in previously treated individuals. To differentiate reinfection and recrudescence, a duration of 1 year has been considered. Recurrence of *H. pylori* after 1 year of initial eradication should be labeled as reinfection.[62] In India, there is significant recurrence of *H. pylori*, and rates may go as high as 60%.[63] It should be noted that asymptomatic *H. pylori* infection does not demand treatment. It is only symptomatic infection, with or without complications, that necessitates *H. pylori* treatment. It is recommended that after therapy of *H. pylori*, the test of cure (e.g., urea breath test, fecal antigen test, etc.) should be performed after 4 weeks of completion of treatment.[61] With respect to the use of vonoprazan in *H. pylori*, Indian studies are required. Nonetheless, it can be considered over PPIs in *H. pylori* management.

- Consensus 9: In eradication regimens for *H. pylori* infection, vonoprazan is recommended in place of PPIs [agree/strongly agree: 100%].

Vonoprazan and NSAID Induced Peptic Ulcers

Chronic use of painkillers such as nonsteroidal anti-inflammatory drugs (NSAIDs) or even low-dose aspirin carries a substantial risk of PUDs. Vonoprazan has been evaluated in this indication in multiple randomized studies. In one study from Japan by Mizokami et al., 642 patients on long-term NSAIDs who were at risk of PUD recurrence were enrolled. Initially, patients were randomized to vonoprazan (10–20 mg) or lansoprazole (15 mg daily) for a 24-week double-blind period, followed by an extension study. During the 24 weeks, both doses of vonoprazan were noninferior to lansoprazole. Endoscopically confirmed ulcers were observed in 3.3, 3.4, and 5.5% of the three groups, respectively. During the extension period, also, vonoprazan was effective and safe.[64] A postmarketing surveillance study of 1 year with the use of vonoprazan in patients with a history of PUD who were receiving NSAIDs also reported an ulcer recurrence rate of 1.04% and a better safety profile. The rate of adverse drug reactions was 0.71%.[65] These data are further supported by a systematic review of 10 articles demonstrating vonoprazan as an effective and safe initial and maintenance therapy for PUD related to chronic use of aspirin or NSAIDs.[66] The AGA practice update guidelines recommend that vonoprazan may be useful in PUD patients who fail to respond to PPIs.[50]

- Consensus 10: Vonoprazan can be an alternative to PPIs as a concomitant therapy in patients at high risk of peptic ulcer with chronic use of NSAIDs [agree/strongly agree: 100%].

Vonoprazan and Laryngopharyngeal Reflux Disease

As discussed previously, LPRD is not an uncommon entity, and adequate treatment of reflux is necessary to provide symptomatic relief. LPRD should be diagnosed adequately in a clinical setting. Primary care physicians should consider the referral of such patients to the otorhinolaryngologist. An interesting observation from Humayun et al. is that most otorhinolaryngologists had prescribed suboptimal PPI dosing in LPRD patients. In their study, PPIs were used once or twice daily in 63 and 31% of patients, respectively.[67] In LPRD, vonoprazan has been evaluated in a small number of studies. In 89 Chinese patients with LPRD, vonoprazan 20 mg once daily was compared to esomeprazole 20 mg twice daily. After 8 weeks, symptom relief, as indicated by the RSI and reflux finding score (RFS), was significant with both therapies. The effective rate of the two treatments was 86.7 and 77.3%, respectively. Thus, vonoprazan once daily was considered noninferior to esomeprazole twice daily for the treatment of LPRD.[68] Another study compared similar treatments for the relief of gastroesophageal reflux-related cough (GERC). By the end of 2 months, vonoprazan was similar in efficacy to esomeprazole in terms of cough symptoms score. However, the reflux symptoms and quality of life were better with vonoprazan.[69] Considering this, there is a need to further explore vonoprazan in Indian patients with LPRD.

- Consensus 11: Vonoprazan may be considered as an alternative to PPIs in the treatment of LPRD [agree: 100%].

Vonoprazan: Long-term Safety

In the randomized clinical trials of vonoprazan for EE, NERD, and *H. pylori*, no major safety

Table 4: *H. pylori* treatment approaches recommended by ACG 2024 clinical guideline

Regimen	*Treatment naïve*	*Previously treated*	
		Empiric therapy	Antibiotic sensitivity proven
Bismuth Quadruple*	Recommended (14 days)		Suggested (14 days)
Rifabutin triple[#]	Suggested (14 days)		Suggested (14 days)
Vonoprazan triple**	–	–	Suggested (14 days)
Vonoprazan + amoxicillin	Suggested (14 days)	May be considered if other treatments are not available	
Levofloxacin triple[!]		–	Suggested[a] (14 days)

*Bismuth salt + nitroimidazole (e.g. metronidazole, tinidazole) + tetracycline (e.g. tetracycline, doxycycline) + PPI; [#]rifabutin + amoxicillin + PPI; **vonoprazan (20 mg) + clarithromycin (500 mg) + amoxicillin (1000 mg) (proven clarithromycin sensitivity); [!]levofloxacin/moxifloxacin (500/400 once) + amoxicillin (500 mg, twice daily)/nitroimidazole + PPI (proven levofloxacin sensitivity); [a]only when Bismuth quadruple or rifabutin therapies have failed or unavailable

Table 5: Indication-wise vonoprazan dosing recommendation in hepatic and renal impairment

Disease	*Indication*	
	EE	*H. pylori*
Hepatic impairment		
Child-Pugh class A	20 mg OD	20 mg BD
Child-Pugh class B	10 mg OD	Not recommended
Child-Pugh class C	10 mg OD	Not recommended
Renal impairment		
eGFR ≥30 mL/minute	20 mg OD	20 mg BD
eGFR <30 mL/minute	10 mg OD	Not recommended

eGFR: estimated glomerular filtration rate

Table 6: Salient features of vonoprazan

* Rapid onset of action (within 30 minutes)
* Acid stable, no need of enteric coating; PPIs are acid labile
* No impact of food, administered with or without food
* Inhibits both active and inactive proton pumps; PPIs inhibit only the active pumps
* Longer lasting acid suppression (durable 24-hour acid control)
* Effective control of nocturnal acid breakthrough
* More rapid healing of EE than PPIs
* First choice (over PPIs) in patients with more severe EE (Los Angeles Grade C & D)
* Improved GERD symptom relief after switching from PPIs
* Effective alternative to high-dose IV PPIs for the prevention of re-bleeding after endoscopic haemostasis in high-risk PU bleeding
* Clinical use in Japan for more than 8 years, approved in 15+ countries including the USA and India
* 5 years safety (Japanese VISION trial), no increased risk of malignant alterations
* No CYP2C19 related drugs interactions, can be administered with antithrombotic drugs like clopidogrel

concerns were reported with its use for up to 1 year. A recent VISION trial was a 5-year open-label randomized trial of vonoprazan for maintenance of EE. Adult patients who had healed EE on endoscopy entered the maintenance phase and were randomized to vonoprazan 10 mg or lansoprazole 15 mg once daily. At the end of 5 years, cumulative recurrence of EE was significantly lower with vonoprazan. Adverse events leading to treatment discontinuation were 4.4 and 1.5% in the two groups, respectively. Compared to lansoprazole, a higher proportion of vonoprazan patients had parietal cell hyperplasia and foveolar hyperplasia, with similar rates of enterochromaffin-like cell hyperplasia and G-cell hyperplasia. Though median serum gastrin levels were significantly higher, there was no increased risk of malignant transformations or gastric neuroendocrine tumors.[70] Another randomized trial assessed vonoprazan compared to PPI for prevention of high-risk PU rebleeding after endoscopic hemostasis. The population included elderly, hemodynamically unstable patients, indicating severe profiles. All patients had endoscopically confirmed high-risk bleeding PU and were randomized to vonoprazan (20 mg twice daily for 3 days followed by 10 mg once daily for 28 days) or pantoprazole (8 mg/hour intravenous for 3 days followed by 20 mg twice daily for 28 days). Patient profiles included some with coronary artery disease, cerebrovascular disease, and other comorbidities. Few patients were receiving aspirin, NSAIDs, warfarin, and direct oral anticoagulants. Thirty-day rebleeding rates were similar in the two groups (7.1 vs 10.4%, respectively), and vonoprazan was considered noninferior to pantoprazole.[71] Another study evaluated vonoprazan for bleeding after endoscopic submucosal dissection (ESD)-induced gastric ulcers in patients who were receiving antithrombotic therapy. Data synthesis from a randomized trial and observational study reported post-ESD bleeding in 8/86 patients in the vonoprazan group and 18/86 patients in the PPI group. This indicated better efficacy of vonoprazan than PPIs in preventing post-ESD bleeding among patients who are receiving antithrombotic medications.[72] Another nationwide database study from Japan identified that in 16,145 patients with ischemic heart disease who were receiving >2 antithrombotic agents (clopidogrel, ticagrelor, ticlopidine, prasugrel, or a low-dose aspirin), vonoprazan was noninferior to PPI in terms of UGI bleed occurrence at 6 months (3.14 vs 4.17%, respectively).[73] These data indicate that there is a less likely possibility of drug-drug interactions with vonoprazan, especially with antithrombotic drugs such as clopidogrel. Given the minimal activity of CYP2C19 in metabolizing vonoprazan, interaction based on CYP2C19-metabolizing medications is minimal. Also, the substantial inclusion of patients with established cardiovascular disease in these studies indicated no likely increased risk of cardiovascular abnormalities. However, further long-term studies are necessary with vonoprazan.

- Consensus 12.1: In the maintenance therapy of GERD, vonoprazan is found to be safe (clinical evidence is up to 5 years—as per Japanese VISION trial) [agree/strongly agree: 100%].
- Consensus 12.2: In patients with cardiovascular comorbidity receiving antiplatelet therapy, vonoprazan may be considered as a treatment option with careful monitoring [agree/strongly agree: 100%].

Vonoprazan in Hepatic and Renal Impairment

As per the approved USFDA label,[45] dosing recommendations for different indications are shown in Table 5.

- Consensus 13.1: Vonoprazan can be considered in patients with renal impairment with careful monitoring (as per dosages suggested in Table 5) [agree/strongly agree: 100%].
- Consensus 13.2: Vonoprazan can be considered in patients with hepatic impairment with careful monitoring (as per dosages suggested in Table 5) [agree/strongly agree: 100%].

Summary

Vonoprazan is a first-in-class P-CAB that is now clinically being used in India. Based on its pharmacology and currently available clinical evidence in different APDs, Table 6 brings some salient features of vonoprazan in comparison to PPIs.

Conclusion

This is the first consensus from India that provides a unified approach for the use of vonoprazan, a novel P-CAB, in the management of different APDs. The unique action of vonoprazan inhibiting active and

inactive proton pumps at gastric parietal cells provides effective acid suppression. Combined with its improved efficacy and safety in mild to severe APDs like GERD, EE, NERD, and *H. pylori* infection, vonoprazan holds promise to be a frontline therapy in APD management. Increasing evidence from the studies for de novo PUD and NSAID-induced ulcers shows substantial promise of this molecule in these indications as well. With a comparable safety profile to those of PPIs and better efficacy, vonoprazan has emerged as an excellent alternative to PPIs in mild to severe forms of APDs. In the Indian context, physicians should ensure the appropriate use of vonoprazan to gain maximum therapeutic benefits in APD patients.

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Author Contributions

All authors contributed to the development of this consensus. All authors read and approved the final manuscript.

Conflict of Interest

Ashwin Kotamkar, Shailesh Pallewar and Amit Qamra are full-time employees of Macleods Pharmaceuticals Ltd.

References

1. Barkun A, Leontiadis G. Systematic review of the symptom burden, quality of life impairment and costs associated with peptic ulcer disease. Am J Med 2010;123(4):358–366.
2. Wang R, Zou D, Ma X, et al. Impact of gastroesophageal reflux disease on daily life: the Systematic Investigation of Gastrointestinal Diseases in China (SILC) epidemiological study. Health Qual Life Outcomes 2010;8:128.
3. Nirwan JS, Hasan SS, Babar ZUD, et al. Global prevalence and risk factors of gastro-oesophageal reflux disease (GORD): systematic review with meta-analysis. Sci Rep 2020;10(1):5814.
4. Bhatia S, Pareek KK, Kumar A, et al. API-ISG consensus guidelines for management of gastroesophageal reflux disease. J Assoc Physicians India 2020;68(10): 69–80.
5. Peiffer S, Pelton M, Keeney L, et al. Risk factors of perioperative mortality from complicated peptic ulcer disease in Africa: systematic review and meta-analysis. BMJ Open Gastroenterol 2020;7(1):e000350.
6. Jones RG, Trowbridge DB, Go MF. Helicobacter pylori infection in peptic ulcer disease and gastric malignancy. Front Biosci 2001;6:E213–E226.
7. Prabhoo RY, Pai UA, Wadhwa A, et al. Multidisciplinary consensus for rationalizing the use of acid suppressants in children and adults: CONFOR. Euroasian J Hepatogastroenterol 2024;14(1):99–119.
8. Park HJ, Park SH, Shim KN, et al. The prevalence and clinical features of non-responsive gastroesophageal reflux disease to practical proton pump inhibitor dose in Korea: a multicenter study. Korean J Gastroenterol 2016;68(1):16–22.
9. Monaco L, Brillantino A, Torelli F, et al. Prevalence of bile reflux in gastroesophageal reflux disease patients not responsive to proton pump inhibitors. World J Gastroenterol 2009;15(3):334–338.
10. Gisbert JP, Pajares JM. Helicobacter pylori "rescue" regimen when proton pump inhibitor-based triple therapies fail. Aliment Pharmacol Ther 2002;16(6):1047–1057.
11. Verma N, Tayal V, Roy V. Proton pump inhibitors: prescribing practices, appropriateness of use, and cost incurred in a tertiary care, public, teaching hospital in New Delhi, India. MAMC J Med Sci 2019;5(3):113–120.
12. Churi S, Jogani A. Prospective assessment of prescribing pattern of intravenous proton pump inhibitors in an Indian tertiary-care teaching hospital. Indian J Pharm Pract 2014;7(4) 2–7.
13. Bhatia S, Shukla A, Johnson D, et al. An expert review and recommendations on the rational use of proton pump inhibitors: Indian perspective. J Assoc Physicians India 2019;67(4):88–96.
14. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Office of Surveillance and Epidemiology (OSE) Epidemiology: ARIA Sufficiency Templates Version: 2018-01-24. Vonoprazan. USFDA; 2024.
15. CDSCO Recommendations of the SEC (Gastroenterology & CDSCO Recommendations of the SEC (Gastroenterology &Hepatology) made in its 1st/24 meeting held on 16.01.2024 & 17.01.2024 at CDSCO (HQ), New Delhi, India. Available from: https://cdsco.gov.in/opencms/opencms/en/Committees/SEC/.
16. Simadibrata DM, Lesmana E, Fass R. A systematic review meta-analysis of the efficacy of vonoprazan for proton pump inhibitor-resistant gastroesophageal reflux diseaseand. J Gastroenterol Hepatol 2024;39(5):796–805.
17. Takeuchi T, Furuta T, Fujiwara Y, et al. Randomised trial of acid inhibition by vonoprazan 10/20 mg once daily vs rabeprazole 10/20 mg twice daily in healthy Japanese volunteers (SAMURAI pH study). Aliment Pharmacol Ther 2020;51:534–543.
18. Huang S, Li B, Pang XY, et al. Efficacy and safety of vonoprazan-based treatment of Helicobacter pylori infection: a systematic review and network meta-analysis. BMC Infect Dis 2024;24:953.
19. Beiderbeck D, Frevel N, von der Gracht HA, et al. Preparing, conducting, and analyzing Delphi surveys: cross-disciplinary practices, new directions, and advancements. MethodsX 2021;8:101401.
20. Taze D, Hartley C, Morgan AW, et al. Developing consensus in histopathology: the role of the Delphi method. Histopathology 2022;81(2):159–167.
21. Sullivan GM, Artino AR Jr. Analyzing and interpreting data from Likert-type scales. J Grad Med Educ 2013;5:541–542.
22. Rai S, Kulkarni A, Ghoshal UC. Prevalence and risk factors for gastroesophageal reflux disease in the Indian population: a meta-analysis and meta-regression study. Indian J Gastroenterol 2021;40:209–219.
23. Bhatia SJ, Makharia GK, Abraham P, et al. Indian consensus on gastroesophageal reflux disease in adults: a position statement of the Indian Society of Gastroenterology. Indian J Gastroenterol 2019;38(5):411–440.
24. Witarto AP, Witarto BS, Pramudito SL, et al. Risk factors and 26-years worldwide prevalence of endoscopic erosive esophagitis from 1997 to 2022: a meta-analysis. Sci Rep 2023;13(1):15249.
25. Rosaida MS, Goh KL. Gastro-oesophageal reflux disease, reflux oesophagitis and non-erosive reflux disease in a multiracial Asian population: a prospective, endoscopy based study. Eur J Gastroenterol Hepatol 2004;16(5):495–501.
26. Moayyedi P, Talley NJ. Gastro-oesophageal reflux disease. Lancet 2006;367(9528):2086–2100.
27. Verma S, Padmanabhan P, Sundar B, et al. Refractory gastroesophageal reflux disease (GERD): a clinical, endoscopic, and histopathological perspective—a single centre cross-sectional study. Gastroenterol Endosc 2024;2(3):107–111.
28. Mathew P, Joshi AS, Shukla A, et al. Risk factors for Barrett's esophagus in Indian patients with gastroesophageal reflux disease. J Gastroenterol Hepatol 2011;26(7):1151–1156.
29. Mishra P, Agrawal D, Chauhan K, et al. Prevalence of laryngopharyngeal reflux disease in Indian population. Indian J Otolaryngol Head Neck Surg 2022;74(Suppl 2):1877–1881.
30. Dhakal OP, Dhakal M. Prevalence of Helicobacter pylori infection & pattern of gastrointestinal involvement in patients undergoing upper gastrointestinal endoscopy in Sikkim. Indian J Med Res 2018;147(5):517–520.
31. Adlekha S, Chadha T, Krishnan P, et al. Prevalence of Helicobacter pylori infection among patients undergoing upper gastrointestinal endoscopy in a medical college hospital in Kerala, India. Ann Med Health Sci Res 2013;3(4):559–563.
32. Chen YC, Malfertheiner P, Yu HT, et al. Global prevalence of Helicobacter pylori infection and incidence of gastric cancer between 1980 and 2022. Gastroenterology 2024;166(4):605–619.
33. Sun J, Huang L, Li R, et al. Comparison of secular trends in peptic ulcer diseases mortality in China, Brazil and India during 1990–2019: an age-period-cohort analysis. Healthcare 2023;11(8):1085.
34. Dean BB, Gano AD Jr, Knight K, et al. Effectiveness of proton pump inhibitors in nonerosive reflux disease. Clin Gastroenterol Hepatol 2004;2(8):656–664.
35. Sifrim D, Zerbib F. Diagnosis and management of patients with reflux symptoms refractory to proton pump inhibitors. Gut 2012;61(9):1340–1354.
36. Ladd AM, Panagopoulos G, Cohen J, et al. Potential costs of inappropriate use of proton pump inhibitors. Am J Med Sci 2014;347:446–451.
37. Shin JM, Kim N. Pharmacokinetics and pharmacodynamics of the proton pump inhibitors. J Neurogastroenterol Motil 2013;19(1):25–35.
38. Nzeako UC, Murray JA. An evaluation of the clinical implications of acid breakthrough in patients on proton pump inhibitor therapy. Aliment Pharmacol Ther 2002;16:1309–1316.
39. Ghoshal UC, Chourasia D, Tripathi S, et al. Relationship of severity of gastroesophageal reflux disease with gastric acid secretory profile and esophageal acid exposure during nocturnal acid breakthrough: a study using 24-h dual-channel pH-metry. Scand J Gastroenterol 2008;43:654–661.
40. El Rouby N, Lima JJ, Johnson JA. Proton pump inhibitors: from CYP2C19 pharmacogenetics to precision medicine. Expert Opin Drug Metab Toxicol 2018;14:447–460.
41. Gunaratnam NT, Jessup TP, Inadomi J, et al. Sub-optimal proton pump inhibitor dosing is prevalent in patients with poorly controlled gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2006;23(10):1473–1477.
42. Waghray A, Waghray N, Perzynski AT, et al. Optimal omeprazole dosing and symptom control: a randomized controlled trial (OSCAR trial). Dig Dis Sci 2019;64(1):158–166.
43. Adu-Gyamfi KO, Palacio C, Jackson C, et al. S470 proton pump inhibitor dosing patterns are less than optimal among new referrals to an outpatient academic gastroenterology clinic. Am J Gastroenterol 2023;118(10S):S342.
44. Garnock-Jones KP. Vonoprazan: first global approval. Drugs 2015;75(4):439–443.
45. Highlights of Prescribing Information. VOQUEZNA (Vonoprazan) Tablets, for Oral use Initial U.S. Approval: 2022. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.

process&ApplNo=215151. [Accessed 28 November 2024].
46. PubChem. PubChem Compound Summary for CID 15981397, Vonoprazan. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Vonoprazan. [Accessed 28 November 2024].
47. Laine L, Sharma P, Mulford DJ, et al. Pharmacodynamics and pharmacokinetics of the potassium-competitive acid blocker vonoprazan and the proton pump inhibitor lansoprazole in US subjects. Am J Gastroenterol 2022;117(7):1158–1561.
48. Sakurai Y, Mori Y, Okamoto H, et al. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects—a randomised open-label cross-over study. Aliment Pharmacol Ther 2015;42(6):719–730.
49. Mulford DJ, Leifke E, Hibberd M, et al. The effect of food on the pharmacokinetics of the potassium-competitive acid blocker Vonoprazan. Clin Pharmacol Drug Dev 2022;11(2):278–284.
50. Patel A, Laine L, Moayyedi P, et al. AGA clinical practice update on integrating potassium-competitive acid blockers into clinical practice: expert review. Gastroenterology 2024;167:1228–1238.
51. Akiyama J, Hosaka H, Kuribayashi S, et al. Efficacy of vonoprazan, a novel potassium-competitive acid blocker, in patients with proton pump inhibitor-refractory acid reflux. Digestion 2020;101(2):174–183.
52. Gotoh Y, Ishibashi E, Honda S, et al. Efficacy of vonoprazan for initial and maintenance therapy in reflux esophagitis, nonerosive esophagitis, and proton pump inhibitor-resistant gastroesophageal reflux disease. Medicine (Baltimore) 2020;99(11):e19520.
53. Iwakiri K, Fujiwara Y, Manabe N, et al. Evidence-based clinical practice guidelines for gastroesophageal reflux disease 2021. J Gastroenterol 2022;57(4):267–285.
54. Maradey-Romero C, Fass R. New and future drug development for gastroesophageal reflux disease. J Neurogastroenterol Motil 2014;20(1):6–16.
55. Iwakiri K, Sakurai Y, Shiino M, et al. A randomized, double-blind study to evaluate the acid-inhibitory effect of vonoprazan (20 mg and 40 mg) in patients with proton-pump inhibitor-resistant erosive esophagitis. Therap Adv Gastroenterol 2017;10(6):439–451.
56. Laine L, DeVault K, Katz P, et al. Vonoprazan versus lansoprazole for healing and maintenance of healing of erosive esophagitis: a randomized trial. Gastroenterology 2023;164(1):61–71.
57. Sigterman KE, van Pinxteren B, Bonis PA, et al. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev 2013;5:CD002095.
58. Fass R, Vaezi M, Sharma P, et al. Randomised clinical trial: efficacy and safety of on-demand vonoprazan versus placebo for non-erosive reflux disease. Aliment Pharmacol Ther 2023;58:1016–1027.
59. Laine L, Spechler S, Yadlapati R, et al. Vonoprazan is efficacious for treatment of heartburn in non-erosive reflux disease: a randomized trial. Clin Gastroenterol Hepatol 2024;22(11):2211–2220.
60. Scott DR, Sachs G, Marcus EA. The role of acid inhibition in Helicobacter pylori eradication. F1000Res 2016;5:F1000 Faculty Rev-1747.
61. Chey WD, Howden CW, Moss SF, et al. ACG clinical guideline: treatment of Helicobacter pylori infection. Am J Gastroenterol 2024;119(9):1730–1753.
62. Khor CJ, Fock KM, Ng TM, et al. Recurrence of Helicobacter pylori infection and duodenal ulcer relapse, following successful eradication in an urban east Asian population. Singapore Med J 2000;41:382–386.
63. Singh A, Narayan J, Singh SP. Helicobacter pylori infection: challenges in India. J Pure Appl Microbiol 2019;13(2): 715–723.
64. Mizokami Y, Oda K, Funao N, et al. Vonoprazan prevents ulcer recurrence during long-term NSAID therapy: randomised, lansoprazole-controlled non-inferiority and single-blind extension study. Gut 2018;67(6):1042–1051.
65. Kawai T, Suzuki C, Honda Y, et al. Long-term safety and effectiveness of vonoprazan for prevention of gastric and duodenal ulcer recurrence in patients on nonsteroidal anti-inflammatory drugs in Japan: a 12-month post-marketing surveillance study. Expert Opin Drug Saf 2023;22(5):425–431.
66. Moraes-Filho JPP, Domingues G, Chinzon D, et al. Vonoprazan in the management of gastric/peptic ulcers: a systematic review of safety data. Prz Gastroenterol 2022;17(4):266–273.
67. Humayun F, Hoff PT, Robinson EA, et al. Dosing of proton pump inhibitors is suboptimal among otolaryngologists treating reflux-induced upper-respiratory disease. Otolaryngol Head Neck Surg 2007;137(6):936–941.
68. Han HL, Lyu QP. The preliminary application of vonoprazan fumarate on laryngopharyngeal reflux disease. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2022;57(11):1323–1327.
69. Zhong S, Zhong M, Fang L, et al. Potassium-competitive acid blocker versus proton pump inhibitor: a pilot study on comparable efficacy in the treatment of gastroesophageal reflux-related cough. Allergy Asthma Immunol Res 2024;16(2):191–201.
70. Uemura N, Kinoshita Y, Haruma K, et al. Vonoprazan as a long-term maintenance treatment for erosive esophagitis: VISION, a 5-year, randomized, open-label study. Clin Gastroenterol Hepatol 2024:S1542.
71. Geeratragool T, Kaosombatwattana U, Boonchote A, et al. Comparison of vonoprazan versus intravenous proton pump inhibitor for prevention of high-risk peptic ulcers rebleeding after successful endoscopic hemostasis: a multicenter randomized noninferiority trial. Gastroenterology 2024;167(4):778–787.
72. Hidaka Y, Imai T, Inaba T, et al. Efficacy of vonoprazan against bleeding from endoscopic submucosal dissection-induced gastric ulcers under antithrombotic medication: a cross-design synthesis of randomized and observational studies. PLoS One 2021;16(12):e0261703.
73. Tsujita K, Deguchi H, Uda A, et al. Upper gastrointestinal bleeding in Japanese patients with ischemic heart disease receiving vonoprazan or a proton pump inhibitor with multiple antithrombotic agents: a nationwide database study. J Cardiol 2020;76(1):51–57.

POINT OF VIEW

Real-world Evidence Simplified for Clinicians

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Abstract

Real-world evidence (RWE) is rapidly becoming a crucial component in healthcare decision-making, complementing traditional clinical trial data. Randomized controlled trials (RCTs) are widely regarded as the most reliable method for assessing the efficacy and safety of medical treatments. RWE can enhance and support the results obtained from traditional RCTs. RWE is derived from real-world data (RWD). Understanding RWE is essential for clinicians as it helps in guiding treatment decisions, assessing the effectiveness of therapies, and monitoring drug safety in broader patient populations. This article explores what clinicians need to know about RWE, its sources, applications, challenges, and future implications in healthcare.

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Introduction

Real-world evidence (RWE) is generated from real-world data (RWD) and provides clinical insights into the usage, benefits, and potential risks of medical therapies. It is collected through various research methods, including observational studies (prospective or retrospective), randomized trials, large simple trials, and pragmatic trials.[1,2]

What is the Difference between Real-world Data and Real-world Evidence

Real-world data refers to information collected outside the structure of traditional randomized controlled trials (RCTs).[1] It encompasses data on patient health, treatment practices, outcomes, and healthcare delivery, sourced from electronic health records (EHRs), claims and billing databases, patient registries, and wearable devices (Fig. 1).

The utility of RWD in clinical practice is becoming increasingly recognized for its potential to provide insights into the effectiveness, safety, and cost-effectiveness of treatments in diverse and routine clinical settings.[3]

Real-world evidence has emerged as a valuable complement to RCTs in clinical practice. Derived from RWD, RWE offers a broader and more practical perspective on how treatments perform in routine healthcare settings (Fig. 2).

Importance of Real-world Evidence

Real-world evidence has emerged as a valuable complement to RCTs in clinical practice.[4,5] Derived from RWD, RWE offers a broader and more practical perspective on how treatments perform in routine healthcare settings.

- Real-world data often provides a broader perspective on how a new treatment works in actual clinical practice compared to relying exclusively on traditional RCTs.
- Real-world evidence can deepen our knowledge of what is effective for various types of patients within a wider context.
- RWE enables researchers to assess the effectiveness of medications and other interventions while considering additional variables and influencing factors.
- The generation of RWE is typically more cost-efficient and faster compared to traditional RCTs.
- RWE offers valuable insights into how treatments perform within specific patient subgroups that may not have been included in RCTs.
- It evaluates the real-world effectiveness of a treatment or intervention, examining how it performs in everyday settings.
- RWE can also help researchers track a patient's outcomes over a lifetime, beyond the limited duration of RCTs.

Due to these advantages, the FDA also utilizes RWD and RWE to track postmarket safety, monitor adverse events, and assist in regulatory decisions in specific cases.[4]

How Real-world Evidence Differ from Randomized Controlled Trial

Real-world evidence and RCTs are two fundamental approaches used in clinical research to evaluate the safety, efficacy, and effectiveness of medical treatments.[5] While both methods provide valuable insights, they differ in their design, application, and the type of evidence they generate.

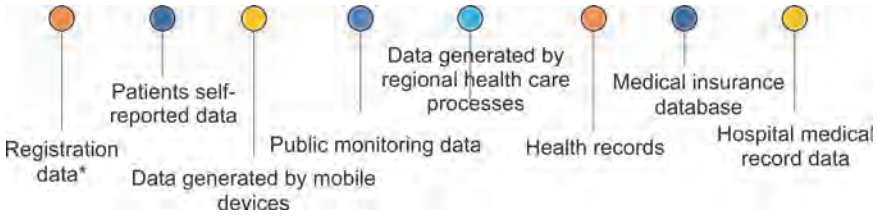

Fig. 1: Sources of RWD

Real-world data
Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Examples of RWD include data derived from electronic health records, medical claims data, data from product or disease registries, and data gathered from other sources (such as digital health technologies) that can inform on health status

Real-world evidence
Clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD

Fig. 2: RWD vs RWE

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Table 1: Comparison of RCTs vs RWE with examples[5]

	RCTs	*RWE*
Study design and methodology	RCTs are considered the "gold standard." Participants are randomly assigned to receive either the intervention being studied or a control (e.g., placebo or standard treatment). This randomization minimizes bias and confounding variables, allowing for a clear attribution of outcomes to the intervention	RWE is derived from RWD collected outside of the controlled environment of RCTs. This data comes from various sources such as electronic health records (EHRs), claims databases, registries, and wearable devices
	RCTs typically use strict inclusion and exclusion criteria to create a homogeneous study population, which enhances internal validity but may limit generalizability to broader patient populations	RWE studies are observational and often include diverse patient populations in real-world clinical settings. While this enhances the generalizability of findings, it also introduces potential biases and confounding factors due to the lack of randomization
Population characteristics	RCTs often include highly selected patient populations based on strict eligibility criteria. This ensures that the participants are relatively homogeneous, which helps isolate the effects of the intervention but may not reflect the broader, more diverse patient populations encountered in everyday clinical practice	RWE studies include a broader range of patients, reflecting the diversity seen in routine clinical practice. This includes patients with various comorbidities, different demographic characteristics, and diverse treatment histories, which enhances external validity and applicability to everyday clinical settings
	Example: Many diabetes RCTs exclude patients with significant comorbidities, which limits the applicability of the findings to real-world patients who often have multiple health conditions	Example: Real-world studies have shown how diabetes medications perform in patients with multiple comorbidities, providing a more comprehensive understanding of their effectiveness across diverse patient groups
Outcome measures	RCTs primarily focus on specific, predefined clinical endpoints (e.g., reduction in HbA1c levels, reduction in cardiovascular events). These endpoints are carefully selected to demonstrate the efficacy of an intervention under ideal conditions	RWE studies often assess a broader range of outcomes, including effectiveness in real-world settings, safety, patient-reported outcomes, adherence to therapy, and healthcare utilization. This provides a more comprehensive picture of how interventions are performed in routine clinical practice
	Example: The DECLARE-TIMI 58 trial evaluated the cardiovascular safety of dapagliflozin in patients with type 2 diabetes by measuring major adverse cardiovascular events (MACE) as the primary endpoint[6]	Example: The DISCOVER study used RWD to examine the real-world effectiveness, safety, and patterns of use of second-line diabetes treatments across diverse healthcare settings and patient populations[7]
Study environment	Conducted under tightly controlled conditions to ensure consistency in the administration of the intervention and monitoring of patients. This controlled environment minimizes confounding factors but may not reflect real-world clinical practice	Conducted in real-world settings, such as hospitals, clinics, and community health centers, where variations in practice patterns, patient behaviors, and adherence can influence outcomes. This setting reflects the complexity and variability of everyday clinical practice
	Example: In RCTs, patients often receive more frequent monitoring and follow-up than they would in routine clinical care, which can impact adherence and outcomes	Example: Real-world studies of SGLT2 inhibitors have shown different adherence rates and outcomes compared to RCTs, influenced by factors such as medication cost, patient preferences, and local healthcare practices
Regulatory and policy impact	RCTs are the primary source of evidence for regulatory approvals of new drugs and interventions. Regulatory agencies, such as the FDA and EMA, require high-quality RCT data to demonstrate the efficacy and safety of new treatments before granting approval	RWE is increasingly being used by regulatory agencies to support decision-making, especially for postmarketing surveillance, label expansions, and comparative effectiveness research. RWE can provide insights into the long-term safety and effectiveness of interventions in broader patient populations
	Example: The FDA used RCT data from the EMPA-REG OUTCOME trial to approve empagliflozin for reducing cardiovascular risk in patients with type 2 diabetes	Example: The FDA has utilized RWE to support the expanded use of certain medications based on RWD demonstrating additional benefits or safety profiles in diverse patient populations
Strengths	Regulatory acceptance as the gold standard for clinical evidence	Ability to study a broader range of patient populations and outcomes
	High internal validity due to randomization and controlled conditions	Provides insights into long-term safety, effectiveness, and healthcare utilization
	Clear attribution of outcomes to the intervention being studied	High external validity and generalizability to routine clinical practice
Limitations	Often costly and time-consuming to conduct	Susceptible to biases and confounding factors due to lack of randomization
	Limited generalizability to real-world populations due to strict inclusion/exclusion criteria	Requires robust statistical methods to address potential biases
	May not capture long-term safety and effectiveness in diverse patient populations	Variability in data quality and completeness
Cost	Costly	Less costly

Table 2: List of recent use of RWE in different stages of drug approval cycle[5]

Name of the drug	*Source of RWE*	*Regulatory agency involved in decision-making*	*Date*	*Regulatory action supported*
Palbociclib	Electronic health record data, claims data, postmarketing safety reports to support clinical efficacy, safety in new patient population	USFDA	April 2019	Supplemental indication approval
Tacrolimus	Retrospective observational study of data from the US SRTR (Scientific Registry of Transplant Recipient)	European Medicines Agency	July 2021	Supplemental NDA approval

Understanding these differences is crucial for healthcare professionals (Table 1).

Usage of Real-world Evidence

Real-world evidence can be widely used throughout the healthcare system.

Real-world evidence studies have been applied to investigate various health and disease aspects, including epidemiology, disease burden, treatment trends, safety, treatment effectiveness, long-term outcomes, and patient-reported measures like satisfaction, quality of life, medication adherence, and overall patient experience. Additionally, it can significantly enhance the evidence obtained from RCTs, addressing gaps in current clinical understanding.[8] RWE can be used for monitoring drug safety and pharmacovigilance, informing clinical guidelines and best practices, supporting comparative effectiveness research, enhancing personalized medicine, and supporting regulatory decision-making.

Latest Examples of the Utilization of Real-world Evidence in Drug Approvals

In March 2017, the US FDA utilized RWE in the form of a historical control group to approve avelumab for the treatment of Merkel cell carcinoma, marking the first time RWE was used in an original drug approval (Table 2).

Real-world Evidence for Physicians and Healthcare Providers

Real-world evidence is increasingly important in clinical practice as it provides insights that are more reflective of everyday patient care, compared to the highly controlled environment of RCTs. From a clinician's perspective, RWE helps improve patient outcomes, supports personalized medicine, informs clinical decision-making, fills evidence gaps, and aids in policy and reimbursement decisions. For example, the Michigan Bariatric Surgery Collaborative uses a tool that predicts, based on individual characteristics, how a patient might respond to different types of bariatric surgery.

Challenges and Considerations

Although RWE offers many benefits and is gaining broader acceptance among different stakeholders, its primary challenge lies in the variability and inconsistent quality of RWD sources, making data organization and integration crucial. Data quality and completeness: RWD can be incomplete or contain errors, making it crucial to ensure data quality and reliability. Bias and confounding: Observational data are prone to bias and confounding, which must be carefully managed through robust study designs and statistical methods. Privacy and ethical considerations: The use of patient data for RWD must comply with ethical standards and regulations, including patient consent and data privacy.[9]

Conclusion

Multiple factors are contributing to the increased interest in RWE, like changes in technology and advancing analytical methods, novel types and variety of RWD, acceptance of RWE from regulatory agencies, and payers. RWE provides an opportunity to evaluate broader populations, generate more evidence, and ask/answer more questions. RWE complements RCTs, but when combined, they may depict a more complete picture of a therapy. Understanding RWE is essential for clinicians as it helps in guiding treatment decisions, assessing the effectiveness of therapies, and monitoring drug safety in broader patient populations.

References

1. Real-World Evidence. U.S. Food and Drug Administration. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence. Published 2020. Accessed September 21, 2024.
2. Realizing the Promise of Real-World Evidence. https://www.fda.gov/news-events/fda-voices/realizing-promise-real-world-evidence. Accessed September 21, 2024.
3. Liu F, Panagiotakos D. Real-world data: a brief review of the methods, applications, challenges and opportunities. BMC Med Res Methodol 2022;22(1):287.
4. Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug.
5. Dang A. Real-world evidence: a primer. Pharmaceut Med 2023;37(1):25–36.
6. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380(4):347–357.
7. Khunti K, Chen H, Cid-Ruzafa J, et al. Glycaemic control in patients with type 2 diabetes initiating second-line therapy: results from the global DISCOVER study programme. Diabetes Obes Metab 2020;22(1):66–78.
8. MarksMan. Healthcare. How RWE can impact clinical trial design and help in decision making? 2018. https://marksmanhealthcare.com/how-rwe-can-impact-clinical-trial-design-and-help-in-decision-making/. Accessed 1 August 2024.
9. Rudrapatna V, Butte A. Opportunities and challenges in using real-world data for health care. J Clin Invest 2020;130(2):565–574.

CASE REPORT

High Altitude De-acclimatization Syndrome: A Case Report

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Abstract

High altitude de-acclimatization syndrome (HADAS) is a clinical entity that arises when individuals return abruptly from high-altitude environments to lower altitudes without undergoing the necessary acclimatization processes. While altitude-related illnesses have been extensively studied, HADAS remains relatively underreported and may pose diagnostic challenges due to its varied and nonspecific clinical presentation. This case report aims to shed light on the importance of recognizing HADAS as a potential consequence of inadequate acclimatization, emphasizing the need for a thorough understanding of altitude-related disorders in individuals with a history of rapid altitude changes.

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Case Description

A 38-year-old male presented with a chief complaint of headache and insomnia persisting for the last 3 days. Notably, the patient had recently undertaken a high-altitude journey, visiting locations such as Badrinath, Kedarnath, and Nepal, where he ascended rapidly *via* helicopter without allowing for proper acclimatization. His self-monitoring revealed fluctuating oxygen saturation levels (SpO_2) between 86 and 96%. Despite being hemodynamically stable with a clear chest and cardiovascular examination, the patient's symptoms prompted an extensive diagnostic workup.

Investigations, including echocardiography, pulmonary function tests, and diffusion capacity (DLCO) assessment, yielded normal results, ruling out common causes of hypoxemia. Arterial blood gas analysis demonstrated a pH of 7.42, PaO_2 of 120 mm Hg, and $PaCO_2$ of 32 mm Hg on room air, indicative of normoxemia. A detailed travel history brought to light that the patient went up by helicopter, did not take acetazolamide, stayed there for 2–3 days, and came down by helicopter, leading to insufficient de-acclimatization to high altitude, raising suspicion for high altitude de-acclimatization syndrome (HADAS).

Diagnostic Assessment

The diagnostic journey involved a systematic approach to exclude potential causes of hypoxemia. The absence of pathological hypoxemia on arterial blood gas analysis, coupled with the patient's travel history, led to the consideration of HADAS as the primary etiology. This diagnosis was further supported by the patient's symptoms and the rapid ascent and descent without adequate acclimatization.

Treatment and Outcome

The patient received a therapeutic intervention consisting of acetazolamide, a diuretic with carbonic anhydrase (CA) inhibitory properties known to aid in acclimatization. Concurrently, hydration and electrolyte supplementation were initiated to address potential imbalances. Remarkably, the patient's symptoms improved rapidly following the administration of acetazolamide, and his SpO_2 levels stabilized at 95%.

Discussion

High altitude de-acclimatization syndrome represents a unique challenge in the realm of altitude-related disorders. The mechanism underlying HADAS is rooted in the intricate interplay between environmental changes and the body's physiological response to high altitudes. Unlike more widely recognized conditions such as acute mountain sickness (AMS) or high-altitude pulmonary edema (HAPE), HADAS may not present with overt symptoms immediately upon descent.[1] Instead, its manifestations, as illustrated in this case, may include headache, insomnia, and fluctuating oxygen saturation levels.[2] The diagnostic journey underscores the importance of a detailed travel history in patients presenting with such symptoms, especially in those with recent high-altitude exposure.

One key aspect involves the process of acclimatization, wherein the body gradually adjusts to lower oxygen levels at higher altitudes. This adaptation includes increased ventilation, changes in blood flow distribution, and alterations in red blood cell production. Prolonged exposure to high altitudes allows for these adjustments to occur, optimizing oxygen delivery to tissues.[3]

However, when individuals abruptly return to lower altitudes without affording the body sufficient time to undergo this acclimatization process, a state of de-acclimatization ensues. The abrupt descent hampers the body's ability to cope with the sudden shift in oxygen levels, leading to a mismatch between the physiological adaptations acquired at high altitudes and the oxygen-rich environment at lower altitudes.[4]

Furthermore, the role of hypoxia-inducible factor-1 (HIF-1) in HADAS cannot be understated. HIF-1 is a transcription factor that orchestrates cellular responses to low oxygen levels. In high-altitude environments, sustained hypoxia triggers HIF-1 activation, promoting adaptive changes. However, when individuals rapidly descend to lower altitudes, HIF-1 continues to be upregulated, contributing to an array of symptoms associated with HADAS.[5]

The pathophysiological cascade also involves alterations in cerebral blood flow and vasoreactivity. Rapid descent disrupts the delicate balance achieved at high altitudes, potentially leading to cerebral vasodilation and increased permeability of the blood-brain barrier. This, in turn, may contribute to the development of symptoms such as headache and insomnia.

The prompt resolution of symptoms observed in our patient following acetazolamide administration aligns with the medication's mechanism of action. Acetazolamide, a CA inhibitor, induces a metabolic acidosis that mimics the acid-base changes associated with acclimatization.[6] This pharmacological intervention aids in the restoration of acid-base balance and

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facilitates the correction of respiratory alkalosis induced by hyperventilation at high altitudes.

Recognition of HADAS is essential for timely intervention and prevention of potential complications. Acetazolamide, by promoting renal excretion of bicarbonate, facilitates metabolic acidosis, thereby aiding in acclimatization and symptom relief. This case emphasizes the need for healthcare providers to remain vigilant to altitude-related disorders, even in the absence of severe hypoxemia or overt clinical signs, particularly in individuals with suboptimal acclimatization practices. Further research is warranted to enhance our understanding of HADAS and refine its management strategies.

Conclusion

In conclusion, the presented case illuminates the significance of considering HADAS in individuals returning from high-altitude environments without adequate acclimatization. This clinical entity, though less recognized, can manifest with subtle yet impactful symptoms, such as headache, insomnia, and fluctuating oxygen saturation levels.

The successful management of our patient underscores the importance of a comprehensive diagnostic approach, encompassing a detailed travel history and exclusion of other potential causes of hypoxemia. Recognition of HADAS allowed for timely intervention with acetazolamide, resulting in a rapid resolution of symptoms and the restoration of oxygen saturation levels to normalcy.

As our understanding of altitude-related illnesses continues to evolve, further research is warranted to refine diagnostic criteria and optimize treatment strategies for HADAS. Sharing such cases contributes to the medical community's collective knowledge and enhances our ability to provide effective care for individuals navigating the challenges of high-altitude environments.

References

1. He B, Wang J, Qian G, et al. Analysis of high-altitude de-acclimatization syndrome after exposure to high altitudes: a cluster-randomized controlled trial. PLoS One 2013;8:e62072.
2. Boning D, Maassen N, Jochum F, et al. After-effects of a high-altitude expedition on blood. Int J Sports Med 1997;18:179–185.
3. Zhou QQ, Yang SY, Yuan ZC, et al. Diagnostic criteria of high-altitude de-adaptation for high-altitude migrants returning to the plains: a multicenter, randomized controlled trial. Med J Chin People's Lib Army 2012;37:146–155.
4. Savourey G, Garcia N, Caravel J, et al. Pre-adaptation, adaptation and de-adaptation to high altitude in humans: hormonal and biochemical changes at sea level. Eur J Appl Physiol 1997;77:37–43.
5. Bigham AW, Lee FS. Human high-altitude adaptation: forward genetics meets the HIF pathway. Genes Dev 2014;28(20):2189–2204.
6. Singh SN, Shyam R, Vats P, et al. Biochemical changes in lowlanders on descent to plains after prolonged stay at high altitude: a cross-sectional study. Def Sci J 2004;54:169.

CASE REPORT

Ischemic Stroke in a Young Individual as an Atypical Presentation of Polycythemia Vera

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Abstract

Polycythemia vera represents a neoplastic proliferative disorder characterized by an abnormal overproduction of cells of myeloid lineage, especially erythrocytes. It can infrequently present as an acute ischemic stroke as the initial manifestation. This presentation is rarer in young patients; hence, it signifies the essence of a complete evaluation to elicit an accurate diagnosis to help prevent morbidity and mortality. In this report, we present a young male with acute onset hemiparesis who, on imaging, was found to have an ischemic infarct in the posterior limb of the internal capsule. On further investigation, the patient had a markedly elevated hematocrit and hemoglobin, and a mutation in JAK2 on genetic analysis. After confirming the diagnosis, phlebotomy was performed, which brought hemoglobin levels closer to the reference range and provided symptomatic relief.

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Introduction

While strokes in the elderly primarily stem from cardiovascular origins such as atherosclerosis and cardioembolism, the causes in younger individuals exhibit a broader spectrum. Among the various contributors to stroke in young patients, hematological disorders represent a smaller yet significant subset. Hematological diseases account for <1% of stroke cases.[1] Polycythemia vera (PV), a neoplastic erythrocytic disorder typically linked to a JAK2 mutation, induces heightened red blood cell mass, resulting in increased blood viscosity and a prothrombotic state. This elevated propensity for vaso-occlusive events elevates the risk of ischemic stroke, which presents as the initial manifestation in approximately 15% of PV cases.[2] We present this case report to promote understanding of the significance of hematological evaluation in young patients with stroke. When encountering a young patient with acute stroke, a comprehensive evaluation should be done to identify the underlying cause. Pinpointing the cause is essential for optimizing the patient's quality of life and treatment outcome, and reducing the economic burden caused by such disability in young patients.

Case Description

A 32-year-old male presented to the medicine emergency with a chief complaint of left-sided hemiparesis for 4 hours. The onset was acute and nonprogressive. The patient denied any history of headache, trauma, loss of consciousness, blurry vision, or weakness on the right side of the body or face. He denied a history of smoking and alcoholism, had no known comorbidities, no family history of similar illness, and never had similar complaints in the past. Physical examination yielded the following findings: (1) Blood pressure—130/90 mm Hg, (2) Pulse rate—90 beats per minute, (3) Temperature—37.4°C, (4) Respiration—18 times per minute. The patient's cognitive function was intact. Stiffness in the neck was noted. Power in the left upper and lower limb was grade I, and in the right upper and lower limb was grade V. Plantar reflex was mute on the left side and downward on the right. Magnetic resonance imaging (MRI) showed an infarct in the posterior limb of internal capsule. Initial treatment was given.

Hematological investigations were done and yielded the following results (Table 1). The renal and liver function tests were within reference values. Based on the investigations, a diagnosis of PV was strongly suspected, which was confirmed by a positive JAK2 mutation on genetic study.

Discussion

Stroke is one of the leading causes of mortality worldwide and the third most common in Western countries.[3] Patients under 45 years of age make up about 12% of total cases of stroke,[3] the incidence of which is on the rise. Risk factors for stroke in young patients include cardiovascular events such as cardioembolism, premature atherosclerosis, dissection of extracranial arteries; migraine; lifestyle factors such as tobacco use and obesity; use of estrogen-containing contraceptives and pregnancy in women; vasculopathies; inherited thrombophilia and hypercoagulable states; and cryptogenic stroke.[3,4] The etiology for stroke in a young patient is highly variable, with a substantial portion of it being "undetermined" and "other" etiology according to the TOAST criteria.[5] Compared to earlier times, identifying the cause of stroke in young adults has significantly improved due to advances in imaging and diagnostics.

Hematological diseases constitute <1% of stroke cases.[1] PV is a myeloid neoplasm with a mutation in JAK2 V617F in >95% cases.[6] The incidence of PV is quite rare, occurring in 0.6–1.6 persons per million population.[7] PV causes an increased risk of cerebrovascular events such as ischemic stroke and transient ischemic attacks. The mechanism by which PV leads to stroke is briefly explained by several theories that have been put forward. PV occurs due to the uncontrolled proliferation of multipotent hematopoietic stem cells, which leads to a large mass of erythropoietic cells along with granulocytes and platelets. This accumulation of various cells leads to a high hematocrit, which further causes an increase in blood viscosity. This leads to a decrease in cerebral blood flow and creation of a prothrombotic state.[7] The decrease in cerebral blood flow can also lead to common neurological symptoms such as dizziness and headache. Endothelial dysfunction and platelet adhesion leading to thrombus formation is another theory.[6] The risk of thrombosis in a PV patient increases with age and elevation in hematocrit. Embolic infarcts in the brain have also been deemed as the cause of stroke in various patients with PV.[6] PV is usually diagnosed incidentally when a complete blood count reveals raised hematocrit and hemoglobin. Some patients complain of headache, dizziness, pruritus, facial plethora, visual disturbance, or present

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Table 1: Hematological and biochemistry analysis

Parameter	*Patient values*	*Reference values*
Hemoglobin	23.9 g/dL	11.0–16.0 g/dL
Hematocrit	72.9%	40.0–54.0%
White blood cell count	$7.57 \times 10^3/mm^3$	$4.00–10.00 \times 10^3/mm^3$
Red blood cell count	$7.07 \times 10^6/mm^3$	$4.50–6.20 \times 10^6/mm^3$
Mean corpuscular volume	106.3 fL	80–100 fL
Platelet count	$1.5 \times 10^5/mm^3$	$1.5–4.5 \times 10^5/mm^3$
Platelet distribution width	22.3%	11.0–19.0%
Serum lactate dehydrogenase (LDH)	569.1 U/L	135.0–225.0 U/L
Serum bilirubin	2.0 mg%	0.2–1.0 mg%

with complications of PV such as thrombosis or hemorrhage. According to some studies, ischemic stroke is the first presenting symptom in about 15% of PV cases,[6] with the higher incidence of stroke coinciding with an older age group at presentation, peak incidence being 50–70 years.

Our patient was a seemingly healthy young adult with no apparent risk factors who presented with symptoms of stroke. MRI of the brain showed an ischemic infarct in the posterior limb of the internal capsule. An indication toward the diagnosis could only be inferred from the abnormalities detected in the hematological assay with hemoglobin at 23.9 g/dL and hematocrit at 72.9% as well as a raised red blood cell count and high lactate dehydrogenase. On further investigation, a JAK2 mutation was found on genetic analysis, confirming the diagnosis of PV.

We hope this case report can shed light on the importance of screening for hematological disorders in the event of a stroke of uncertain etiology, especially in the younger age group. In up to 4% of young adults affected by stroke, a significant contributor to brain ischemia arises from an underlying hematologic disorder or coagulopathy that increases susceptibility to thrombosis.[1] The contribution of a prothrombotic state to cerebrovascular disease is unclear in the elderly, probably due to the masking of any other etiology by the more prevalent effects of atherosclerosis.

Conclusion

Our case report addresses the incidence of ischemic stroke in a young patient as a rare presentation of PV. It also highlights the importance of hematological screening of young patients presenting with stroke of uncertain etiology.

References

1. Hart RG, Kanter MC. Hematologic disorders and ischemic stroke. A selective review. Stroke 1990;21(8):1111–1121.
2. Anand NN, Padma V, Kanna SS. An interesting case of acute ischemic stroke in the young. Sre Bal J Med Sci 2022;1(1).
3. Martin PJ, Enevoldson TP, Humphrey PR. Causes of ischaemic stroke in the young. Postgrad Med J 1997;73(855):8–16.
4. George MG. Risk factors for ischemic stroke in younger adults. Stroke 2020;51(3):729–735.
5. Smajlović D. Strokes in young adults: epidemiology and prevention. Vasc Health Risk Manag 2015;11:157–164.
6. Cao YY, Cao J, Bi ZJ, et al. Hemorrhagic transformation after acute ischemic stroke caused by polycythemia vera: report of two case. World J Clin Cases 2021;9(25):7551–7557.
7. Zoraster RM, Rison RA. Acute embolic cerebral ischemia as an initial presentation of polycythemia vera: a case report. J Med Case Reports 2013;7:131.

CASE REPORT

Typhoid Fever Complicated by Sepsis and ARDS in Pregnancy: A Rare Case

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Abstract

A woman in her thirties and in her second trimester of pregnancy presented with fever, shaking chills, and shortness of breath of 5–6 days duration. She developed progressive hypoxemia and tachypnea, leading to the development of acute respiratory distress syndrome (ARDS). An aerobic blood culture showed positivity for *Salmonella typhi*. Her worsening respiratory distress was treated with oxygenation through a high-flow nasal cannula. She was stabilized with intravenous (IV) antibiotics and other supportive measures and was discharged home with a live fetus in utero.

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Background

Acute respiratory failure is very uncommon in pregnancy but is associated with high risk of maternal and fetal morbidity and mortality. It may occur due to a variety of medical conditions of both infectious and noninfectious etiology.[1] Several immediate precipitants such as pneumonia, cardiogenic pulmonary edema, acute respiratory distress syndrome (ARDS), asthma, pulmonary embolism, and amniotic fluid embolism have been implicated to cause acute respiratory failure in pregnant women.[2] Early diagnosis of underlying conditions is of utmost importance as it is helpful in directing management approach.

Typhoid fever is one of the most common infectious diseases in the tropical region. It can lead to various systemic complications if left untreated. However, involvement of the respiratory system is limited to mild respiratory symptoms like a dry cough. ARDS is rarely reported in adult individuals with typhoid fever and has not been reported so far in pregnant women with typhoid fever. ARDS is ubiquitous among pregnant women in intensive care unit, contributing directly and indirectly to maternal death. However, a literature review revealed hardly any case report of ARDS as a complication of typhoid fever in pregnancy.[3]

Case Description

A woman in her thirties, multigravida and 26 weeks pregnant, visited a tertiary healthcare hospital with a history of high-grade fever with shivering, chills, and occasional shortness of breath and cough for the last 10 days. Her significant past medical history included the termination of a 6-month-old pregnancy 2 years ago due to fetal anomaly.

Her vital parameters at emergency were: Glasgow Coma Scale (GCS)—15/15, blood pressure (BP)—90/60 mm Hg, tachycardia, heart rate (HR)—142/min with 95–96% saturation in room air. There were no skin rashes, petechiae, or ecchymosis without any engorged neck veins or palpable lymph nodes. Her chest, cardiac, and abdominal examinations were unremarkable. On day 2 in hospital, she developed episodes of hypoxia with intermittent high-grade fever and gradually worsening respiratory distress with orthopnea and increasing oxygen demand. On examination, she was conscious but appeared toxic and tachypneic. Her BP was 90/60 mm Hg. Auscultation revealed decreased air entry on both sides and scattered crepitations with expiratory wheeze. Her saturation was 82% with 4 L of oxygen via nasal cannula, respiratory rate was 46/min, and temperature was 102°F. Fetal Doppler was done with fetal heart sound (FHS) 157 bpm. Echocardiography showed good biventricular systolic function with adequate diastolic compliance with an ejection fraction of 62%. As chest X-ray could not be performed, lung assessment was done using serial lung ultrasonogram, which initially revealed well-defined spacing lines starting from the pleural line and reaching the edge of the screen. These B1 lines reflect thickening of interlobular septa. Later, lung consolidations with significant aeration loss revealed hypoechoic areas. On the day of admission, her arterial blood gas (ABG) showed: pH—7.490, pCO_2—27.4, pO_2—68.8 with P/f ratio of 328 mm Hg, which deteriorated in spite of supplemental oxygen therapy on day 2 of admission as follows: pH—7.500, pCO_2—28.3, pO_2—50.1 with P/f ratio of 135. Based on these data, she was shifted to medical intensive care unit (MICU) from the general ward. Despite initial oxygen therapy with a nasal cannula and high-flow mask, her saturation did not improve, so she was put on high-flow nasal cannula (HFNC) with the highest settings as follows: temperature—37°F, flow—60 L/min, SpO_2—90%. Initially, intravenous (IV) 2 gm of ceftriaxone was started empirically, which was escalated to 1 gm of Inj meropenem in view of critical condition of the patient with a precious pregnancy. Subsequently, the blood culture report showed growth of *Salmonella typhi* sensitive to meropenem. Hence, no change in antimicrobial therapy was done. Opinions of a pulmonologist and obstetrician were taken into account.

Investigations

- The lab reports revealed a hemoglobin level of 7.7 g/dL, total leukocyte count (TLC)—4,300/mm^3 (neutrophils—90) and presence of toxic granules, platelet count—1,65,000/mm^3, C-reactive protein (CRP)—191.6 on the day of admission, which changed with time on day 3 as Hb—7.8 g/dL, TLC—9,500/mm^3 (neutrophis—75), platelet count—2,20,000/mm^3, and CRP—25.3 mg/dL. Blood electrolytes, kidney function test (KFT), and liver function test (LFT) were within normal limits. Blood and urine cultures were sent, which showed no microbial growth.
- No radiological investigations were performed to preserve her pregnancy from radiation exposure.
- Procalcitonin—9.76 ng/mL, D-dimer—7.89 mg/L, prothrombin time–international normalized ratio (PT–INR)—0.95, and NT-proBNP—1,830 pg/mL.

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Treatment

The patient was treated in MICU with initial empirical therapy of IV ceftriaxone 2 gm twice daily. Once the patient developed hypoxic respiratory failure, antimicrobials were escalated to IV meropenem 1 gm thrice daily in view of the precious pregnancy and critical condition of the patient. After getting the blood culture and sensitivity report showing presence of *S. typhi*, sensitive to meropenem, no change in antimicrobial therapy was carried out.[3]

Outcome and Follow-up

The patient was initially kept on nasal cannula oxygen therapy but due to progressive hypoxia, she was put on HFNC oxygen along with escalated antimicrobial therapy. Eventually, she responded well to IV antimicrobials and HFNC oxygenation, and her oxygen support was slowly tapered off. Daily FHS checking was done with hourly evaluation of the mother. With progression of the disease, her overall condition improved, her oxygen demand decreased with time, and she was discharged in hemodynamically stable condition with a viable single live fetus. She is now under regular follow-up at medicine and gynecology outpatient department.

Discussion

Acute respiratory distress syndrome is a rare and potentially fatal complication of typhoid fever. In this case, this fatal condition occurred at 26 weeks of pregnancy with sepsis. ARDS-related maternal mortality ranges from 9 to 44%, and perinatal mortality ranges from 20 to 30%.[4] The pathophysiology of extraintestinal complications of typhoid fever depends on the ingested inoculum size, virulence of the strain, immune response of the host, history of previous exposure, and locally present protective factors. Usually *S. typhi* enters the bloodstream resulting in transient bacteremia. The organisms are rapidly phagocytosed via macrophages and monocytes of the reticuloendothelial system. However, the viable remnant bacilli multiply in the reticuloendothelial system and re-enter the bloodstream causing secondary bacteremia.[5]

Pulmonary manifestations in typhoid fever are less commonly reported in forms of bronchitis, pneumonia, lung abscess, empyema, and rarely ARDS mainly found in an immunocompromised patient with acquired immunodeficiency syndrome (AIDS), leukemia, Hodgkin's disease, sarcoidosis, and kidney transplant recipients. The extremities of ages are generally involved. Nevertheless, this case of a pregnant woman with a rare complication of typhoid fever is rare and unusual. The literature about its pathophysiology is scarce. It has been noted that *Salmonella* causes lung tissue damage by activating the complement system leading to blood corpuscle infiltrations leading to pulmonary fibrosis. Others have proposed that endotoxemia induces an increased alveolar capillary permeability leading to alveolar edema and proteinosis. Regardless of underlying pathology and proposed mechanism, ARDS has its stages of disease progression which include: damage of the alveolar-capillary membrane, a proliferative phase of improved lung function with healing, and a final fibrotic stage ending the acute phase of the disease.[6]

Evidence shows that blood cultures have 40–80% positivity in the diagnosis of *S. typhi* and others including stool cultures around 30–40%. Bone marrow cultures show sensitivity of nearly 90%, which signifies that bone marrow culture is the most sensitive diagnostic tool especially in complicated cases or in those cases where antimicrobial therapy has already been started or diagnosis remains uncertain. In this case, without any delay or waiting for the culture sensitivity report, prophylactic antibiotics was started with cephalosporins and moxifloxacin. Then on day 2, it was escalated to IV meropenem keeping in mind the criticality of the situation and continuation of the precious pregnancy.[7]

Acute respiratory distress syndrome is a rare complication of typhoid fever in the adult population; only a handful of cases have been reported in literature review but none has been reported in pregnancy so far. Most of the cases of typhoid fever with ARDS resulted in fatalities in spite of mechanical ventilation. This case was different because of the association of pregnancy with typhoid fever, which limited the scope for imaging and use of appropriate medications. She was treated with HFNC oxygenation along with initial empirical antibiotic therapy to which she responded well. She survived this fatal complication of typhoid fever and was discharged home with a live healthy fetus. This case highlights the importance of early antibiotic therapy and oxygenation through HFNC with good clinical outcome. The patient is currently on regular follow-up in antenatal clinic.

Learning Points/Take Home Messages

- Typhoid fever is one of the most common infectious diseases in the tropical region.
- It is sometimes complicated by the involvement of various organ systems including the respiratory system, which is manifested commonly by bronchitis, pneumonia, etc. However, ARDS is an extremely rare occurrence. Most of the cases of ARDS in typhoid were reported in the pediatric age group. Only a handful of cases were reported in adult patients. However, none of the cases was found in association with pregnancy.
- This case could be managed well with HFNC oxygenation due to our recent experience handling COVID-19 ARDS patients.
- Though the outcome of ARDS in typhoid fever is universally grim as reported in literature, our case made an excellent recovery with a preserved healthy fetus.

References

1. Mighty HE. Acute respiratory failure in pregnancy. Clin Obstet Gynecol 2010;53(2):360–368.
2. Chaouat G. Innately moving away from the Th1/Th2 paradigm in pregnancy. Clin Exp Immunol 2003;131:393–395.
3. Touchan F, Hall JD, Lee RV. Typhoid fever during pregnancy: case report and review. Obstet Med 2009;2(4):161–163.
4. Collop NA, Sahn SA. Critical illness in pregnancy. An analysis of 20 patients admitted to a medical intensive care unit. Chest 1993;103:1548–1552.
5. Sánchez-Vargas FM, Abu-El-Haija MA, Gómez-Duarte OG. Salmonella infections: an update on epidemiology, management, and prevention. Travel Med Infect Dis 9:263–277.
6. Chen CY, Chen CP, Wang KG, et al. Factors implicated in the outcome of pregnancies complicated by acute respiratory failure. J Reprod Med 2003;48:641–648.
7. Seoud M, Saade G, Uwaydah M, et al. Typhoid fever in pregnancy. Obstet Gynecol 1998;71:711–714.

CASE REPORT

PLA2G6-associated Neurodegeneration: A Rare Case Report of Dystonia–Parkinsonism Phenotype with a Novel Genotypic Variant

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Abstract

PLA2G6-associated neurodegeneration (PLAN) is a complex heterogenous group of neurodegenerative diseases that results from mutations in a gene known as *PLA2G6*. PLAN comprises three phenotypes with overlapping clinical and radiologic features: (1) Infantile neuroaxonal dystrophy (INAD), (2) Atypical neuroaxonal dystrophy (ANAD), and (3) *PLA2G6*-related dystonia–parkinsonism complex (PLAN-DPC). The onset of *PLA2G6*-related DPC occurs in adulthood, and patients often have normal birth and development. These patients show clinical manifestations of Parkinsonian syndrome, characterized by bradykinesia and tremors with dystonia, in addition to cognitive regression as well as gait instability. Here, we report a case of PLAN-DPC phenotype in a 20-year-old girl. This case report highlights the detection of a novel variant of *PLA2G6* gene mutation, c.757G>A, which has an allelic frequency of 0.001% in the gene database.

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Introduction

PLA2G6-associated neurodegeneration (PLAN) is a heredodegenerative condition due to mutations in the gene known as *PLA2G6*, causing complex and heterogenous disease presentations.

PLAN consists of a broad clinical spectrum with distinguished radiological features that could be categorized into three main phenotypes:

1. Infantile neuroaxonal dystrophy (INAD)
2. Atypical neuroaxonal dystrophy (ANAD)
3. *PLA2G6*-related dystonia–parkinsonism complex (PLAN-DPC)

INAD and ANAD, with onset in childhood, present with extrapyramidal features in the form of stiffness, dystonia (predominantly axial), truncal ataxia, optic atrophy, and progressive psychomotor deterioration in some children.

PLA2G6-related dystonia–parkinsonism complex often manifests in the adult age group with clinical features of Parkinsonian syndrome in the form of tremors, bradykinesia, and dystonia, along with gait imbalance and cognitive regression.

Magnetic resonance imaging (MRI) in patients with this condition often reveals iron deposition in the basal ganglia, especially globus pallidus and substantia nigra, and cerebellar atrophy, depending on disease severity and duration.[1]

These phenotypes often present with diverse clinical variability, though the age of disease onset and clinical manifestations are the main criteria used to make distinctions among the PLAN subtypes.

PLA2G6 gene (phospholipase A2 group 6) encodes a protein, phospholipase A2 enzyme (iPLA2), which is expressed in various tissues in our body and catalyzes various intracellular metabolic events. The association of *PLA2G6* mutations with INAD and ANAD phenotypes is often established in various case reports. The same mutation causing PLAN-DPC phenotype is being increasingly recognized.[2]

Here, we report a case of PLAN-DPC phenotype in a 20-year-old girl. This case report highlights the detection of a novel variant of *PLA2G6* gene mutation, c.757G>A, which has an allelic frequency of 0.001% in the gene database.

Case Description

A 20-year-old female, born out of third-degree consanguineous parentage with no birth or neonatal complications, had normal growth and development. She studied up to grade 10 with average scholastic performance. She was asymptomatic up to 12 years of age when she developed deterioration of handwriting followed by a low-pitched voice. Over the next 4 years, she developed slowness of gait with stiffness of all limbs and jaw-opening difficulty. By 19 years of age, she had marked slowness in activities of daily living with a mask-like face and voice tremor.

Now, at the age of 20 years, she needs support to walk due to stiffness of limbs, gait imbalance, and foot dystonia. There is no history of seizures or cognitive decline.

A history of similar illness was observed in family members. The patient's mother, aged 41 years, has spasticity of both lower limbs with predominant pyramidal signs in all limbs, with the onset of symptoms at the age of 35 years. Her maternal uncle, aged 36 years, has had a similar illness since the age of 20 years and is bedridden at present.

General examination revealed Parkinsonian features in the form of hypomimia, bradykinesia, and tremors of both hands. Vital signs were normal. Ocular motility and examination of other cranial nerves were unremarkable. Spinomotor examination revealed increased muscle tone throughout with preserved power and brisk deep tendon reflexes, except for ankle jerks, which were absent bilaterally. Plantar reflexes were downgoing with normal sensory and cerebellar examination. Gait was spastic and shuffling with turning en bloc, needing support.

Biochemical tests including thyroid and liver function tests and other metabolic parameters, serum copper, and ceruloplasmin levels were within normal range. Cerebrospinal fluid (CSF) analysis showed no abnormality. Brain MRI showed marked cerebellar atrophy (Figs 1A and B). T2 sequence did not show any iron deposition (Figs 2A

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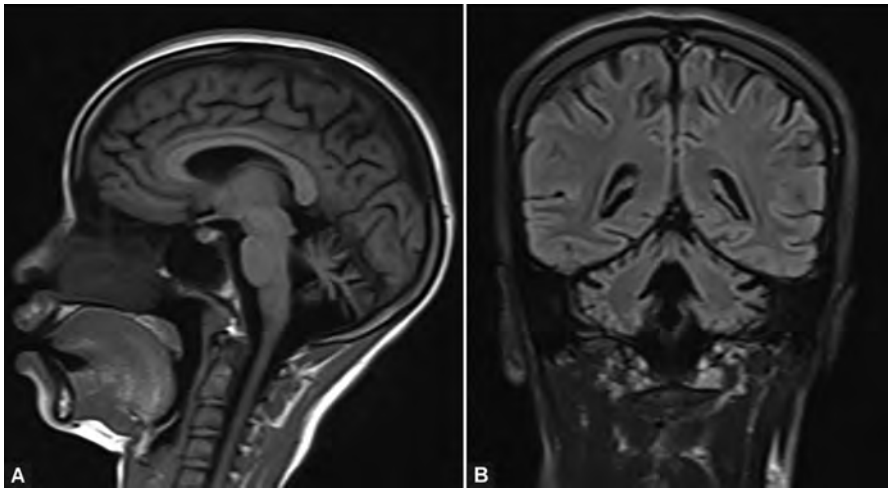
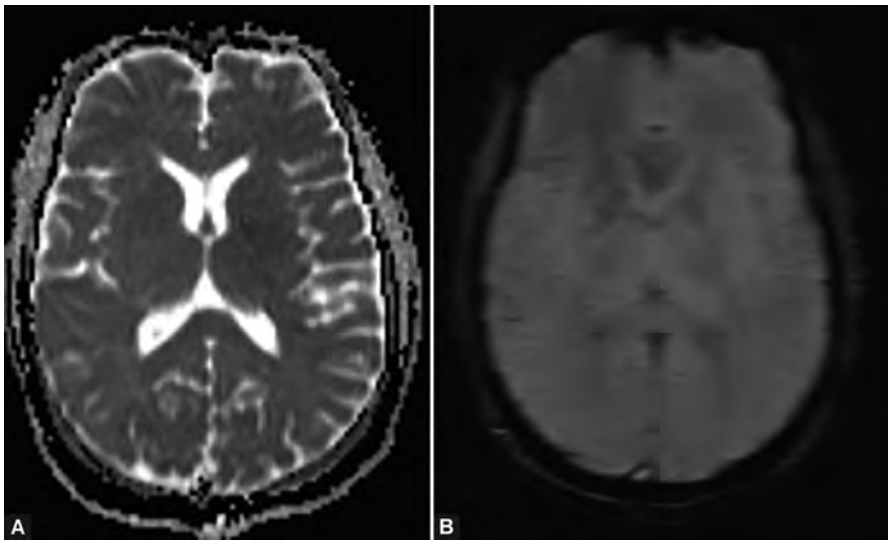


Figs 1A and B: Magnetic resonance imaging of brain T1 sagittal (A) and coronal FLAIR (B) sequences show prominent bilateral cerebellar folia with reduced volume of cerebellar hemispheres, smaller vermis, widening of fourth ventricle and retrocerebellar cistern—suggestive of diffuse cerebellar atrophy



Figs 2A and B: Magnetic resonance imaging of brain T2 axial (A) and axial SWI (B) sequences revealed absence of hypointensities and absence of signal loss in bilateral basal ganglia respectively—suggesting the absence of iron accumulation

and B). Electroencephalography (EEG) was normal.

Genetic testing reported a homozygous c.757G>A missense mutation of PLA2G6 gene resulting in p.Gly253Ser transition, which is likely a pathogenic variant. This is a novel variant that has not been reported so far in the 1,000 genomes and gnomAD databases.

Discussion

PLA2G6-associated neurodegeneration is a rare disease with a prevalence of approximately 1:1,000,000,[3] inherited in an autosomal recessive manner. As molecular genetic studies have been increasingly used in clinical practice, many cases of PLAN are being reported.

The *PLA2G6* gene is located on 22q13.11,[4] with 17 exons, and encodes the protein, group VI calcium-independent phospholipase A2 (iPLA2 β). This pathogenic protein, encoded by the mutated *PLA2G6* gene, is implicated in pathophysiologic mechanisms causing neurodegeneration. It deranges intracellular metabolism by affecting various processes regulating oxidative stress, free radical injury, fatty acid oxidation, and apoptosis. The metabolism of docosahexaenoic acid (DHA) involved in neural development and neuroprotectin D1 (NPD1), an anti-inflammatory protein, are also affected by mutated iPLA2 β.[5]

The genetic modifications of abnormal *PLA2G6* gene include deletions, missense mutations, truncated mutants, and copy number variants (CNVs). This case reports a homozygous missense variation in exon 5 of the *PLA2G6* gene (chr22) that results in the substitution of amino acid serine for glycine at codon 253 (p.Gly253Ser). This genotypic variant and its association with PLAN-DPC phenotype have not been reported so far.

This young female diagnosed to have PLAN with dystonia and parkinsonism had onset of symptoms at the age of 12 years. Clinical features of Parkinsonism in the form of stiffness and slowness progressed during the course of the illness. In addition to motor disturbances, behavioral changes and seizures are seen in some cases, though not observed in our case.

Radiological abnormalities in the form of various degrees of iron accumulation and cerebellar atrophy are considered only minor criteria in detecting DP phenotype, as there is wide variation ranging from gross abnormalities to subtle or no changes, as in our patient.[6]

Important differentials for the current phenotype include other forms of neurodegeneration with brain iron accumulation, atypical PKAN (pantothenate kinase-associated neurodegeneration), Kufor–Rakeb syndrome, MPAN (mitochondrial membrane protein-associated neurodegeneration), and BPAN (beta-propeller protein-associated neurodegeneration).[3]

Research is being carried out to discern various genes implicated in NBIA causation, their physiopathologic mechanisms, and targeted therapies. Up to this point of time, treatment is primarily symptomatic as there are no disease modification therapies. Our patient is being treated with levodopa and has some improvement in stiffness and dystonia. Addressing secondary complications, diet and nutrition, physical and occupational therapy are vital in the treatment of these patients.[7]

It is important to emphasize genetic counseling in the management protocol of these patients, especially those belonging to reproductive age group. Prenatal testing is advised in pregnancies with high risk of developing this disease.[8]

Conclusion

As cases of PLAN-DPC are increasingly being reported, the heterogeneity in their clinical characteristics and disease course is witnessed. With more publications and knowledge sharing about this entity, our

understanding regarding typical and atypical presentations of PLAN will continue to improve. To conclude, this disorder should be one of the important differential diagnoses when approaching a case of young-onset neurodegenerative disorders.

References

1. Gregory A, Westaway SK, Holm IE, et al. Neurodegeneration associated with genetic defects in phospholipase A_2. Neurology 2008;71:1402–1409.
2. Khateeb S, Flusser H, Ofir R, et al. PLA2G6 mutation underlies infantile neuroaxonal dystrophy. Am J Hum Genet 2006;79:942–948.
3. Gregory A, Kurian MA, Maher ER. PLA2G6-associated neurodegeneration. In: Pagon RA, Adam MP, Bird TD (Eds). Gene Reviews™. Seattle: University of Washington; 1993–2013.
4. Ma Z, Wang X, Nowatzke W, et al. Human pancreatic islets express mRNA species encoding two distinct catalytically active isoforms of group VI phospholipase A2 (iPLA2) that arise from an exon-skipping mechanism of alternative splicing of the transcript from the iPLA2 gene on chromosome 22q13.1. J Biol Chem 1999;274:9607–9616.
5. Rogers LK, Valentine CJ, Keim SA. DHA supplementation: current implications in pregnancy and childhood. Pharmacol Res 2013;70:13–19.
6. Karkheiran S, Shahidi GA, Walker RH, et al. PLA2G6-associated dystonia-parkinsonism: case report and literature review. Tremor Other Hyperkinet Mov 2015;5:317.
7. Zorzi G, Zibordi F, Chiapparini L, et al. Therapeutic advances in neurodegeneration with brain iron accumulation. Semin Pediatr Neurol 2012;19:82–86.
8. Hayflick SJ, Kurian MA, Hogarth P. Neurodegeneration with brain iron accumulation. Handb Clin Neurol 2018;147:293–305.

CASE REPORT

Nonislet Cell Tumor Hypoglycemia: A Rare Paraneoplastic Syndrome

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Abstract

Nonislet cell tumor hypoglycemia (NICTH) is a rare and underreported cause of hypoglycemia due to excessive production of insulin-like growth factor 2 (IGF-2) and its intermediate forms, which activate the insulin receptor. Typically, certain malignancies can cause NICTH, usually as a paraneoplastic syndrome. Diagnosis requires a raised IGF-2/IGF-1 ratio. Surgery forms the cornerstone of management, while glucocorticoids are an alternative when surgery is not possible. We present a unique case of a 27-year-old male, who was a follow-up case of chronic hepatitis B infection and presented with a gall bladder fossa mass and recurrent, severe episodes of hypoglycemia. Workup revealed low insulin and C-peptide and suppressed IGF-1 with normal pituitary function. Clinicians should consider the possible diagnosis of NICTH when laboratory and immunohistochemical (IHC) data do not support more common causes, such as insulinoma.

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Introduction

Nonislet cell tumor hypoglycemia (NICTH) is one of the rarest causes of hypoglycemia. NICTH has been linked with several epithelial and mesenchymal tumors. It may be misdiagnosed due to its rarity, nonconforming presentation, and ambiguous lab findings. It can cause potentially fatal hypoglycemia until definite management is done. We report one such case of NICTH, secondary to hepatocellular carcinoma.

Case Description

A 27-year-old male presented in the outpatient department with upper abdominal dull aching, mild pain for 2 weeks. There were no associated complaints of vomiting, heartburn, altered bowel habits, or melena. He was a known case of chronic hepatitis B, diagnosed 9 months ago, and was on tenofovir disoproxil for the same. On physical examination, there was no pallor, icterus, or lymphadenopathy. Abdominal examination revealed soft, non-tender, mild hepatomegaly.

Laboratory workup (Table 1) showed mild anemia with liver and renal function tests within the normal range. Hepatitis B virus DNA levels were undetectable. Ultrasonography was suggestive of a mixed echogenic mass measuring 8 × 9 cm in the gallbladder fossa with ascites. Triple phase CT abdomen showed a multilobulated lesion in segment V with a large exophytic component in the subhepatic region. The lesion was hypoenhancing in all phases of contrast. The liver was studded with multiple hypoenhancing lesions in both lobes, the largest measuring 6 × 6 cm in segment IVA/VIII. Serum AFP levels were grossly elevated at 1627.93 ng/mL (0–8.5 ng/mL). Whole body positron emission tomography-computed tomography (PET-CT) revealed a heterogeneously enhancing FDG-avid mass in the gallbladder fossa infiltrating segment IV/V of the liver with metastatic deposits in the liver, omentum, and pelvic mesentery (Fig. 1).

Trucut biopsy from the mass and liver lesions was suggestive of a low-grade epithelial lesion with extensive desmoplasia without any evidence of cirrhosis. Immunohistochemical (IHC) studies showed immunopositivity for PanCK and glypican-3 and were negative for synaptophysin, chromogranin, neuron-specific enolase (NSE), thyroglobulin, CA19.9, CK5/6, CK7, CK20, P40, CD56, CD30, and SALL-4, suggesting the possibility of well-differentiated hepatocellular carcinoma or metastatic germ cell tumor.

Despite an equivocal radiologic picture, on the basis of histopathologic evidence and raised AFP and protein induced by vitamin K absence or antagonist-II (PIVKA) levels, we kept the working diagnosis of hepatocellular carcinoma and started him on sorafenib. However, after 40 days of therapy, he presented with sudden onset loss of consciousness, vomiting, and profuse diaphoresis. Spot blood sugar was 25 mg/dL, and he recovered completely with dextrose infusion. The patient was kept on continuous 10% dextrose IV infusion due to recurrent episodes of hypoglycemia upon withdrawal.

Glucose fasting test (72 hours), performed to rule out insulinoma, showed normal C-peptide (0.153 ng/mL) and insulin (<0.4 mIU/mL) levels. With suspicion of NICTH, we assessed IGF-1 levels, which were suppressed (17.30 ng/mL; 27-year-old male: 94–259 ng/mL); insulin-like growth factor 2 (IGF-2) levels couldn't be assessed due to nonavailability. Tests for diagnosis of diabetes and pituitary function were within normal reference limits for the patient's age (Table 2).

Further, to localize the lesion, DOTA NOC PET scan was done, which showed multiple, variably sized DOTA NOC avid (SUVmax 8.3) lesions in both lobes of the liver, the largest measuring 5 × 4 cm in segment VIII, associated with mildly DOTA NOC avid diffuse, nodular omental thickening.

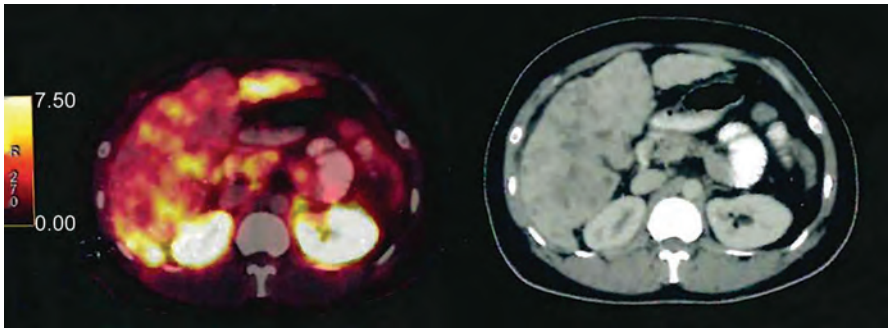

Fig. 1: PET and triple phase CT abdomen

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Table 1: Laboratory investigations

Tests	*6/8/22*	*19/9/22*	*21/9/22*	*26/11/22*	*1/2/23*	*11/2/23*	*13/2/23*
Hb	10.9 gm/dL		10.9		14.5	13.3	15
TLC	10800/mm^3		10900		19000	19300	22000
Platelets	2,63,000/uL		2,80,000		4,00,000	5,21,000	4,61,000
AST/ALT	27.2/28.7 U/L		39/21		23.87/164.3	23.22/204.94	
T. bilirubin	0.39 mg/dL		0.55		0.48	0.62	
Albumin	3.66 gm/dL		4.38		2.76	2.88	
PT/INR					18.6/1.432 sec	18.6/1.432	18.1/1.46
Creatinine					0.35 mg/dL		
Na^+					134.4 mEq/L		
K^+					4.063 mEq/L		
HbSAg			Reactive	Reactive	Reactive		
AFP	1627.93 ng/mL (0–8.5)			3460			
PIVKA-II				6023.63 mAU/mL (1–40)			
HBV DNA				1.34 × 102 IU/mL			
CA 19.9		19.3 U/mL (0–37)					
LSM	7.6 kPa (no fibrosis)	7.6					

Table 2: Endocrinology investigations

Date	*Endocrinology tests*	*Results*
9/2/23	C-peptide (fasting)	0.153 ng/mL (1.1–5)
	Insulin (fasting)	<0.4 microIU/mL (2–25)
13/2/23	Fasting blood sugar	19.52 mg/dL (60–140)
	PP blood sugar	138 mg/dL (140–190)
	HbA1c	5.4 (<5.8 nondiabetic)
19/2/23	IGF-1	17.3 ng/mL (94–259)
	Cortisol (8 am)	12.5 ug/dL (10–20)
	fT3	3.3 pg/mL (2.2–4.3)
	TSH	2.587 uIU/mL (0.38–5.3)
	fT4	0.9 ng/mL (0.8–1.6)
	PRL	38.76 ng/mL (0–20)
	LH	9.04 mIU/mL (1–12)
	FSH	2.27 mIU/mL (1–12)

Table 3: Tumors causing NICTH

Hepatocellular carcinoma
Fibrosarcoma
Mesothelioma
Adrenocortical carcinoma
Hemangiopericytoma
Stomach carcinoma
Pancreatic carcinoma
Medullary carcinoma thyroid
Lymphoma/leukemia
Carcinoid syndrome

The patient was started on long-acting octreotide infusion and glucocorticoids. However, his hypoglycemia persisted, and he opted for palliative care at home.

Discussion

Hypoglycemia can be caused by an assortment of factors. It is commonly seen in diabetic patients on insulin or oral hypoglycemic drug therapy (especially sulfonylureas). NICTH is associated with mesenchymal and epithelial tumors. Two subtypes of NICTH have been described so far. Type A is characterized by excessive malignant utilization of glucose in cachectic patients with depleted glycogen stores and malfunctioning gluconeogenesis. This type is seen during advanced malignancies when tumor burden is high. In type B NICTH, there is excessive ectopic secretion of immature IGF-2 (pro-IGF-2).[1]

Nonislet cell tumor hypoglycemia was first recognized >90 years ago in a case of hepatic malignancy.[2] The most common malignancy associated with NICTH is assumed to be hepatocellular carcinoma. However, the list of tumors implicated in NICTH is rising (Table 3). With the increasing occurrence of hepatocellular carcinoma, the occurrence of NICTH should increase but is similar so far, likely due to under/misdiagnosis.[3]

In the past, the mechanism of IGF-2 induced hypoglycemia remained elusive, until the recognition of immature pro-IGF-2 (or big IGF-2) in the 1980s.[4]

Hypoglycemia can be the presenting symptom in 50% of patients with IGF-2 associated malignancies. Alternatively, the diagnosis of cancer may herald hypoglycemia.[5,6] Typically, fasting hypoglycemia is observed. Due to the persistent episodes of hypoglycemia, neuroglycopenic symptoms such as confusion, psychosis, amnesia, and seizures may be the predominant clinical features of NICTH.

Insulin-like growth factor 2 has pleiotropic actions which lead to hypoglycemia. The main mechanism is cessation of hepatic glucose output. IGF-2, *via* activation of the insulin receptor, can inhibit gluconeogenesis, glycogenolysis, and ketogenesis (Fig. 2).

In order to narrow down the possible cause of hypoglycemia, plasma insulin, C-peptide,

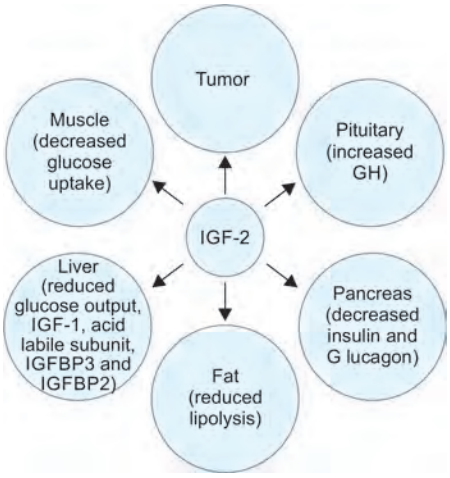

Fig. 2: Effects of excess IGF-2

proinsulin, and beta-hydroxybutyrate must be measured during an episode of hypoglycemia. NICTH will present with reduced levels of insulin, C-peptide, proinsulin, and beta-hydroxybutyrate.[6] Further workup of NICTH includes quantification of IGF-1 and IGF-2 levels. IGF-1 is suppressed, while the levels of IGF-2 may be normal or raised. An IGF-2/IGF-1 molar ratio of >10 confirms NICTH. Hypoinsulinemic hypoglycemia with reduced IGF-1 is robust biochemical proof for NICTH. IGF-2: IGF-1 ratio of >10 is a corresponding investigation in the absence of availability of assays for IGF-2 (which is of importance in the Indian scenario).[1]

Surgical excision of the offending tumor forms the cornerstone of treatment of NICTH. It results in an instantaneous solution for hypoglycemia.[7,8] Debulking should be an option when complete surgical excision is not feasible. Glucagon and glucocorticoids may be used for immediate resolution of hypoglycemia; however, the effect is short-term only.[8]

Our case highlights multiple learning points for clinical practice. Our patient with chronic hepatitis B developing hepatocellular carcinoma without underlying cirrhosis (about 20% of total incidence) and decreased HBV DNA levels is a rare scenario.[9,10]

Despite the typically raised AFP and PIVKA levels, the hepatocellular carcinoma was nonenhancing on CT scan (30% of total incidence of HCC), as opposed to the classical presentation of early enhancement on the arterial phase and rapid washout on the portal venous phase.[11]

It had a large exophytic component, extending into the gall bladder fossa region, which is unusual for hepatocellular carcinoma, as they tend to remain within the confines of the liver.[12]

The hypoglycemia presented much later into the course of illness, after the diagnosis of hepatocellular carcinoma, clinically presenting as type A NICTH but was actually type B NICTH. This highlights the overlap in the clinical presentation of the two types.

Conclusion

Nonislet cell tumor hypoglycemia is an underreported cause of hypoglycemia that can easily be underdiagnosed. Physicians need to have a high index of suspicion, as the incidence is on the rise, given the increasing lifespan of patients with hepatitis and hepatocellular carcinoma. It is also being diagnosed in association with an increasing number of different types of malignancies. NICTH can cause severe hypoglycemia presenting with neuroglycopenic symptoms and should be considered in a cancer patient presenting with altered sensorium.

References

1. Dutta P, Aggarwal A, Gogate Y, et al. Non-islet cell tumor-induced hypoglycemia: a report of five cases and brief review of the literature. Endocrinol Diabetes Metab Case Rep 2013;2013:130046.
2. Nadler WH, Wolfer JA. Hepatogenic hypoglycemia associated with primary liver cell carcinoma. Arch Intern Med (Chic) 1929;44(5):700–710.
3. McFadzean AJ, Yeung RT. Further observations on hypoglycaemia in hepatocellular carcinoma. Am J Med 1969;47(2):220–235.
4. Daughaday WH, Emanuele MA, Brooks MH, et al. Synthesis and secretion of insulin-like growth factor II by a leiomyosarcoma with associated hypoglycemia. N Engl J Med 1988;319(22):1434–1440.
5. Dizon AM, Kowalyk S, Hoogwerf BJ. Neuroglycopenic and other symptoms in patients with insulinomas. Am J Med 1999;106(3):307–310.
6. Crocker DW, Veith FJ. Mesodermal tumors associated with hypoglycemia review of literature and report of a case. Ann Surg 1965;161(3):418–427.
7. Garla V, Sonani H, Palabindala V, et al. Non-islet cell hypoglycemia: case series and review of the literature. Front Endocrinol (Lausanne) 2019;10:316.
8. Teale JD, Wark G. The effectiveness of different treatment options for non-islet cell tumour hypoglycaemia. Clin Endocrinol (Oxf) 2004;60(4):457–460.
9. Desai A, Sandhu S, Lai JP, et al. Hepatocellular carcinoma in non-cirrhotic liver: a comprehensive review. World J Hepatol 2019;11(1):1–18.
10. Tang A, Hallouch O, Chernyak V, et al. Epidemiology of hepatocellular carcinoma: target population for surveillance and diagnosis. Abdom Radiol (NY) 2018;43(1):13–25.
11. Kovac JD, Ivanovic A, Milovanovic T, et al. An overview of hepatocellular carcinoma with atypical enhancement pattern: spectrum of magnetic resonance imaging findings with pathologic correlation. Radiol Oncol 2021;55(2):130–143.
12. Oriakhi M, Andrabi SA, Olutoyin A, et al. A rare presentation of hepatocellular carcinoma infiltrating the gallbladder. Cureus 2019;11(7):e5140.

CASE REPORT

Concomitant Fat Embolism Syndrome and Pulmonary Embolism in an Orthopedic Trauma Patient

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Abstract

Simultaneous acute pulmonary embolism (PE) and fat embolism syndrome (FES) in a trauma patient is very rare. Acute PE is a frequent complication and, at times, a fatal disease. Its most common presenting symptom is dyspnea, followed by chest pain and cough. FES is a rare clinical syndrome defined by the presence of fat globules in the pulmonary circulation. It can occur in a vast variety of clinical conditions, especially in those where fat is manipulated. Almost all cases of FES are due to long bone and pelvic fractures. It is essential to differentiate between FES and PE, as the management of both these conditions is altogether different. PE and FES are usually seen separately, and it is rare to have concomitant FES and PE in the same patient. There is a paucity of case reports in the literature wherein patients developed concomitant FES and PE. We present a case of a roadside traffic accident (RTA) with long bone fractures, who developed this unusual and rarer clinical entity of concomitant FES and PE in the perioperative period. Its presentation, diagnosis, and successful management are discussed, along with a literature review.

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Introduction

Fat embolism (FE) and fat embolism syndrome (FES) are two different terms and are not interchangeable. Whereas FE refers to the presence of circulating fat particles in the circulation and pulmonary parenchyma, FES refers to the clinical symptoms of fat embolism. FES is seen in a variety of conditions, which could be trauma-related (orthopedic and nonorthopedic) and nontrauma-related. It is commonly seen in conditions where fat is manipulated, and almost all cases are seen following long bone and pelvic fractures, as their marrow has a high content of fat. Multiple fractures, open fractures, and delays in the time for reduction of the fracture are some of the factors associated with higher risks.[1–3] The prevalence of FES in trauma patients is about 1–2%, with a higher incidence in bilateral femur fractures (4.8–7.5%) and about 11% after intramedullary nail fixation of such fractures.[4] Pulmonary embolism (PE) is caused by obstruction of the pulmonary artery or its branches and is commonly seen in polytrauma patients. Its incidence varies between 10 and 42%.[5] Patients affected with FES develop a typical triad consisting of hypoxemia, neurologic abnormalities, and a petechial rash. However, none of these features are specific for FES. Patients with PE commonly develop dyspnea, cough, and pleuritic pain, besides other symptoms. Thus, in a patient with long bone fractures and hypoxemia and dyspnea, it is essential to differentiate between FES and PE, as the management entirely differs. However, trauma patients presenting with long bone fractures, hypoxemia, and the coexistence of PE and FES can be a nightmare for any clinician. There are not too many case reports in the literature on concomitant FES and PE.

We present an unusual case of an orthopedic trauma patient with long bone fractures who developed hypoxemia and dyspnea during closed reduction and fixation of a femur shaft fracture. She was later diagnosed with concomitant FES and PE and was successfully managed and discharged. Such cases are rare in the literature.

Case Description

A 26-year-old lady sustained an RTA on 18th April 2024 at 11:30 AM and had mild epistaxis, a loss of consciousness for 30 minutes, and fractures of the right femur and tibial shaft (Fig. 1). She was admitted locally in a nursing home, and closed reduction with internal fixation was done on 19th April 2024 under spinal anesthesia. Intraoperatively, she developed breathing difficulty, hypoxemia, and fever. She was then shifted to Fortis Escorts Hospital, Jaipur (FEHJ), for further management. Her 2D echocardiogram done outside showed normal left ventricular function, right ventricular enlargement, and its dysfunction. In triage, her pulse rate was 130/minute, respiratory rate 22/minute, SpO_2 98% on 10 L/minute oxygen support with a face mask, axillary temperature of 99.8°F, and blood pressure 96/60 mm Hg. Her arterial blood gas showed pH 7.37, pCO_2 37.6 mm Hg, pO_2 165.6 mm Hg, bicarbonate 21.3 mEq/L, and lactates 1.04 mmol/L, consistent with chronic respiratory alkalosis. Clinically, occasional scattered crepitations were present with vesicular breath sounds. She was operated on in the afternoon on 19th April 2024 for the right femur and had a slab applied to her right leg. Her D-dimer was very high—14,101 ng/mL. She was admitted for further management with a clinical possibility of FES vs PE. Her urine and plasma were sent to look for fat globules, and a 5000 IU unfractionated heparin IV bolus dose was given in triage. A computed tomography pulmonary angiogram (CTPA) was done on 19th May 2024, which showed a partial to near-complete lumen-occluding hypodense thrombus (HU = +23 to +54) in the right upper lobar pulmonary artery, extending into its segmental and subsegmental branches. Minimal lumen-occluding hypodense thrombus was seen in the anterior and superior lingular segmental and subsegmental branches of the left upper lobar pulmonary artery, and a partial lumen-occluding thrombus was seen in the subsegmental branches of the left lower lobar pulmonary artery—features suggesting bilateral pulmonary embolism (Fig. 2)—along with ground-glass opacities potentially indicative of FES (Fig. 3). Her hematology and biochemistry reports are mentioned in Table 1. She was given intravenous unfractionated heparin (UFH) in continuous infusion with aPTT monitoring as per protocol. Her noncontrast computed tomogram (NCCT) of the brain and nasal bone was normal. She had no cerebral symptoms, petechiae, or thrombocytopenia. A venous

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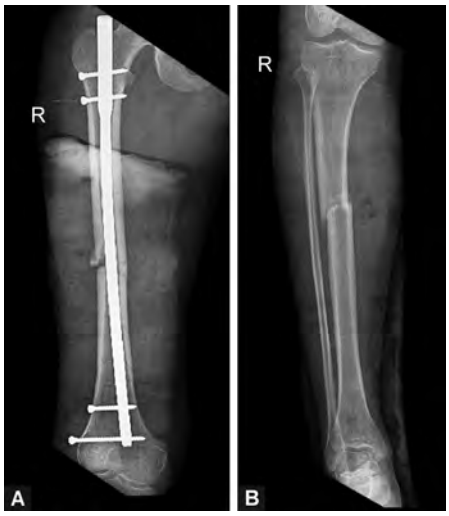


Figs 1A and B: X-ray of the right femur showing fracture of the right femur shaft with intramedullary nail fixation (A) and fracture shaft of the right tibial bone (B)

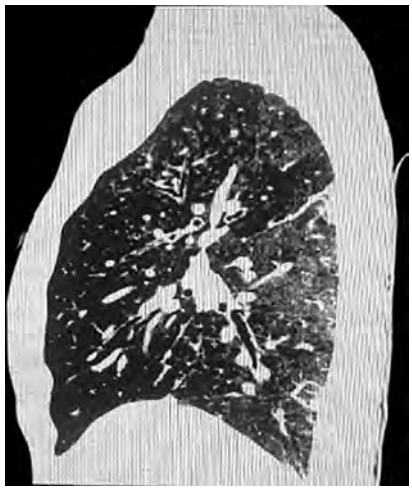


Fig. 3: Computerized tomogram of the chest showing ground-glass opacities potentially indicative of FES

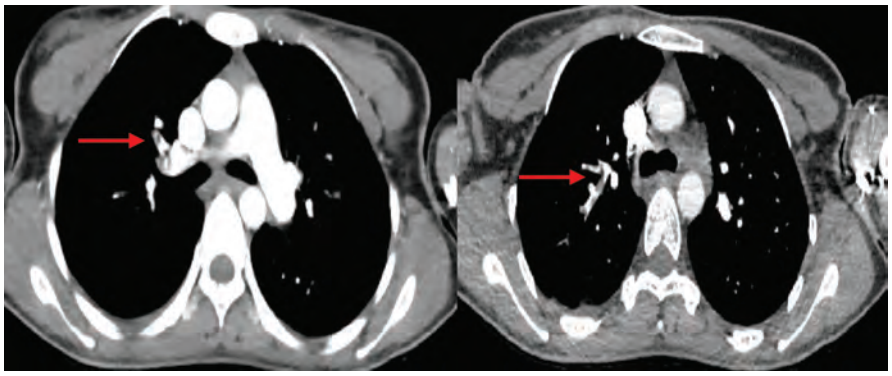
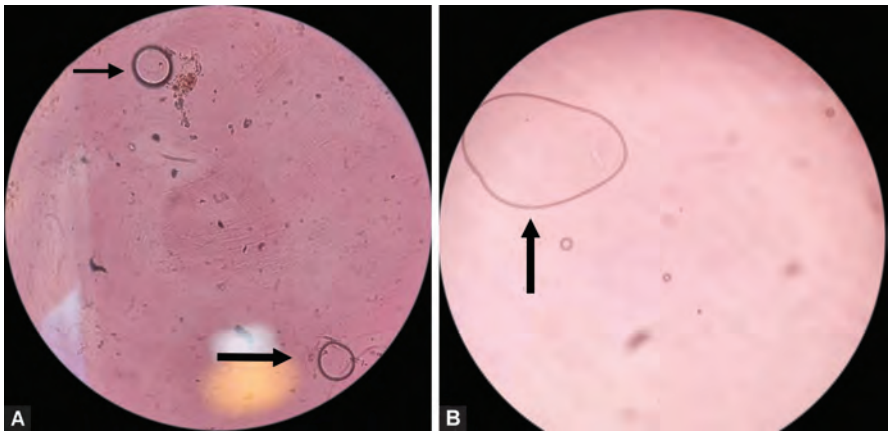


Fig. 2: CTPA showing pulmonary embolism (arrow)



Figs 4A and B: Fat globules seen under a microscope in plasma (A) and urine (B)

Doppler could not be done, as she had a slab on her right leg. A repeat 2D echocardiogram done on 20th April 2024 showed normal right-side heart function, mild to moderate tricuspid regurgitation with a right ventricular systolic pressure of 36 mm Hg + right atrial pressure, a dilated inferior vena cava (20 mm in width) with <25% collapsibility, and a left ventricular ejection fraction of 55%. A bilateral lower limb CT venous angiogram was done, which was unremarkable, and no evidence of deep venous thrombosis in the lower limbs was found.

She required noninvasive ventilation (NIV) support and vasopressors for hypotension on 19th May 2024, soon after admission. On 20th April 2024, day 3, her plasma and urine were reported showing the presence of fat globules (Fig. 4), confirming FES. Inj. Hydrocortisone 100 mg, intravenous, thrice a day, was added along with other supportive treatments. A fundoscopic examination was also done on 20th April 2024, and a few pale spots were seen over the macular area in the right eye. She also developed a sudden drop in hemoglobin, and 2 units of packed red blood cells were transfused. No source of obvious bleeding could be identified, and UFH was continued to treat PE. She was off NIV by the evening of 20th April 2024 and off oxygen support on 23rd April 2024. Closed reduction and internal fixation of the right tibia fracture shaft was done on 23rd April 2024 under spinal anesthesia. She was shifted to the ward on 24th April 2024. UFH was transitioned to apixaban, and she was discharged to her home on 25th April 2024.

Discussion

We have presented a case of orthopedic trauma with long bone fractures who developed concomitant PE and FES and was successfully managed and discharged. It is usually an unthinkable clinical scenario, and very few cases are reported in the literature. Precisely, fat embolism is the presence of fat globules within the circulation. In the majority of patients, it remains asymptomatic. However, if they do develop FES, it can be potentially fatal with a wide variety of symptoms, including end organ damage. FES, though originally described by the symptomatic triad of respiratory distress, neurological manifestations, and petechial rash, still has uncertainty regarding its diagnosis, prevention, and management.[6,7] Further, none of these symptoms are specific for FES, and its diagnosis is mainly clinical. The most common early findings are respiratory symptoms, with hypoxemia, dyspnea, and tachypnea being the most frequent. Hypoxemia was reported in up to 96% of cases in one series.[8] Neurological abnormalities are the next to manifest and range from acute confusional state, headaches, lethargy, irritability, delirium, stupor, seizures, focal deficits, to coma. Fortunately, these abnormalities are nearly always reversible and are reported in up to 59% of FES patients.[8,9] The last component of the triad to develop is the characteristic red-brown, small, bruise-like petechial rash due to the occlusion of dermal capillaries by fat emboli. It appears on the nondependent parts of the body and is seen in only 20–50% (on average, one-third) of cases.[8,10] The symptoms typically develop gradually over 24–72 hours.[11]

Table 1: Hematological and biochemical parameters

	19/04	*20/04*	*21/04*	*22/04*	*23/04*	*24/04*	*25/04*
CRP (0–5 mg/L)	103.8				67.4		
D-Dimer (<255 ng/mL DDU)	3100		908.6		906.4		
Creatinine (0.5–0.9 mg/dL)	0.66	0.61	0.44	0.55	0.48		
HB (gm/dL)	8.9	8.1	7.2	6.5	8.9	8.8	8.5
TLC (10^3/mm^3)	10.2	9.5	7.9	13.6	9.2	11	10.8
DLC (%)	P87L6	P89L7	P85L10	P70l14	P72L20	P87L08	P
Platelets (10^3/mm^3)	160	160	150	150	150	170	213
SGOT/SGPT (<32 U/L)	34/19						
S. Bilirubin T/D (<1.2 mg/dL)	0.74/0.34						
PT/INR	19.2/1.75						15.9/1.45
aPTT	28.2	122			43	33	23.5
Procalcitonin ng/mL (N <0.046)					12.79		
Lipase! 13–60 U/L)		7.1					
NT-proBNP (pg/mL)	1223						
CK MB (0.30–6.22 IU/L)	6.1						
CPK (39–308 U/L)	1226						
Trop T (<14 pg/mL)	7.8						

aPTT, Activated partial thromboplastin time; CK-MB, Creatine kinase–myocardial band; CPK, Creatine phosphokinase; CRP, C-reactive protein; DLC, Differential leukocyte count; Hb, hemoglobulin; PT-INR, Prothrombin time–International ratio; SGOT, Serum glutamic oxaloacetic transaminase; SGPT, Serum glutamate pyruvate transaminase; TLC, Total leukocyte count; Trop T, Troponin T

The presenting features of PE are diverse, ranging from no symptoms to shock or sudden death. The most common presenting symptom is dyspnea (breathlessness), followed by chest pain (classically pleuritic but often dull and worse with breathing) and cough. As it could even be asymptomatic, it is critical to have a high level of suspicion in clinically relevant cases so that it is not missed.[12] The most authentic test for the diagnosis of PE is the CTPA, where the presence of intraluminal filling defects in the pulmonary artery confirms the diagnosis.[12]

FES and PE are the two most common differential diagnoses of respiratory distress in patients with orthopedic trauma, often presenting with hypoxemia and/or dyspnea. However, having both these conditions simultaneously or consecutively could be an ordeal for any clinician. Our patient developed hypoxemia, dyspnea, and tachypnea 24 hours after trauma and during CRIF surgery for a right femur shaft fracture. Her D-dimer was very high (14,101 ng/mL), and 2D echocardiography showed findings consistent with potential new right ventricular strain, suggesting possible PE. She also required NIV support. She was anticoagulated upon her arrival at FEHJ. Later, her CTPA showed findings consistent with PE, and she was given intravenous unfractionated heparin (UFH) as per protocol for PE. When to initiate anticoagulant therapy in trauma patients with pulmonary embolisms is also debated. In the present case, we initiated anticoagulant therapy in triage on strong clinical suspicion and continued as per protocol once the diagnosis of pulmonary embolism was confirmed. We also did not find any active bleeding source prohibiting anticoagulation. Further, as in other case reports, we were not able to identify the source of the embolus, but we postulate that the thrombus was already present by the time of surgery, as the D-dimer was markedly raised, and it embolized during surgical manipulation. To prevent recurrence, the option of an inferior vena cava filter was discussed with the patient and family, but it was refused.

In a typical case of FES with a progressive clinical course, fracture of long bones or intramedullary instrumentation (such as nailing) is the actuating event. Following this instigating event, fat globules from bone marrow enter the venous circulation and embolize to the pulmonary capillary bed, thereby causing alveolar damage and dysfunction. This fat may also enter the systemic circulation *via* a patent foramen ovale, arteriovenous shunts, the pulmonary capillary bed, or all three, and afterward embolize and damage other organs.[7] Our patient had no neurological symptoms or petechial rash. However, on day 3, her plasma and urine were reported to be positive for fat globules, her hemoglobin dropped without any obvious source of bleeding, and CTPA showed evidence of ground-glass opacities suggesting possible concomitant FES. She fulfilled the Gurd and William diagnostic criteria (one major sign—respiratory symptoms plus bilateral radiographic findings and 5 minor signs—tachycardia, pyrexia, urinary changes—fat globules, sudden drop in hemoglobin levels, and high erythrocyte sedimentation rate) for FES.[13] We could not demonstrate fat globules in sputum, as the patient did not have any expectoration. However, her overlapping symptoms (PE vs FES) and laboratory findings developing within 72 hours are typical of FES with concomitant PE. Patchy ground-glass opacities seen on the patient's CTPA, along with features of PE, are considered indicative of concomitant fat embolism with PE.[14] We could demonstrate the presence of fat globules in venous plasma, and this could be used as a potential test when other specimens, such as sputum, are not available. The management of FES is supportive in cases of orthopedic trauma. Early fixation of fractures may prevent FES. We did fixation of her right tibial fracture as soon as she stabilized. However, whether or not this strategy of early fixation of fractures works as a treatment for those with established FES is not known.

The role of systemic corticosteroids in FES is contended. The rationale for their use is based on their anti-inflammatory effects and some evidence that supports their role in preventing FES.[15,16] In view of her clinical condition, we considered it appropriate to give her systemic hydrocortisone, 100 mg three times daily for 3 days. However, the increased risk of steroid-associated infections should be considered with a balanced approach.

To conclude, in any polytrauma patient who presents with breathing difficulty or respiratory distress, FES and PE are the usual initial clinical diagnoses. The incidence of concomitant FES and PE is very rare, with only a handful of cases being reported. Whether it happens simultaneously, consecutively, or which occurs first is very difficult to diagnose and not of much importance in clinical practice. Nevertheless, FES and/or PE in any polytrauma patient with worsening respiratory distress are of concern due to their fatality and differing treatment modalities.

Key Points

- The highest risk patients for FES and PE are those with multiple long bone or pelvic fractures. Very rarely, they may present concomitantly.
- Clinicians dealing with such cases should maintain the highest level of clinical suspicion to avoid missing relevant cases.
- The gold standard to reduce risks of FES is early fixation of long bone fractures.
- The presence of fat globules in urine, sputum, and even plasma could be used to support clinical suspicion.

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References

1. Stein PD, Yaekoub AY, Matta F, et al. Fat embolism syndrome. Am J Med Sci 2008;336:472.
2. Kainoh T, Iriyama H, Komori A, et al. Risk factors of fat embolism syndrome after trauma: a nested case-control study with the use of a nationwide trauma registry in Japan. Chest 2021;159:1064.
3. Eriksson EA, Pellegrini DC, Vanderkolk WE, et al. Incidence of pulmonary fat embolism at autopsy: an undiagnosed epidemic. J Trauma 2011;71:312.
4. George J, George R, Dixit R, et al. Fat embolism syndrome. Lung India 2013;30(1):47–53.
5. Jaganathan S, Thirugnanam B, Mukunthan N, et al. Concomitant fat embolism syndrome and pulmonary embolism—a hidden enemy in polytrauma patient: a case report. Indian J Crit Care Case Rep 2023;2(4):100–102.
6. Gurd AR. Fat embolism: an aid to diagnosis. J Bone Jt Surg Br 1970;52:732e7.
7. Luff D, Hewson DW. Fat embolism syndrome. BJA Education 2021;21(9):322–328.
8. Bulger EM, Smith DG, Maier RV, et al. Fat embolism syndrome. A 10-year review. Arch Surg 1997;132:435.
9. Johnson MJ, Lucas GL. Fat embolism syndrome. Orthopedics 1996;19:41–48.
10. Georgopoulos D, Bouros D. Fat embolism syndrome: clinical examination is still the preferable diagnostic method. Chest 2003;123:982.
11. Mellor A, Soni N. Fat embolism. Anaesthesia 2001;56:145–154.
12. Stein PD, Beemath A, Matta F, et al. Clinical characteristics of patients with acute pulmonary embolism: data from PIOPED II. Am J Med 2007;120:871.
13. Khosla R. Diagnosing pulmonary embolism. Indian J Crit Care Med 2006;10(2):105–111.
14. Yeak RDK, Liew SK. Concomitant fat embolism syndrome and pulmonary embolism in a patient with patent foramen ovale. Acta Orthop Traumatol Turc 2020;54(4):465–468.
15. Sen RK, Tripathy SK, Krishnan V. Role of corticosteroid as a prophylactic measure in fat embolism syndrome: a literature review. Musculoskelet Surg 2012;96:1.
16. Sen RK, Prakash S, Tripathy SK, et al. Inhalational Ciclesonide found beneficial in prevention of fat embolism syndrome and improvement of hypoxia in isolated skeletal trauma victims. Eur J Trauma Emerg Surg 2016.

Porcelain Aorta: Time to Recognize

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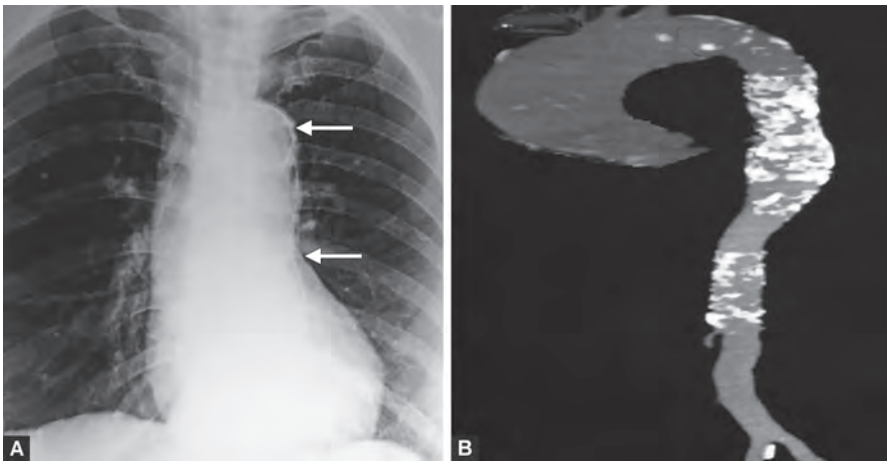
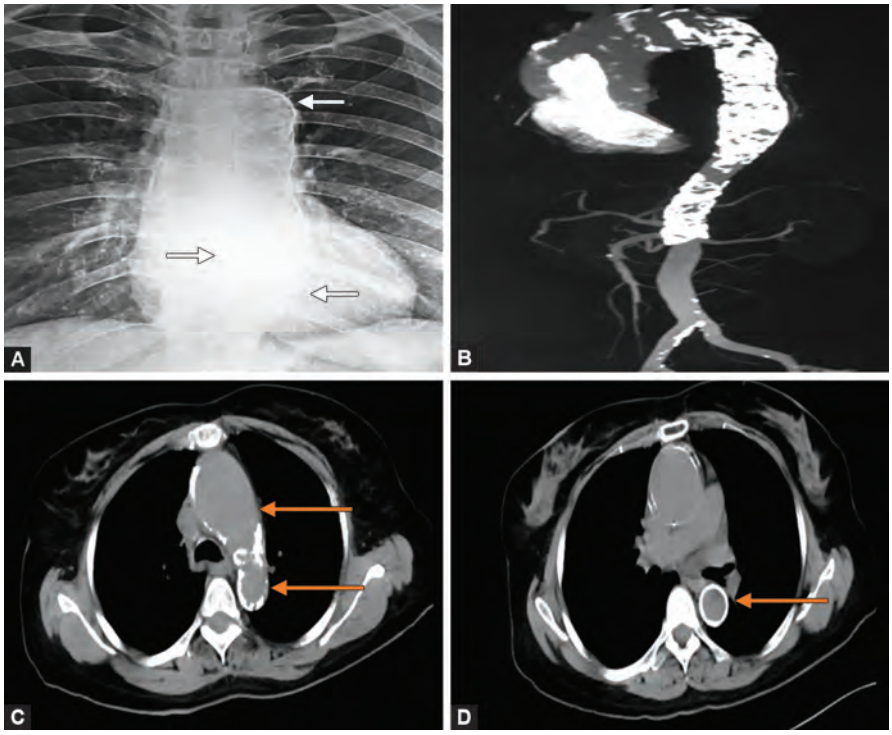


Figs 1A and B: Chest X-ray PA view and CT aortogram in 2012. (A) Chest skiagram PA view shows a CTR of 0.5, clear lung fields, and extensive calcification outlining the dilated aortic knuckle, thoracic, and descending aorta; (B) CT aortogram shows asymmetric extensive calcification of the wall of dilated thoracic and descending aorta and mild calcification of the ascending aorta



Figs 2A to D: Chest X-ray PA view and CT aortogram in 2022. (A) Chest skiagram PA view shows a CTR of 0.6, further dilation of the ascending aorta, and extensive calcification of the ascending aorta, aortic arch, thoracic, and descending aorta; (B) CT aortogram reveals extension of calcification in the ascending aorta with its aneurysmal dilation as well as ectasia in the descending aorta and extension of calcification up to the origins of the renal arteries and celiac trunk; (C) CT aortogram (axial images) demonstrates nearly circumferential heavy calcification of the ascending aorta extending to the aortic arch; (D) CT aortogram (axial images) demonstrates extensive circumferential or nearly circumferential calcification of the thoracic aorta

A 54-year-old female was evaluated in 2012 for management of hypertension and dyslipidemia. Clinical examination was unremarkable except for blood pressure (BP) 160/90 mm Hg and a grade 2/6 ejection systolic murmur along the left sternal border. A skiagram of the chest (posterior–anterior view) revealed a cardiothoracic ratio (CTR) of 0.5, clear lung fields, and extensive calcification outlining the dilated ascending and thoracic aorta (arrows, Fig. 1A), prompting the diagnosis of porcelain aorta (PA). Two-dimensional transthoracic echocardiography (TTE) demonstrated concentric left ventricular hypertrophy (LVH), thickening of aortic valve, dilation of the ascending aorta without any aortic regurgitation (AR) or gradient across the valve, its outflow, and in the supravalvular region. Computed tomography (CT) aortogram showed asymmetric extensive calcification of the wall of dilated thoracic and descending aorta and mild calcification of the ascending aorta (Fig. 1B). Biochemical tests were normal except for deranged lipid profile. During the last 10-year follow-up, she has remained asymptomatic with well-controlled BP and lipids on amlodipine, ramipril, statins, and aspirin. Follow-up X-ray shows a CTR of 0.6, further dilation of the ascending aorta, and extensive calcification in ascending, aortic arch, thoracic, and descending aorta (arrow, Fig. 2A). CT aortogram revealed extension of calcification in the ascending aorta with its aneurysmal dilation as well as ectasia in descending aorta and extension of calcification up to the origins of the renal arteries and celiac trunk (Figs 2B to D). Serial TTE did not demonstrate any AR or hemodynamic alteration.

The recognition of PA has clinical implications for physicians, interventional cardiologists, and cardiac surgeons equally. Multiple definitions of PA are available in the literature. PA is a structural aortic wall disease characterized by extensive circumferential

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or near-circumferential calcification of the thoracic, ascending aorta extending to the aortic arch[1] (Figs 2C and D). It is usually an incidental finding in patients being evaluated by a physician for a cardiovascular (CV) or pulmonary disorder. PA is often associated with coronary and valvular calcification, reflecting an underlying widespread atherosclerotic process. Ascending aorta or arch calcification has been correlated with a higher risk of CV events and mortality. The exact incidence is low in the general population but increases in the elderly and in patients being investigated for chronic kidney disease, radiation-induced CV disease, and systemic inflammatory disorders such as systemic lupus erythematosus and Takayasu's arteritis.

Two separate mechanisms lead to the formation of aortic calcification: atherosclerosis involving the intima and calcification of the medial layer in the absence of atheroma. Diagnosis can be made by fluoroscopy, chest X-ray, CT, TTE, transesophageal echo (TEE), and intraoperative ultrasound. A CT-based calcification score has been proposed for assessing postoperative procedural risk of cerebrovascular accident following aortic, coronary surgery, or transcatheter aortic valve implantation (TAVI).[2]

These patients can remain stable for long periods as was our patient during 12 years of follow-up, without any major change on CT aortogram. Management involves aggressive control of risk factors to prevent aortic dilation and any adverse CV events.

The crucial implication is an increased risk of stroke during open-heart surgery caused by embolization of atheromatous material resulting from manipulation of the ascending aorta. Aortic calcification can interfere with aortic cannulation, clamping, aortotomy, coronary anastomosis, or intra-aortic balloon placement and needs modification of conventional techniques to avoid complications.[3,4] The current era is one of TAVI, which can be successfully and safely performed in patients with severe aortic stenosis who may be ineligible for cardiac surgery.[5] All clinicians should be aware of the clinical implications of PA and diagnose this entity by chest X-ray, fluoroscopy, or CT.

References

1. Abramowitz Y, Jilaihawi H, Chakravarty T, et al. Porcelain aorta: a comprehensive review. Circulation 2015;131(9):827–836.
2. Amorim PA, Penov K, Lehmkuhl L, et al. Not all porcelain is the same: classification of circular aortic calcifications (porcelain aorta) according to the impact on therapeutic approach. Thorac Cardiovasc Surg 2013;61(7):559–563.
3. Adesanya TM, Kilic A. Dealing with a porcelain aorta during coronary artery bypass grafting. Case Rep Surg 2014;2014:582425.
4. Sirin G, Sarkislali K, Konakci M, et al. Extraanatomical coronary artery bypass grafting in patients with severely atherosclerotic (porcelain) aorta. J Cardiothorac Surg 2013;8:86.
5. Gunasekaran S, Sivaprakasm MC, Chandrasekeran GA, et al. TAVI in severe aortic stenosis with porcelain aorta: first reports from India with coronary and carotid support. IHJ Cardiovasc Case Rep 2018;2:177–180.

Challenges Faced in a CAPD Patient with Hemoperitoneum

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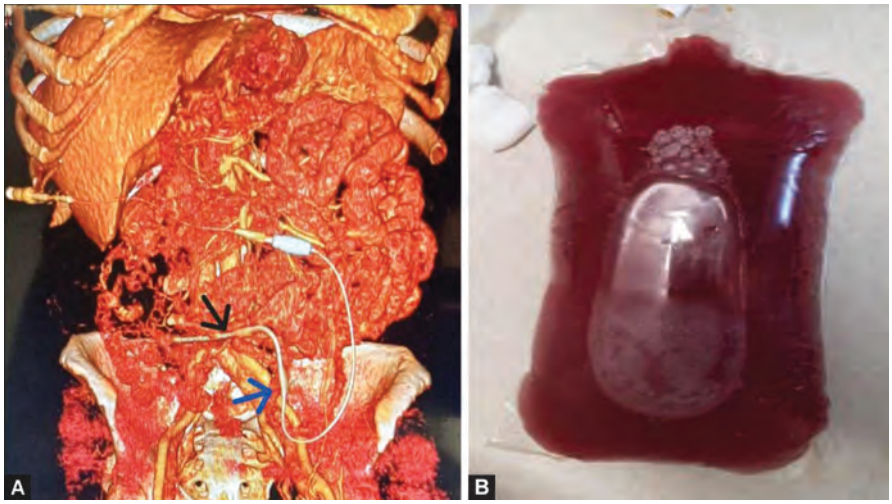
A 54-year-old, nondiabetic male who had an ABOi spousal kidney transplant in May 2023 underwent graft nephrectomy elsewhere due to dysfunction. He was initially on hemodialysis (HD) from July 2023 and was switched over to continuous ambulatory peritoneal dialysis (CAPD) in January 2024 due to poor hemodynamic status. He had a Swan neck Tenckhoff catheter (Fig. 1A). He noticed intermittent reddish effluent (Fig. 1B) since March 15, 2024. He denied trauma to the abdomen and was not on anticoagulant or antiplatelet drugs. His complete blood count (CBC) and electrolytes were: Hemoglobin (Hb)—7.8 g/dL, white blood cell (WBC) count—10 × 10^3 µL, platelet count—186 × 10^3 µL, creatinine—10.01 mg/dL, sodium—139 mmol/L, potassium—4.08 mmol/L, bicarbonate—23.7 mmol/L with normal coagulation profile [prothrombin time (PT)—17 seconds, international normalized ratio (INR)—1.51 ratio] and normal liver function tests. Hepatitis B surface antigen (HBsAg) and anti-HCV Ab were negative.

As the patient was switched over to CAPD meeting adequacy parameters, the bleeding was not due to uremia. Initially, he was given two or three rapid exchanges with room temperature dialysate with 1,000 U of heparin per 2-L bag to cause peritoneal vasoconstriction, which decreased the bleeding temporarily. Computed tomography (CT) of the abdomen showed a large multilobulated mass lesion 9.8 × 9.6 × 6.5 cm in segment VI of the liver extending to segments VII and VIII, suggestive of hepatocellular carcinoma (HCC) (Fig. 2A). Serum alpha-fetoprotein (AFP) was 12.12 IU/mL (40% of HCC have normal AFP levels).[1] CEA was 2.96 ng/mL. Positron emission tomography-computed tomography (PET-CT) scan showed no metastasis. The tumor was resected completely, and the rest of the liver was normal on histology. Histopathology showed moderately differentiated HCC with moderate cytologic atypia and scattered mitosis (Figs 2B and C). Figure 2C shows normal peritoneum without secondaries, unlikely to be metastasis. During the surgery, the peritoneal dialysis (PD) catheter was removed, and the patient was switched over to HD through his left forearm arteriovenous (AV) fistula. He had cardiac arrhythmia during the HD session. He developed peritoneal infection with multidrug resistant (MDR) *Klebsiella pneumoniae* and *Proteus mirabilis*, and he succumbed.

Common causes of hemoperitoneum in PD patients are due to trauma, catheter-related peritoneal infections, anticoagulant/antiplatelet drug use, peritoneal metastasis, and coagulopathy.[2] In our patient, HCC was directly bleeding into the peritoneum, probably due to microbleed. An alternative therapy in our patient would have been embolization of the tumor and probably continuation of PD.[3] Pretransplant CT imaging, which was done elsewhere, showed a small hypodense lesion (<1 cm) in the



Figs 1A and B: (A) PD catheter (black arrow—intraperitoneal segment, blue arrow—extraperitoneal segment); (B) Dialysis effluent showing hemoperitoneum

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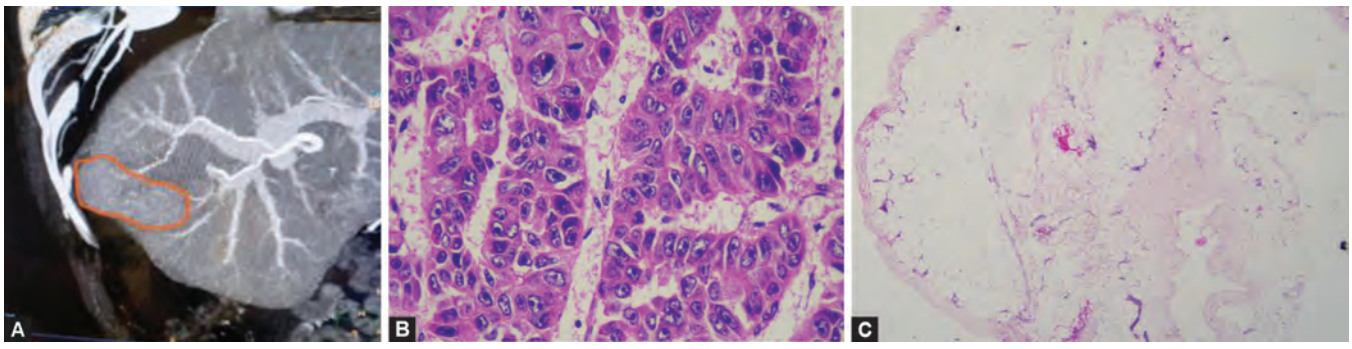

Figs 2A to C: (A) Arterial phase hyperenhancement—HCC; (B) Moderately differentiated HCC with moderate cytologic atypia and scattered mitosis; (C) Peritoneal tissue with no metastatic deposits or focal lesion

posterior lobe of the liver. Immunosuppressive therapy after transplantation led to rapid growth of the tumor.[4] This case highlights how malignancy in an immunosuppressed patient can present as hemoperitoneum and the need to manage such cases with a multidisciplinary approach.

References

1. Lee CW, Tsai HI, Lee WC, et al. Normal alpha-fetoprotein hepatocellular carcinoma: are they really normal? J Clin Med 2019;8(10):1736.
2. Goel N, Haddad DB, Jain D. Hemoperitoneum after cardiopulmonary resuscitation in peritoneal dialysis patients: a tale of two cases. Int J Nephrol Renovasc Dis 2020:379–383.
3. Lin WC, Chang CW, Chang CW, et al. Challenges of transarterial therapy for hepatocellular carcinoma in patients with chronic kidney disease. Medicine 2019;98(35):e17007.
4. Ietto G, Gritti M, Pettinato G, et al. Tumors after kidney transplantation: a population study. World J Surg Oncol 2023;21(1):18.

From Balding to Lustrous Locks: Levothyroxine Therapy's Transformative Impact on Hair Loss in Juvenile Hypothyroidism

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A 13-year-old girl was referred to the endocrinology outpatient clinic with chief complaints of significant hair loss leading to balding and poor height gain noted since the age of 5 years. She was born full term with a normal birth weight and had achieved all appropriate developmental milestones. Physical examination (Fig. 1) revealed a pulse of 56 beats per minute, height of 102 cm [<3rd percentile, height standard deviation score (Ht SDS) = −6.92], and weight of 22 kg. She had dry skin, facial puffiness, and a protuberant abdomen. There was diffuse hair loss involving the frontal, temporal, and occipital areas of the scalp with no scarring. Hair loss was noted in the lateral one-third of the eyebrows as well. Her thyroid function tests showed a thyroid stimulating hormone (TSH) level above 100 mIU/mL with low T4 and T3. The bone age was suggestive of 5 years. Antithyroid peroxidase (anti-TPO) testing was not done as it was not available at our center. She was diagnosed with juvenile hypothyroidism and was initially treated with 25 µg of levothyroxine, which was escalated to a full replacement dose after 2 weeks. Two months later, during the follow-up visit (Figs 2A and B), the child was more active and cheerful, facial puffiness had reduced, and there was substantial improvement in hair growth as well. Repeat thyroid function tests showed a TSH level of 1.51 mIU/mL with normal T4 and T3.

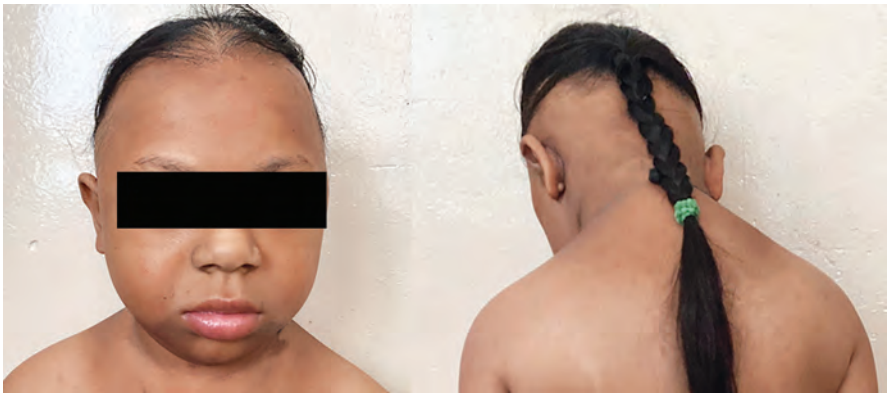
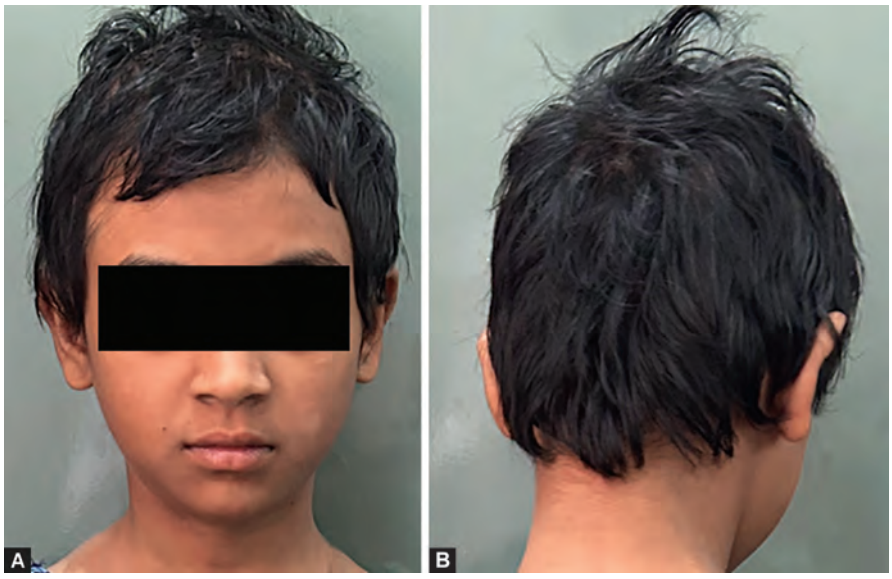


Fig. 1: Clinical photographs of the child at presentation showing apparent balding and madarosis



Figs 2A and B: Clinical photographs of the same child showing significant growth of scalp hair and eyebrows after receiving levothyroxine replacement

Hair growth occurs in four stages: the *anagen* phase (hair grows), the *catagen* phase (follicle shrinks and hair detaches), the *telogen* phase (new hair grows under old hair), and the *exogen* phase (old hair sheds and new hair replaces it). Thyroid hormones (THs) directly affect hair follicle function and pigmentation, promoting hair growth and regulating its cycle.[1] Hypothyroidism causes temporary hair loss by the phenomenon of *telogen effluvium*.[2] THs promote mitochondrial function, regulating energy metabolism in hair follicles, leading to an increase in specific mitochondrial genes and proteins. This directly affects hair follicle biology, and abnormal thyroid hormone production can cause hair loss. The exact mechanisms are still unclear. The thyrotropin-releasing hormone and its receptor are present in human scalp hair follicles, suggesting a possible hypothalamic–pituitary–thyroid pathway outside the hair follicles.[3]

Vincent et al.'s study[4] on hypothyroid patients showed various patterns of hair loss: Diffuse alopecia was the most common at 70%, followed by androgenetic alopecia at 14%, alopecia areata at 11%, alopecia universalis at 0.41%, diminished facial hair at 0.57%, cicatricial alopecia at 0.32%, alopecia totalis at 0.16%, and diminished body hair at 0.16%.

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Initially, levothyroxine treatment may cause a temporary increase in hair loss, which might be mistakenly blamed on the medication, leading to discontinued treatment and potentially worsening hair loss. This is due to the activation of resting hair follicles in the first month of therapy. However, the new hair is healthy, and over time, hair growth improves.

Levothyroxine therapy typically stops hair loss and promotes hair growth. However, in persistent cases of hypothyroidism, hair follicles might become atrophic. This could prevent hair growth, even with treatment.

Hair loss can be a significant presenting feature of juvenile hypothyroidism, along with poor growth, dry skin, and facial puffiness. Prompt initiation of levothyroxine therapy can lead to remarkable improvement in hair growth, as observed in this case. Hair loss associated with hypothyroidism is fully reversible with adequate thyroid hormone replacement.

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References

1. Hussein RS, Atia T, Bin Dayel S. Impact of thyroid dysfunction on hair disorders. Cureus 2023;15(8):e43266.
2. van Beek N, Bodó E, Kromminga A, et al. Thyroid hormones directly alter human hair follicle functions: anagen prolongation and stimulation of both hair matrix keratinocyte proliferation and hair pigmentation. J Clin Endocrinol Metab 2008;93(11):4381–4388.
3. Aboalola D, Aouabdi S, Ramadan M, et al. An update on alopecia and its association with thyroid autoimmune diseases. touchREV Endocrinol 2023;19(2):54–59.
4. Vincent M, Yogiraj K. A descriptive study of alopecia patterns and their relation to thyroid dysfunction. Int J Trichol 2013;5(1):57–60.

Barbara McClintock and Cytogenetics

JV Pai-Dhungat

Barbara McClintock with gene translocation. Stamp USA, 2003

Chromosome with details of material and centromere. Note map of Australia right upper corner. Stamp Australia, 2003

Barbara McClintock (1902–1992) was born in Hartford, Connecticut. She completed her undergraduate course in genetics at Cornell's College of Agriculture in 1919. The botany department was then involved in the study of maize genetics work. She found she could identify individual maize chromosomes under the microscope, and the 10 chromosomes of maize led to plant breeding experiments with chromosomal analysis. Within a few weeks, Barbara applied new staining techniques, identified the part of the embryo most suitable for cytological studies, and launched the new science of cytogenetics. McClintock earned her PhD in 1927, and from 1928 to 1935, she continued working with a small committed group of researchers at various institutions.

She made several discoveries in the field, establishing relations between chromosomes and genes. For the first time, she established that genetic recombination was a physical exchange of chromosomal segments and published it in 1931. McClintock also discovered that exposure to X-rays was responsible for altering the pattern and type of gene expression in descendant cells.

In 1948, she published her findings that the chromosome-breaking locus was something hitherto unknown for any genetic locus. It moved from one chromosomal location to another, a phenomenon she called translocation. Her seminal discovery published in PNAS (1950) attracted a lot of attention with mostly negative comments. When she presented her work at the symposium in 1951, the significance and implications were not understood. She was discouraged and became resentful of the disparity between her prospects and those of her male counterparts.

As with Gregor Mendel's experiments, it took decades before the significance of McClintock's discovery of transposition gained acceptance. Thirty-five years after her publication of the first evidence of transposition, McClintock was finally awarded an unshared Nobel Prize for Physiology or Medicine in 1983. McClintock's work was fully recognized when, in the 1970s, a series of experiments by molecular biologists proved that pieces of bacterial DNA do indeed jump on the chromosomes. Barbara McClintock died in a New York hospital in 1992 at the age of 90 years.

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Steroid Induced Dialated Cardiomyopathy

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Sir,

A 37-year-old male patient presents with complaints of progressively increased shortness of breath, pedal edema, puffiness of the face, distension of the abdomen, generalized swelling of the body, and oliguria for the last 15 days. There is no history of chest pain, palpitations, or cough. The patient gives a history of inhalational therapy prescribed at his local place and oral steroids (tab Betnesol) from a local medical store for the past 3 years for his attacks of breathlessness. The patient is a chronic smoker and alcoholic for the past 10 years.

On examination, the patient is conscious, cooperative, and oriented to time, place, and person. Pulse rate is 100 bpm, regular, and normal in volume. Blood pressure is 100/60 mm Hg, respiratory rate is 20 cpm, and SpO_2 is 99% on room air.

General examination reveals no pallor, icterus, or cyanosis. There is no clubbing, but neck veins are distended, and pedal edema is present. Moon facies and buffalo hump are also present.

On systemic examination, the abdomen is protuberant, with purple striae over the lower abdomen. The liver is palpable, firm in consistency, with a smooth surface, round margins, and nontender. The liver span is 15 cm in the mid-clavicular line. The spleen is not palpable, and mild ascites are present. Breath sounds are equal on both sides, with wheeze and crepitations heard all over the lung fields. S1 and S2 are normal, with no murmur. Central nervous system (CNS) examination is within normal limits.

Laboratory investigations on the day of admission were as follows: Hb 15.4 gm/dL, WBC 10,072/µL (P 84.7%, L 13.1%, M 2.1%, E 0%), platelets 203,000/µL, blood urea 100 mg/dL, creatinine 1.3 mg/dL, serum Na 139 mmol/L, K 3.9 mmol/L, Cl 101 mmol/L. Total S. bilirubin 2.3 mg%, direct bilirubin 1.3 mg%, SGOT 297 IU/L, SGPT 744 IU/L, total protein 6.3 gm%, S. albumin 4 gm%, GGT 1,113.2, S. triglycerides 131 mg/dL, S. total cholesterol 151 mg/dL, S. HDL 33 mg/dL. CK-NAC 99 IU/L, CK-MB 47 IU/L, LDH 564 IU/L. Trop-I 0.02, HIV, HBsAg, and Anti-HCV are nonreactive.

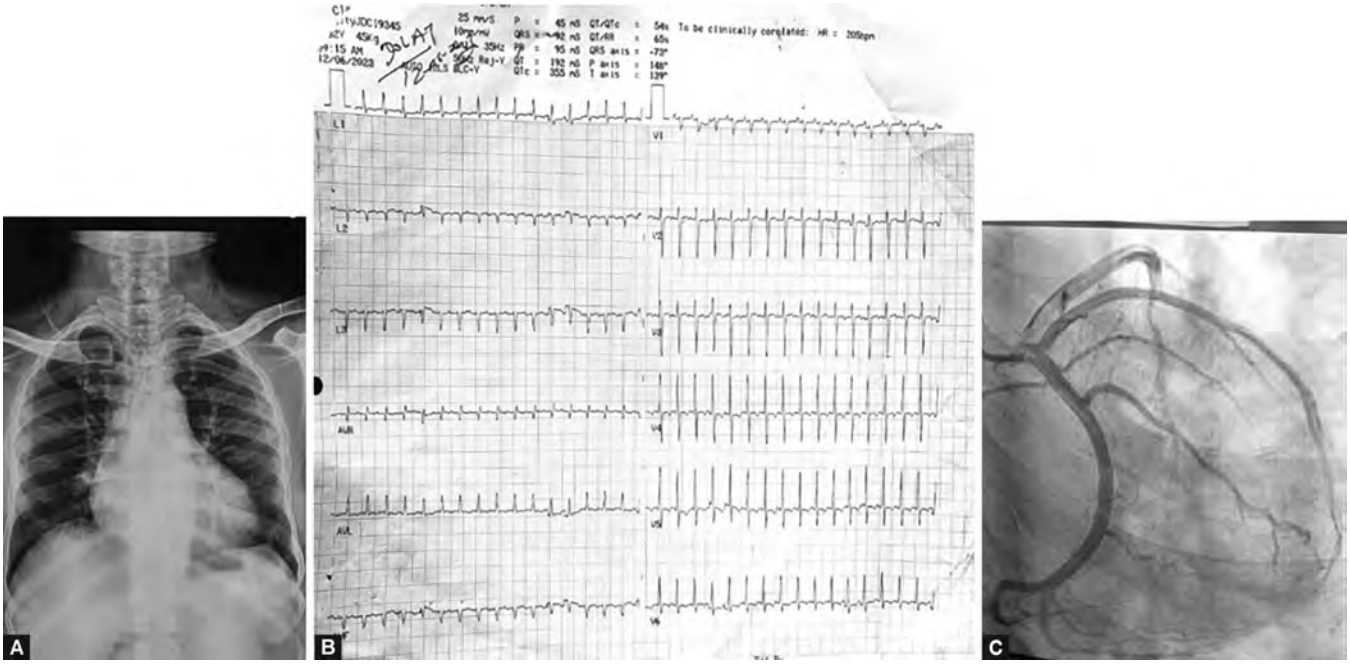
Chest X-ray PA view shows cardiomegaly and features of pulmonary edema (Fig. 1A). Ultrasound (USG) abdomen shows mild hepatomegaly with heterogeneous echotexture and mild free fluid. Two-dimensional (2D) echocardiography showed dilatation of all four cardiac chambers, left ventricle (LV) ejection fraction 10%, grade II diastolic dysfunction, and mild MR.

With the diagnosis of congestive heart failure (CHF) of unknown cause, the patient was put on decongestant therapy, dobutamine infusion, tab digoxin, and supportive treatment.

During the hospital stay, the patient developed three episodes of hypotension (BP 70/40 mm Hg), tachycardia (HR 162 bpm), hypoxia (SpO_2 88% on room air), and extensive wheeze bilaterally. The electrocardiogram (ECG) showed focal atrial tachycardia with a heart rate of 180/minute (Fig. 1B). In the first two episodes, the patient responded within a few hours with vasopressor, oxygen support, and nebulization therapy, resulting in stabilization of pulse, blood pressure, and oxygen saturation. Computed tomography (CT) pulmonary angiography did not show any evidence of pulmonary thromboembolism. The D-dimer was within normal limits (587.71).

The third episode of focal atrial tachycardia and hypotension was treated with amiodarone at 0.5 mg/minute, norepinephrine infusion at 0.3 µg/kg/minute, and other supportive treatment. After 24 hours, the patient attained sinus rhythm (heart rate 88/minute). Renal function tests and serum electrolytes returned to baseline after 6 days of admission, and liver function tests returned to normal levels after 18 days of admission. Repeat USG abdomen on the 14th day of admission revealed normal size and texture of the liver and no ascites, ruling out alcohol-related chronic liver disease (CLD).

Coronary angiography showed normal coronary vessels (Fig. 1C). The morning 6 AM serum cortisol level (50 mcg/dL) showed a raised value. The diagnosis of steroid-induced dilated cardiomyopathy (DCMP), in view of CHF and the presence of cushingoid features, with hypercortisolism due to exogenous steroids, was highly suggestive after exclusion of other relevant possibilities due to normal coronary vasculature and no alcohol-related



Figs 1A to C: Cardiomegaly and pulmonary edema features

liver damage. Cardiac magnetic resonance imaging (MRI) and the procedure for cardiac muscle biopsy were not feasible at our institute.

Treatment with L-carnitine, coenzyme Q, and digoxin was initiated in addition to oral amiodarone. The patient was discharged in stable condition after 21 days of hospital stay.

After discharge, the patient was clinically followed up regularly every fortnight. Follow-up studies at 6-month intervals revealed a conscious, cooperative patient oriented to time, place, and person. The pulse rate was 78/minute, BP 110/70 mm Hg, SpO_2 99% on room air, and RR 16/minute. General examination revealed normal JVP, no pedal edema, no signs of CHF, and no signs of cushingoid features. On systemic examination, the abdomen was soft, nontender, and without organomegaly. Breath sounds were equal on both sides, with bilateral wheeze heard all over the lung fields. S1 and S2 were normal, with no murmur. CNS examination was within normal limits. Chest X-ray (PA view) showed cardiomegaly. USG abdomen was within normal limits. 2D ECHO showed a dilated left atrium (LA) and LV, global hypokinesia of left ventricular ejection fraction (LVEF) 15–20%, mild mitral regurgitation (MR), mild tricuspid regurgitation (TR), and LV apical layering of clot.

Discussion

Cardiotoxicity is one of the major side effects of glucocorticoids when used in excess. Adverse cardiovascular risk from glucocorticoid use may be dose-dependent[1] or due to involvement of the renin-aldosterone system, which can induce myocardial remodeling.

Over a period of 1-year and 5-years cumulative risks of all-cause cardiovascular risks, such as acute myocardial infarction (MI), atrial fibrillation (AF), and CHF, increased from 1.4 and 7.1% to 8.9 and 28.0%, respectively, in no steroid vs steroid-dependent (prednisolone equivalent dose of >25 mg). Even the slightest dose of steroid (<5 mg) is also associated with the risk of cardiovascular disease.[1]

Synthetic glucocorticoids, like dexamethasone, alter the expression of ion channel genes that are important for calcium kinetics and contractile functions of the heart and are responsible for cardiac malfunctioning.[2]

A study on 19 cases of Cushing's syndrome with cardiomyopathy by Miao et al. identified DCMP in 15 cases (78.94%) and hypertrophic cardiomyopathy in four cases (21.05%).[3]

Steroid-induced cardiomyopathy due to an overdose of anabolic steroids is reported[4] and has also been described with the use of prednisolone.[5] In both of these case reports, there was significant improvement in LVEF after 10 and 4 months of stoppage of steroids, respectively, whereas in our case, though fully recovered clinically, LVEF showed only marginal improvement.

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References

1. Pujades-Rodriguez M, Morgan AW, Cubbon RM, et al. Dose-dependent oral glucocorticoid cardiovascular risks in people with immune-mediated inflammatory diseases: a population-based cohort study. PLoS Med 2020;17:e1003432.
2. De P, Roy SG, Kar D, et al. Excess of glucocorticoid induces myocardial remodeling and alteration of calcium signaling in cardiomyocytes. J Endocrinol 2011;209(1):105–114.
3. Miao S, Lu L, Li L, et al. Clinical characteristics for the improvement of Cushing's syndrome complicated with cardiomyopathy after treatment with a literature review. Front Cardiovasc Med 2021;8:777964.
4. Joseph J, Naqvi SY, Sturm E. Reversible anabolic androgenic steroid-induced cardiomyopathy. Cardiovasc Disord Med 2017;2:1–3.
5. Uehara H, Okuyama M, Oe Y, et al. Glucocorticoid-induced cardiomyopathy caused by uncontrollable asthma. Cureus 2023;15(8):e43780.

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