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Hipertansiyon Diyaliz ve Transplantasyon Vakfı

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Dear Readers,

We are pleased to present the new issue of the *Journal of European Internal Medicine Professionals (JEIMP)*, featuring a concise yet clinically meaningful selection of original articles, case reports, and a letter to the editor that address contemporary questions across internal medicine, with particular emphasis on metabolic disorders, critical care, and nephrology.

A central theme of this issue is the clinical interplay between metabolic diseases and systemic outcomes. Original investigations explore the impact of diabetes mellitus on the clinical course and early outcomes of Guillain–Barré syndrome, offering insights into how chronic metabolic conditions may influence acute neurological disorders. In parallel, a retrospective cohort study evaluates short-term changes in glycemic parameters following proton pump inhibitor therapy in patients with type 2 diabetes mellitus, highlighting an often-overlooked pharmacometabolic interaction with potential implications for routine clinical practice.

Another key focus of this issue is prognostication in critical care. An original study examining early lactate clearance as an independent predictor of in-hospital mortality reinforces the importance of dynamic biomarkers in guiding risk stratification and therapeutic decision-making in intensive care settings.

Renal and gastrointestinal case-based insights further enrich this issue. A notable case report presents familial nephrocalcinosis associated with heterozygous *SLC34A1* and *TRPV5* variants, emphasizing the role of genetic factors and disordered vitamin D metabolism in calcium-phosphate homeostasis. Additionally, a rare case of dysphagia and refractory gastroesophageal reflux due to an antral web underscores the importance of considering structural etiologies in patients with persistent upper gastrointestinal symptoms.

The Letter to the Editor section contributes to ongoing academic dialogue, providing critical commentary on current approaches to gout management and reinforcing the value of scholarly discussion in refining clinical practice.

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CONTENT

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Hipertansiyon Diyaliz ve Transplantasyon Vakfı

JEIMP

The Journal of European Internal Medicine Professionals

Original Article

Impact of Diabetes Mellitus on the Clinical Course and Early Outcomes in Guillain–Barré Syndrome: Single Center Experience

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Abstract

Background: This research was designed to evaluate whether comorbid diabetes mellitus (DM) influences the clinical presentation, severity of illness, and short-term functional recovery in individuals suffering from Guillain–Barré syndrome (GBS).

Methods: We performed a retrospective cohort study of 77 adult patients with GBS managed at a tertiary care neurological center from January 2020 through December 2025. Participants were categorized into two distinct groups: those with pre-existing type 2 diabetes mellitus (T2DM) (GBS+DM) and those without (GBS–DM). The comparison focused on demographic data, electrophysiological variants, Medical Research Council (MRC) sum scores, Modified Erasmus GBS Outcome Scores (mEGOS), and discharge functional capacity measured by the Hughes disability scale.

Results: In the total sample, 14 patients (18.2%) had diabetes mellitus. The GBS+DM group tended to be older; however, this difference was not statistically significant ($p = 0.142$). The mean mEGOS score was slightly higher in the diabetic cohort (3.8 ± 2.4) than in the non-diabetic group (3.4 ± 2.7), but the difference was not statistically significant ($p = 0.364$). No significant differences were observed regarding electrophysiological subtypes or early functional recovery between the cohorts. Nevertheless, a consistent numerical trend toward greater disability and less favorable prognostic markers was noted in the DM group.

Conclusion: Although not statistically significant, our data suggest that the presence of DM might be associated with a more severe clinical course and slower early recovery in GBS patients. Further validation through large-scale, prospective, multicenter trials is essential to definitively characterize the impact of DM on GBS outcomes.

Keywords: Guillain-Barre Syndrome; Diabetes Mellitus; Prognosis; Muscle Strength; Treatment Outcome; Autoimmune Diseases

INTRODUCTION

Guillain–Barré syndrome (GBS) is an acute-onset, immune-mediated inflammatory polyradiculoneuropathy affecting the peripheral nerves and nerve roots. With an annual incidence of approximately 1–2 per 100,000, GBS represents the most common cause of acute paralytic neuropathy in adults (1,2). Although the clinical course is typically monophasic, disease severity and recovery trajectories may vary substantially among patients. Despite effective immunomodulatory treatments such as intravenous immunoglobulin (IVIg) or plasmapheresis, a considerable proportion of patients develop persistent neurological sequelae. While overall mortality is reported to be below 5%, approximately 15–20% of patients are unable to walk independently six months after disease onset (3,4). These findings underscore the clinical importance of early prognostic assessment in GBS.

Several prognostic scoring systems have been developed to predict early disease course and long-term functional outcomes in GBS. Among these, the modified Erasmus GBS Outcome Score (mEGOS) is a widely validated and commonly used tool in clinical practice. The mEGOS incorporates patient age, history of preceding diarrhea, and the severity of muscle weakness as reflected by the Medical Research Council (MRC) sum score to estimate the risk of inability to walk independently at six months after disease onset (5–8). Higher mEGOS scores have consistently been associated with poorer functional outcomes.

Diabetes mellitus (DM) is a chronic metabolic disorder with increasing global prevalence and multisystem involvement. The peripheral nervous system is among the most commonly affected systems, and diabetic neuropathy may lead to progressive axonal degeneration and myelin damage over time (9). In recent years, accumulating evidence suggests that the presence of DM may adversely affect the clinical course and prognosis of GBS. In a retrospective study including 257 patients with GBS, Perić et al. reported that 17% of patients had concomitant DM and demonstrated that DM was significantly associated with poor short-term outcomes even after adjustment for age (10). Similarly, in a prospective study by Bae et al., patients with DM exhibited significantly worse functional outcomes at three months, and DM was identified as an independent risk factor for failure to regain independent ambulation. Notably, sudden cardiac arrest and deaths related to autonomic instability were observed exclusively in patients with DM in that study (11).

Proposed mechanisms underlying the unfavorable impact of DM on GBS include the presence of subclinical or overt axonal damage related to chronic hyperglycemia, which may exacerbate acute immune-mediated nerve injury. In addition, hyperglycemia-induced inflammatory activation, microvascular perfusion impairment, and metabolic stress may further aggravate peripheral nerve damage (12). Nevertheless, studies directly comparing the clinical characteristics and early outcomes of patients with GBS with and without DM across different populations remain limited.

In this study, we aimed to evaluate the impact of concomitant diabetes mellitus on clinical characteristics, disease severity, and early functional outcomes in patients with GBS treated at our center. By comparing patients with and without DM in terms of demographic features, baseline muscle strength (MRC sum score), mEGOS, need for mechanical ventilation, and functional status at discharge, we sought to elucidate the potential prognostic role of DM in GBS. Evidence regarding the impact of diabetes mellitus on the early clinical course of Guillain–Barré syndrome remains limited, particularly in real-world clinical cohorts.

METHODS

Protocol and Search Strategy

This retrospective cohort study, conducted at a single tertiary center, involved adult patients admitted to our Neurology Department with a diagnosis of GBS between January 2020 and December 2025. The Brighton criteria, which integrate clinical findings with electrophysiological and laboratory evidence, were used to confirm GBS diagnoses. Ethical approval for the protocol was granted by the local ethics committee on November 20, 2025 (Decision No: 848), and the study adhered to the principles of the Declaration of Helsinki.

The study population was categorized into two distinct cohorts based on glycemic status: the “GBS with DM” group, comprising patients with pre-existing type 2 diabetes mellitus, and the “GBS without DM” group, consisting of those without a history of diabetes mellitus. Enrollment followed a consecutive pattern, including all patients irrespective of clinical subtype, disease severity, or therapeutic interventions received.

Data on patient demographics (age and sex), potential triggers occurring within the six weeks preceding GBS (such as vaccinations, infections, or diarrheal episodes), clinical examination findings, and laboratory parameters were systematically retrieved from electronic medical records. Based on the results of nerve conduction studies, GBS cases were classified into electrophysiological subtypes: acute inflammatory demyelinating polyradiculoneuropathy (AIDP) or axonal variants, including acute motor/motor–sensory axonal neuropathy (AMAN/AMSAN) (13,14).

Assessment of motor strength was performed at admission and during hospitalization using the Medical Research Council (MRC) scale. The MRC sum score, ranging from 0 to 60, was calculated by assessing three muscle groups in each limb. Higher scores indicate greater muscle strength. For descriptive purposes, MRC scores were categorized into five groups reflecting the severity of motor weakness: (1) normal strength (60), (2) mild weakness (48–59), (3) moderate weakness (36–47), (4) severe weakness (24–35), and (5) extreme weakness (<24). To estimate the probability of regaining independent walking at six months, the modified Erasmus GBS Outcome Score (mEGOS) was calculated for each patient, incorporating admission MRC score, age, and history of preceding diarrhea.

Functional recovery was assessed using the GBS disability scale at discharge and, where available, at three-month follow-up. Secondary clinical endpoints included the need for mechanical ventilation, duration of intensive care unit stay, and total length of hospital stay.

Nerve Conduction Studies

Electrophysiological evaluations were performed using a Cadwell Sierra Summit system (Cadwell Laboratories Inc., USA) in the neurophysiology laboratory. All procedures followed standardized clinical protocols, maintaining skin temperature above 32°C for the upper extremities and 30°C for the lower extremities. Motor and sensory nerve conduction velocities, distal

latencies, and compound muscle action potential (CMAP) amplitudes were assessed in the median, ulnar, peroneal, and tibial nerves. F-wave responses were recorded to evaluate proximal nerve segments. Sensory nerve action potentials (SNAPs) were analyzed for the median, ulnar, and sural nerves. Based on the criteria established by Rajabally et al., patients were classified into the electrophysiological subtypes of AIDP, AMAN, or AMSAN (13).

STATISTICAL ANALYSIS

Statistical analyses and data processing were performed using IBM SPSS Statistics software (Version 25.0; IBM Corp., Armonk, NY, USA). Depending on data distribution, continuous variables are presented as mean ± standard deviation or median (interquartile range). Categorical variables are summarized as frequencies and percentages. To compare mEGOS and early functional outcomes between the cohorts, the independent samples t-test was used for normally distributed variables, whereas the Mann–Whitney U test was used for non-normally distributed variables. Categorical variables were compared using the Pearson chi-square test or Fisher exact test. Statistical significance was defined as a p-value < 0.05.

RESULTS

Study Characteristics

A total of 77 patients with GBS were included in the study. The mean age was 51.9 ± 18.4 years; 46 patients (59.7%) were male and 31 (40.3%) were female. Fourteen patients (18.2%) had concomitant diabetes mellitus, while 63 patients (81.8%) did not. In the DM group, 10 patients (71.4%) were male, compared with 36 patients (57.1%) in the non-DM group. No statistically significant differences were observed between the groups regarding age or sex distribution (both p > 0.05).

Table 1. Demographic and Clinical Characteristics of Patients With Guillain–Barré Syndrome With and Without Diabetes Mellitus

Characteristics	DM (+), n=63	DM (+), n=14	p value
Age, mean	50.7 ± 19.2	58.7 ± 11.7	0.142
Medical history			
Hypertension, n	3	0	0.029
CAD, n	5	4	0.052
Hyperlipidemia, n	18	6	0.297
MRC total score	2.6 ± 1.3	2.6 ± 1.1	0.779
Electrophysiological classification (Rajabally criteria)			
AIDP	50	13	
AMAN	8	1	
AMSAN	1	0	
Unclassified	4	0	

GBS, Guillain–Barré syndrome; DM, diabetes mellitus; CAD, coronary artery disease; MRC, Medical Research Council; AIDP, acute inflammatory demyelinating polyradiculoneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor–sensory axonal neuropathy.

Electrophysiological evaluation revealed demyelinating features in 13 patients (92.9%) and axonal involvement in 1 patient (7.1%) in the DM group. In the non-DM group, 50 patients (79.4%) exhibited demyelinating features and 13 patients (20.6%) showed axonal involvement. There was no statistically significant difference in electrophysiological subtype distribution between the groups (p = 0.444) (**Table 1**).

Disease Severity and Clinical Features

The mean admission mEGOS score was 3.38 ± 2.67 in the non-DM group and 3.78 ± 2.35 in the DM group, with no statistically significant difference between the groups (p = 0.364) (**Table 2**).

The severity of motor weakness was evaluated using the Medical Research Council (MRC) sum score. Mild weakness (corresponding to higher MRC scores) was observed in 3 patients (21.4%) in the DM group and in 13 patients (20.6%) in the non-DM group, with no statistically significant difference between groups (p > 0.05).

Early Functional Outcomes

Early functional outcome, as assessed by the GBS disability scale at discharge, was 15.04 ± 17.16 in the non-DM group and 15.57 ± 16.56 in the DM group. No statistically significant difference was detected between the groups (p = 0.443).

Overall, no statistically significant differences were observed between patients with GBS with and without DM in terms of demographic characteristics, electrophysiological subtypes, baseline disease severity, or early functional parameters. However, numerically higher admission mEGOS and GBS disability scale scores in the DM group suggest that further studies are warranted to clarify the potential impact of diabetes mellitus on GBS prognosis.

DISCUSSION

In the present study, no statistically significant differences were observed between GBS patients with and without concomitant DM regarding demographic features, electrophysiological subtypes, baseline clinical

Table 2. Modified Erasmus Guillain–Barré Syndrome Outcome Score (mEGOS) and Early Prognostic Parameters

Parameter	DM (+), n=63	DM (+), n=14	p value
mEGOS score	3.4 ± 2.7	3.8 ± 2.4	0.364
Probability of improvement at 6 months (%)	15.1 ± 17.2	15.6 ± 16.6	0.443

GBS, Guillain–Barré syndrome; mEGOS, modified Erasmus Guillain–Barré Syndrome Outcome Score; DM, diabetes mellitus.

severity, or early functional outcomes. Nevertheless, the observation of numerically higher admission mEGOS and GBS disability scales in the DM group suggests that the potential influence of diabetes mellitus on the clinical course of GBS merits further investigation in larger, prospective cohorts.

Bae et al. reported significantly worse three-month functional outcomes in GBS patients with DM and identified DM as an independent risk factor for failure to regain independent ambulation (11). Similarly, Perić et al. demonstrated that DM was significantly associated with poor short-term outcomes even after adjustment for age (10). In contrast, although mEGOS and disability scores were numerically higher in our DM group, these differences did not reach statistical significance.

Several pathophysiological mechanisms have been proposed to explain the adverse impact of DM on GBS outcomes. Chronic hyperglycemia may lead to subclinical or overt axonal damage in peripheral nerves, thereby amplifying the effects of acute immune-mediated nerve injury. In our study, we focused on patients with a pre-existing diagnosis of type 2 DM. However, emerging evidence suggests that not only overt diabetes but also impaired fasting glucose or stress-induced glycemic fluctuations may correlate with GBS severity. While we did not perform oral glucose tolerance tests due to the retrospective design and the potential for acute illness-related stress to confound results, the interplay between early-stage glucose metabolism and neuroinflammation remains a critical area for investigation. Indeed, Bae et al. reported more pronounced distal nerve conduction abnormalities in GBS patients with DM, suggesting the additive effect of diabetic axonal damage (11). Furthermore, hyperglycemia may exacerbate peripheral nerve injury through increased inflammatory cytokine production, impaired microvascular perfusion, and enhanced oxidative stress (12,15-17).

Previous studies have also suggested an increased risk of autonomic instability, cardiac arrhythmias, and sudden cardiac arrest in GBS patients with DM (11). The absence of mortality in our cohort may be attributable to the limited sample size and the relatively small number of elderly or hyperacute cases.

From a clinical perspective, these findings have important implications. In patients with GBS and concomitant DM, clinicians should be aware of the potential for a more severe disease course and maintain a lower threshold for intensive care monitoring due to the risk of respiratory failure and autonomic dysfunction. Early planning of rehabilitation and appropriate counseling of patients and caregivers regarding potentially slower functional recovery are also essential. Prognostic tools such as the mEGOS may provide valuable guidance in clinical decision-making, particularly in patients with DM.

Although this study contributes to the limited body of literature examining the interaction between metabolic disorders and immune-mediated neuropathies, several important limitations should be considered when interpreting the findings. First, the relatively small sample size, particularly within the diabetic subgroup, may have reduced the statistical power required to detect subtle differences between the groups. Another limitation is the lack of documentation of diabetes-specific clinical parameters, including HbA1c levels, duration of diabetes, treatment adherence, and the severity of pre-existing diabetic complications. In addition, the absence of data regarding pre-admission glycemic control prevented us from determining whether well-controlled versus poorly controlled diabetes mellitus has differential effects on Guillain–Barré syndrome outcomes. Future multicenter prospective studies with larger cohorts, incorporating detailed metabolic parameters such as HbA1c levels, duration of diabetes, and metabolic control status, as well as systematic screening for glucose intolerance in non-diabetic GBS patients, may provide a more comprehensive understanding of the relationship between diabetes mellitus and Guillain–Barré syndrome.

CONCLUSION

In conclusion, diabetes mellitus in patients with Guillain–Barré syndrome should be considered a potential risk factor influencing early functional outcomes. Larger, multicenter, prospective studies are required to clarify the underlying mechanisms and to develop targeted strategies aimed at improving prognosis in patients with GBS and concomitant diabetes mellitus.

DECLARATIONS

Ethics Committee Approval: Ethical approval for the protocol was granted by the Adana City Training and Research Hospital Scientific Research Ethics Committee on November 20, 2025 (Decision No: 848), and the study strictly adhered to the principles of the Declaration of Helsinki.

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Authors' Contributions: Elif Banu Soker: Conception, Design, Supervision, Fundings, Literature Review, Writing ,Critical Review Pamir Bastin: Materials, Data Collection and/or Processing, Literature Review Seda Mençekoğlu Bastin: Materials, Data Collection and/or Processing, Literature Review Halil Can Alaydın: Analysis and/or Interpretation, Crical Review Derya Ozdogru : Supervision, Fundings, Literature Review, Miray Erdem: Supervision, Fundings, Literature Review, Writing Halit Fidanci: Design, Supervision, Analysis and/or Interpretation ,Writing.

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Original Article

Short-Term Changes in Glycemic Parameters Following Proton Pump Inhibitor Therapy in Patients With Type 2 Diabetes Mellitus: A Retrospective Cohort Study

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Abstract

Background: Emerging evidence suggests that proton pump inhibitors (PPIs) may influence glucose metabolism through mechanisms such as gastrin-mediated stimulation of pancreatic β-cell activity and alterations in gut microbiota composition. However, clinical studies evaluating the metabolic effects of PPIs in patients with type 2 diabetes mellitus (T2DM) have yielded inconsistent findings. The present study aimed to evaluate short-term changes in glycemic parameters after initiation of PPI therapy in patients with T2DM and to explore clinical characteristics associated with reductions in fasting glucose.

Methods: This retrospective observational study included 66 adults with T2DM who were newly prescribed a PPI in a gastroenterology outpatient setting. Clinical and laboratory data were obtained from electronic medical records and verified through the national prescription monitoring system. Fasting glucose, postmeal glucose, glycated hemoglobin (HbA1c), and body mass index (BMI) were recorded at baseline and during a three-month follow-up period. Changes in glycemic parameters were analyzed using paired statistical tests, and logistic regression was used to identify factors associated with reductions in fasting glucose.

Results: The mean age of participants was 57.93 ± 10.90 years, and the mean BMI was 29.31 ± 2.98 kg/m². During the three-month follow-up period, mean fasting glucose decreased significantly from 132.12 ± 19.61 mg/dL to 122.13 ± 23.52 mg/dL ($p < 0.001$). Postmeal glucose and HbA1c levels showed numerical reductions but did not reach statistical significance. A decrease in fasting glucose was observed in 47 of 66 participants (71.2%). Patients who experienced fasting glucose reduction were significantly older, had lower BMI, and had a shorter duration of diabetes compared with those without reduction. Multivariate analysis demonstrated that older age, lower BMI, and shorter diabetes duration were independently associated with fasting glucose reduction.

Conclusions: PPI therapy was associated with a modest reduction in fasting glucose during short-term follow-up, whereas HbA1c and postmeal glucose levels did not change significantly. The observed association appeared to vary according to patient characteristics, particularly BMI and duration of diabetes. These findings suggest that metabolic responses to PPI therapy may differ across clinical subgroups of patients with T2DM and warrant further investigation in larger prospective studies.

Keywords: Diabetes Mellitus, Type 2, Proton Pump Inhibitors, Blood Glucose, Glycated Hemoglobin, Body Mass Index

INTRODUCTION

Proton pump inhibitors (PPIs) are among the most commonly prescribed medications worldwide for the treatment of acid-related gastrointestinal disorders, including gastroesophageal reflux disease, peptic ulcer disease, and dyspepsia (1,2). Their mechanism of action involves irreversible inhibition of the gastric H^+/K^+-ATPase enzyme, resulting in potent and sustained suppression of gastric acid secretion (1,3). Owing to their high efficacy and favorable safety profile, PPIs are frequently prescribed for prolonged periods and are widely used in patients with multiple comorbidities, including type 2 diabetes mellitus (T2DM) (4,5).

In recent years, increasing attention has been directed toward the potential extra-gastric metabolic effects of PPIs, particularly their possible influence on glucose metabolism (5,6). Several biological mechanisms have been proposed to explain a potential interaction between PPI therapy and glycemic regulation. One

commonly discussed pathway involves PPI-induced hypergastrinemia, which may stimulate pancreatic β-cell activity and enhance insulin secretion (7,8). Experimental and clinical studies have suggested that elevated gastrin levels may promote β-cell regeneration and improve glucose tolerance (5–8). In addition to gastrin-mediated mechanisms, alterations in gastrointestinal pH and gut microbiota composition associated with PPI therapy may also influence metabolic pathways involved in glucose homeostasis (9).

Despite these mechanistic hypotheses, clinical evidence regarding the impact of PPIs on glycemic control remains inconsistent. Some randomized controlled trials and observational studies have reported modest improvements in fasting glucose or glycated hemoglobin (HbA1c) levels among patients with T2DM receiving PPI therapy (4,10,11). Conversely, other investigations have demonstrated minimal or no measurable effects on glycemic indices (12,13). Furthermore, several studies have suggested that the metabolic impact of PPIs may vary according to patient characteristics such as duration of diabetes, body mass index (BMI), baseline glycemic status, and concurrent antidiabetic treatments (4,10–13). These heterogeneous findings highlight the need for additional clinical data to clarify whether specific subgroups of patients with T2DM may experience metabolic changes during PPI therapy.

Given the widespread use of PPIs among patients with diabetes, understanding potential interactions between these medications and glucose metabolism may have important clinical implications. The present study aimed to investigate the association between PPI therapy and short-term changes in blood glucose levels in patients with T2DM. In addition, we sought to explore whether specific clinical characteristics, including age, BMI, and duration of diabetes, were associated with a greater likelihood of fasting glucose reduction among PPI users.

METHODS

Protocol and Search Strategy

This retrospective observational study used routinely collected clinical data from patients who attended the gastroenterology outpatient clinics of Atılım University and Medicana International Ankara Hospital between January 2021 and December 2022. The study was designed as a within-subject before–after analysis evaluating changes in glycemic parameters following initiation of PPI therapy in patients with T2DM. Clinical and laboratory data were obtained from the hospital electronic medical record system. Medication exposure and prescription continuity were verified through the national electronic prescription monitoring system maintained by the Republic of Türkiye Ministry of Health (e-Nabız). The primary objective was to evaluate short-term changes in fasting and postmeal glucose levels, as well as glycated hemoglobin (HbA1c), following initiation of PPI therapy during routine clinical care.

Participants

Adult patients aged 18 years or older with a confirmed diagnosis of T2DM who were newly prescribed a PPI during the study period were eligible for inclusion. Patients were required to have available baseline clinical data and at least one follow-up evaluation within approximately three months after initiation of PPI therapy. Patients with diabetic gastroparesis, rheumatologic diseases requiring immunosuppressive therapy, chronic kidney disease stage 3 or higher, active malignancy, or acute systemic illness during the observation period were excluded. Individuals receiving anti-ulcer medications other than PPIs were also excluded. To minimize potential confounding related to prior drug exposure, patients who had used PPIs before the index prescription were not included. In addition, patients who discontinued PPI therapy during the follow-up period, experienced prolonged hospitalization, or had substantial changes in their antihyperglycemic treatment regimen were excluded. Verification of medication exposure, treatment continuity, and potential therapy changes was performed through review of the national prescription database and hospital outpatient registries.

PPI Exposure Assessment

PPI therapy was prescribed for routine clinical indications, including dyspepsia, gastritis, gastroduodenitis, or gastroesophageal reflux disease. The most commonly prescribed PPIs were lansoprazole 40 mg, esomeprazole 40 mg, and pantoprazole 40 mg. The type of PPI prescribed was recorded; however, the study was not designed to compare metabolic effects between individual PPI agents. Continuous PPI use for approximately three months was verified using the national electronic medication monitoring system and physician outpatient records. Diagnostic indications for PPI prescriptions were identified using International Classification of Diseases (ICD) codes K29 and K30 recorded in the hospital information system.

Clinical and Laboratory Measurements

Baseline demographic and clinical characteristics, including age, sex, BMI, duration of diabetes, and comorbid conditions, were extracted from the electronic medical record at the time of PPI initiation. Laboratory measurements included fasting glucose (FG), postmeal glucose (PMG), and HbA1c. BMI values were calculated using height and weight measurements recorded during outpatient visits. Baseline laboratory parameters were

defined as the most recent measurements recorded prior to initiation of PPI therapy. Follow-up laboratory data were obtained from subsequent outpatient visits occurring approximately one, two, and three months after initiation of PPI treatment when available. HbA1c and BMI measurements were primarily evaluated at baseline and at month three because intermediate measurements were not routinely performed in clinical practice.

To explore clinical predictors of glycemic response, patients were categorized according to the direction of change in fasting glucose between baseline and the third month of follow-up. Patients demonstrating a decrease in fasting glucose were classified as the glucose reduction group, whereas those without a decrease were classified as the non-reduction group. The magnitude of reduction was not used as a classification criterion; instead, the analysis focused on identifying baseline characteristics associated with the presence or absence of fasting glucose reduction.

Sample Size Estimation

Before data extraction, a minimum sample size of 62 participants was estimated using G*Power software (version 3.1.9.7), assuming an effect size of 0.70, a significance level (α) of 0.05, and a statistical power of 95% (1−β = 0.95). A total of 66 eligible patients met the inclusion criteria and were included in the final analysis.

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS for Windows (version 17.0; IBM). The distribution of continuous variables was evaluated using the Kolmogorov–Smirnov test. Continuous variables with normal distribution are presented as mean ± standard deviation, whereas non-normally distributed variables are reported as median values with minimum and maximum ranges. Categorical variables are summarized as frequencies and percentages. Changes in glycemic parameters before and after PPI therapy were evaluated using paired-sample t-tests. Comparisons between patients with and without fasting glucose reduction were performed using chi-square tests for categorical variables and independent sample tests for continuous variables as appropriate. To identify factors associated with fasting glucose reduction, logistic regression analyses were performed including clinically relevant variables such as age, BMI, and duration of diabetes. Receiver operating characteristic (ROC) curve analysis was conducted as an exploratory analysis to evaluate the discriminatory ability of age, BMI, and diabetes duration for predicting fasting glucose reduction at month three and to identify potential cutoff values. All statistical tests were two-tailed, and a p value of less than 0.05 was considered statistically significant.

RESULTS

Study Characteristics

A total of 66 patients with type 2 diabetes mellitus were included in the analysis. The study population consisted of 31 men and 35 women, with a mean age of 57.93 ± 10.90 years. Age distribution did not differ significantly between male and female participants (p = 0.756). The median duration of diabetes was 6 years (range: 1–29 years). The mean baseline BMI was 29.31 ± 2.98 kg/m². The most common indications for PPI therapy were dyspepsia (24.24%), acute gastritis (21.21%), gastroduodenitis (19.69%), and gastroesophageal reflux disease (15.2%). The prescribed PPIs included lansoprazole (n = 23), esomeprazole (n = 21), pantoprazole (n = 19), and rabeprazole (n = 3). The mean follow-up duration after initiation of PPI therapy was 86 days.

Changes in Glycemic Parameters

Changes in glycemic parameters during the three-month follow-up period are summarized in **Table 1**. Mean fasting glucose decreased significantly from 132.12 ± 19.61 mg/dL at baseline to 122.13 ± 23.52 mg/dL at month three (p < 0.001), corresponding to an approximate reduction of 6%. Postmeal glucose levels demonstrated a numerical decline during follow-up but did not reach statistical significance (p = 0.126). Similarly, HbA1c decreased modestly from 8.15 ± 1.07% at baseline to 8.00 ± 1.09% at month three, although this change was not statistically significant (p = 0.146). BMI remained stable during the study period (29.31 ± 2.98 vs. 29.24 ± 3.06 kg/m²; p = 0.899).

Frequency of Fasting Glucose Reduction

A decrease in fasting glucose at month three was observed in 47 of the 66 participants (71.2%). In this

Table 1. Changes in Glycemic Parameters After Initiation of Proton Pump Inhibitor Therapy.

Variable	Baseline	Month 1	Month 2	Month 3	P value (baseline vs month 3)
Fasting glucose (mg/dL)	132.12 ± 19.61	126.28 ± 25.01	124.46 ± 25.73	122.13 ± 23.52	<0.001
Postmeal glucose (mg/dL)	183.84 ± 31.92	175.96 ± 53.44	187.80 ± 55.64	174.33 ± 51.99	0.126
HbA1c (%)	8.15 ± 1.07	NA	NA	8.00 ± 1.09	0.146
BMI (kg/m²)	29.31 ± 2.98	NA	NA	29.24 ± 3.06	0.899

HbA1c, glycated hemoglobin A1c; BMI, body mass index

Table 2. Comparison of Two Groups After Proton Pump Inhibitor Therapy.

Variable	Reduction (+) N=47	Reduction (−) N=19	P value
Age (years)	59.82 ± 10.18	53.26 ± 11.47	0.026
Sex (male/female)	22 / 25	9 / 10	1.000
BMI (kg/m²)	28.44 ± 2.17	31.45 ± 3.63	0.003
Baseline fasting glucose (mg/dL)	134.68 ± 20.95	125.78 ± 14.40	0.054
Fasting glucose Month 1	125.12 ± 26.11	129.15 ± 22.46	0.558
Fasting glucose Month 2	123.74 ± 27.40	126.26 ± 21.62	0.722
Fasting glucose Month 3	112.70 ± 17.74	145.47 ± 19.64	<0.001
Baseline PMG	184.23 ± 30.19	182.89 ± 36.72	0.879
PMG Month 1	174.91 ± 51.34	177.15 ± 59.52	0.754
PMG Month 2	171.53 ± 59.53	181.05 ± 45.35	0.535
PMG Month 3	169.27 ± 52.96	186.84 ± 46.32	0.211
Baseline HbA1c (%)	8.17 ± 1.07	7.63 ± 1.12	0.395
HbA1c Month 3 (%)	8.01 ± 1.16	7.74 ± 0.86	0.274
Diabetes duration (years)	6.70 ± 4.64	10.63 ± 5.95	0.005

PMG, postmeal glucose; HbA1c, glycated hemoglobin A1c; BMI, body mass index

subgroup, the mean reduction in fasting glucose was 15.78%. Conversely, 19 patients (28.8%) did not demonstrate a reduction in fasting glucose during the observation period.

Comparison Between Reduction and Non-Reduction Groups

Clinical and laboratory characteristics of patients with and without fasting glucose reduction are presented in **Table 2**. Patients in the reduction group were significantly older than those in the non-reduction group (59.82 ± 10.18 vs. 53.26 ± 11.47 years, p = 0.026). Baseline BMI was also significantly lower in the reduction group (28.44 ± 2.17 vs. 31.45 ± 3.63 kg/m², p = 0.003). In addition, patients demonstrating fasting glucose reduction had a significantly shorter duration of diabetes (6.70 ± 4.64 vs. 10.63 ± 5.95 years, p = 0.005). Baseline fasting glucose levels were slightly higher in the reduction group; however, this difference did not reach statistical significance (p = 0.054). During follow-up, fasting glucose levels progressively declined in the reduction group, reaching 112.70 ± 17.74 mg/dL at month three, whereas fasting glucose increased to 145.47 ± 19.64 mg/dL in the non-reduction group (p < 0.001). Postmeal glucose levels tended to decrease in the reduction group and increase slightly in the non-reduction group, although these differences did not reach statistical significance. HbA1c levels also demonstrated minor changes in both groups but remained statistically non-significant.

Predictors of Fasting Glucose Reduction

Logistic regression analysis was performed to evaluate potential predictors of fasting glucose reduction among PPI users (**Table 3**). In univariate analysis, age (p = 0.030), duration of diabetes (p = 0.029), and BMI (p = 0.002) were significantly associated with glucose reduction. Multivariate logistic regression analysis confirmed that older age (p = 0.001), shorter duration of diabetes (p = 0.045), and lower BMI (p = 0.005) were independently associated with a greater likelihood of fasting glucose reduction following PPI therapy.

Receiver Operating Characteristic Analysis

Receiver operating characteristic (ROC) curve analysis was performed as an exploratory analysis to assess the discriminatory ability of age, BMI, and diabetes duration for predicting fasting glucose reduction at month three among PPI users. The positive outcome was defined as a decrease in fasting glucose at month three compared with baseline. Age demonstrated modest discriminatory ability, with an area under the curve (AUC) of approximately 0.64 (95% CI 0.51–0.76). An optimal cutoff value of 57 years yielded a sensitivity of 66% and a specificity of 34%. Patients older than 57 years showed a higher rate of fasting glucose reduction than those aged 57 years or younger (81.6% vs. 59.3%, p = 0.048). BMI demonstrated stronger predictive

Table 3. Logistic Regression Analysis of Factors Associated with Glucose Reduction Following Proton Pump Inhibitor Therapy.

Variable	Univariate OR	95% CI	P value	Multivariate OR	95% CI	P value
Age	0.946	0.900–0.995	0.030	1.658	1.242–2.213	0.001
Diabetes duration	1.044	0.963–1.132	0.029	1.046	0.972–1.125	0.045
BMI	1.484	1.158–1.902	0.002	0.909	0.851–0.972	0.005

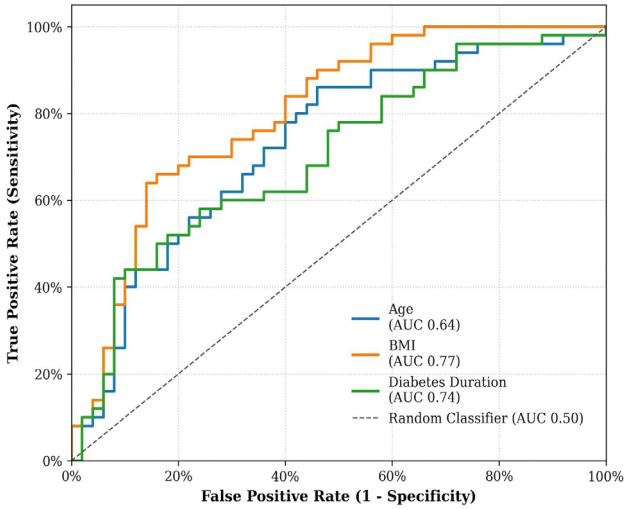

Figure 1. Receiver operating characteristic (ROC) curves for age, BMI, and diabetes duration as predictors of fasting glucose reduction at month 3 among proton pump inhibitor users with type 2 diabetes mellitus.

performance, with an AUC of approximately 0.77 (95% CI 0.64–0.88). A cutoff value of 29.40 kg/m² provided a sensitivity of 74.5% and a specificity of 68.4% for identifying individuals likely to experience fasting glucose reduction. Diabetes duration also showed predictive value, yielding an AUC of approximately 0.74 (95% CI 0.61–0.86). A cutoff value of 6.5 years was identified, indicating that patients with longer diabetes duration were less likely to demonstrate improvement in fasting glucose levels ($p < 0.001$). The ROC curves are presented in **Figure 1**.

DISCUSSION

The present study evaluated short-term changes in glycemic parameters following initiation of proton pump inhibitor therapy in patients with type 2 diabetes mellitus. The primary finding was a significant reduction in fasting glucose during the three-month follow-up period, whereas postmeal glucose and HbA1c levels did not demonstrate statistically significant changes. In addition, exploratory analyses suggested that certain patient characteristics, including older age, lower BMI, and shorter duration of diabetes, were associated with a higher likelihood of fasting glucose reduction during PPI therapy.

Interest in the potential metabolic effects of PPIs has increased in recent years, although the available clinical evidence remains heterogeneous (4,10–13). Some randomized controlled trials and observational studies have reported modest improvements in glycemic parameters among patients receiving PPI therapy, while other studies have found minimal or no measurable metabolic effects (10,11,14). In the present cohort, fasting glucose reduction was observed in more than two-thirds of participants, suggesting that PPI exposure may be associated with short-term changes in fasting glycemic regulation in a subset of patients. However, the absence of a significant change in HbA1c indicates that the overall impact on long-term glycemic control may be limited within the relatively short observation period.

Several biological mechanisms have been proposed to explain a potential interaction between PPIs and glucose metabolism. One commonly discussed pathway involves PPI-induced hypergastrinemia (15–17). Gastrin has been suggested to stimulate pancreatic β-cell activity and may contribute to enhanced insulin secretion under certain physiological conditions. Experimental studies have demonstrated that increased gastrin levels may promote β-cell regeneration and improve insulin production, potentially contributing to improved glucose regulation (15,16,18). In addition to gastrin-mediated mechanisms, PPI therapy may influence metabolic pathways through alterations in gastrointestinal pH and gut microbiota composition, both of which have been implicated in glucose homeostasis (9,19,20). However, because biomarkers such as insulin, C-peptide, proinsulin, gastrin levels, or indices of insulin resistance were not measured in the present study, these mechanistic explanations remain speculative.

An important observation of the present study is that the glycemic response to PPI therapy appeared to vary according to baseline patient characteristics. Individuals who demonstrated fasting glucose reduction had lower BMI and shorter duration of diabetes compared with those without reduction. These findings may be biologically plausible because longer diabetes duration is often associated with progressive decline in pancreatic β-cell function, while higher BMI is frequently linked to greater insulin resistance. Under such conditions, therapies that primarily influence insulin secretion might have greater metabolic impact in individuals with relatively preserved β-cell function. Nevertheless, these findings should be interpreted cautiously because the observational design does not allow causal inference.

Interestingly, older age was also associated with a greater probability of fasting glucose reduction in this cohort. The underlying mechanism remains unclear. One possible explanation is that age-related differences in pharmacokinetic or pharmacodynamic responses to PPIs may influence systemic metabolic effects of these drugs (21,22). Alternatively, age-related differences in metabolic characteristics or treatment patterns may contribute to this observation. Because these factors were not specifically investigated in the present study, further research is required to clarify the relationship

between age and metabolic responses to PPI therapy.

Despite the observed reduction in fasting glucose, neither postmeal glucose nor HbA1c levels changed significantly during the study period. This finding may be explained by the relatively short follow-up duration. HbA1c reflects average glycemic exposure over approximately two to three months, and modest short-term reductions in fasting glucose may not necessarily translate into detectable HbA1c changes during a limited observation period. In addition, variability in postprandial glucose measurements obtained during routine clinical practice may reduce the ability to detect subtle changes in postmeal glycemic responses.

The findings of the present study should also be interpreted in the context of previous research addressing the metabolic effects of PPIs. While some studies have suggested potential improvements in glycemic parameters among PPI users, others have reported neutral results. Differences in study design, patient populations, baseline glycemic status, duration of therapy, and concurrent antidiabetic treatments may contribute to the variability observed across studies (6,12,23). The present investigation provides real-world observational data suggesting that fasting glucose reduction may occur in a subset of patients with T2DM during short-term PPI therapy.

Several limitations of this study should be acknowledged. First, the retrospective observational design limits the ability to establish causal relationships between PPI therapy and changes in glycemic parameters. Second, the sample size was relatively modest and derived from a single clinical center, which may limit the generalizability of the findings. Third, mechanistic biomarkers such as insulin, C-peptide, proinsulin, gastrin levels, or indices of insulin resistance were not available, preventing direct evaluation of potential physiological pathways underlying the observed associations. Fourth, dietary adherence and lifestyle factors during the study period could not be fully standardized and may have influenced glycemic outcomes. Finally, although major changes in antidiabetic therapy were excluded, subtle variations in medication adherence or clinical management cannot be completely ruled out in a real-world observational setting.

Despite these limitations, the present study provides additional clinical insight into the potential metabolic effects of PPI therapy in patients with T2DM. The findings suggest that short-term PPI therapy may be associated with modest reductions in fasting glucose in a subset of patients, particularly those with lower BMI and shorter duration of diabetes. However, these observations should be considered hypothesis-generating rather than definitive evidence of a therapeutic metabolic effect.

Future prospective studies with larger sample sizes and longer follow-up durations are needed to better clarify the relationship between PPI therapy and glucose metabolism. Studies incorporating detailed metabolic biomarkers and standardized glycemic measurements may further help determine whether specific subgroups of patients with T2DM could experience clinically meaningful metabolic changes during PPI therapy.

CONCLUSION

In this retrospective cohort study of patients with type 2 diabetes mellitus, initiation of proton pump inhibitor therapy was associated with a modest reduction in fasting glucose during short-term follow-up, while postmeal glucose and HbA1c levels did not change significantly. The findings suggest that the glycemic response to PPI therapy may vary according to baseline clinical characteristics, particularly body mass index and duration of diabetes. Although these results provide real-world evidence that a subset of patients with T2DM may experience short-term improvements in fasting glucose following PPI therapy, the observational design and limited sample size preclude causal inference. Larger prospective studies incorporating detailed metabolic assessments are required to clarify the potential role of PPIs in glucose metabolism and to identify patient populations that may derive metabolic benefit.

DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the institutional ethics committee (Approval No: BSH 2022/19_a). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Consent to Participate: Because the study was retrospective and based on routinely collected clinical data, written informed consent was not required.

Availability of Data and Materials: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing Interests: The authors declare that they have no competing interests.

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Authors' Contributions: All authors contributed to the conception and design of the study. Data collection and analysis were performed by the authors. All authors contributed to the interpretation of the results and the preparation of the manuscript. All authors read and

approved the final manuscript.

Use of Artificial Intelligence: Artificial intelligence (AI) tools were used solely for language editing and improvement of the manuscript. No AI tools were used in the study design, data collection, data analysis, or interpretation of the results. The authors take full responsibility for the content of the manuscript.

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Original Article

Early Lactate Clearance as an Independent Predictor of In-Hospital Mortality: A Retrospective Cohort Study

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Abstract

Background: Serum lactate is widely used as a biomarker of tissue hypoperfusion in critically ill patients. While elevated baseline lactate levels are associated with adverse outcomes, dynamic changes in lactate concentration (particularly early lactate clearance) may provide superior prognostic information. Data regarding the predictive value of early lactate clearance in secondary-care medical intensive care units (ICUs) remains limited. We aim to evaluate the association between early (0–6-hour) lactate clearance and in-hospital mortality in adult patients admitted to a secondary-care medical ICU.

Methods: This retrospective cohort study included 114 adult patients admitted to a general medical ICU between 2018 and 2019. Patients with serum lactate measured within the first hour of ICU admission and repeated at approximately 6 hours were eligible. Lactate clearance was calculated as: [(Lactate0 – Lactate1) / Lactate0] × 100. The primary outcome was in-hospital mortality. Secondary outcomes included ICU length of stay, mechanical ventilation requirement, and acute kidney injury (AKI). Multivariable logistic regression analysis was performed to assess the independent association between lactate clearance and mortality, adjusting for baseline lactate, SOFA score, age, and vasopressor use.

Results: The cohort consisted of 59 males (51.8%) and 55 females (48.2%), with a median age of 65 years (interquartile range [IQR], 52–78 years; range, 18–94 years). Mean baseline lactate was 3.82 ± 2.14 mmol/L, and mean lactate clearance was 18.7 ± 21.3%. Patients with low lactate clearance (<10%) had significantly higher mortality compared with those achieving ≥20% clearance (64.3% vs. 15.9%, p<0.001). In multivariable analysis, lactate clearance remained independently associated with reduced mortality (OR 0.78 per 10% increase; 95% CI 0.67–0.91; p=0.002). The model demonstrated good discrimination (AUC 0.87). Lower lactate clearance was also associated with longer ICU stays, increased mechanical ventilation requirements, and a higher incidence of AKI, though the observational nature of this study precludes establishing causality.

Conclusions: Early lactate clearance is a strong and independent predictor of in-hospital mortality in a secondary-care medical ICU population. Dynamic lactate assessment within the first 6 hours may improve early risk stratification and guide resuscitation strategies in critically ill patients.

Keywords: Acidosis, Lactic, Intensive Care Units, Sepsis, Critical Illness, Prognosis

INTRODUCTION

Early identification of high-risk patients in the intensive care unit (ICU) remains a central challenge in critical care medicine (1). Despite advances in monitoring and organ support, in-hospital mortality among critically ill patients (particularly those with circulatory failure, sepsis, or acute respiratory compromise) continues to be substantial (2,3). Timely risk stratification is essential not only for prognostication but also for guiding the intensity and direction of resuscitative strategies during the initial hours of ICU admission (4).

Serum lactate has long been recognized as a surrogate marker of tissue hypoperfusion and impaired cellular oxygen utilization (5,6). Elevated lactate levels at presentation are consistently associated with increased mortality across diverse critical illness phenotypes, especially in patients with sepsis and septic shock (7,8). However, a single baseline lactate measurement provides only a static snapshot of metabolic stress and may not adequately reflect the dynamic response to resuscitation (9,10). Multiple factors, including tissue perfusion, adrenergic stimulation, hepatic metabolism,

and mitochondrial function, influence lactate production and clearance (5,11). Consequently, dynamic assessment (rather than isolated baseline measurement) may offer more clinically meaningful prognostic information.

Early lactate clearance, typically defined as the percentage reduction in serum lactate concentration within the first 6–12 hours after presentation, has emerged as a potential marker of effective resuscitation (12,13). Several studies have suggested that higher lactate clearance is associated with improved survival, while persistently elevated lactate levels or poor clearance correlate with ongoing tissue hypoxia and worse outcomes (6,12,13). From a pathophysiological standpoint, inadequate lactate clearance during the early phase of critical illness may reflect unresolved shock, insufficient hemodynamic optimization, or evolving organ dysfunction. Therefore, lactate kinetics may integrate both disease severity and treatment response into a single measurable parameter.

Nevertheless, most existing evidence has been derived from tertiary referral centers or highly selected populations, frequently limited to patients with septic shock (1,11). The generalizability of these findings to secondary-care medical ICUs where patient heterogeneity, resource availability, and case-mix may differ is less well established. In such settings, practical and accessible biomarkers that support early risk stratification are particularly valuable.

Accordingly, the present study aimed to evaluate the association between early (0–6-hour) lactate clearance and in-hospital mortality in adult patients admitted to a secondary-care general medical ICU. We further sought to determine whether lactate clearance provides independent prognostic information beyond baseline lactate levels and established markers of disease severity.

METHODS

Protocol and Search Strategy

This single-center retrospective cohort study was conducted in a tertiary-care general medical intensive care unit (ICU) and included adult patients admitted between January 1, 2018, and December 31, 2019. All consecutive patients aged 18 years or older who had a serum lactate measurement obtained within the first hour of ICU admission and a repeat lactate measurement approximately 6 hours later (±2 hours) were eligible for inclusion. Patients were excluded if their ICU length of stay was less than 24 hours, if the required time-stamped lactate measurements were missing or unreliable, or if they were admitted solely for short-term elective postoperative monitoring. Data were extracted retrospectively from the hospital information management system and ICU electronic records. The study protocol was approved by the institutional ethics committee, and the requirement for informed consent was waived due to the retrospective design and anonymized data handling.

The primary exposure variable was early lactate clearance, calculated using the formula: $[(Lactate_0 - Lactate_6) / Lactate_0] \times 100$, where $Lactate_0$ represents the initial serum lactate level measured within the first hour of ICU admission and $Lactate_6$ represents the repeat measurement at approximately 6 hours. Lactate clearance was analyzed both as a continuous variable (per 10% increase) and as a categorical variable. The categorical thresholds (≥20% for high clearance, 10–19% for intermediate clearance, and <10% for low clearance) were defined a priori based on established literatüre. Additionally, a data-derived optimal cut-off was determined using receiver operating characteristic (ROC) analysis to further explore the predictive performance in our specific cohort. The primary outcome was in-hospital mortality. Secondary outcomes included ICU mortality, ICU length of stay, requirement for invasive mechanical ventilation, duration of mechanical ventilation, and development of acute kidney injury (AKI), defined according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria when serum creatinine data were available.

Demographic variables, including age and sex, were recorded for all patients. Clinical data included primary admission diagnosis, presence of sepsis or septic shock, vasopressor requirement within the first 6 hours, and need for invasive mechanical ventilation. Laboratory variables included baseline lactate, serum creatinine, bilirubin, C-reactive protein, arterial blood gas parameters (pH, base excess), and other routinely measured biochemical markers. Severity of illness was assessed using Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. SOFA scores were available for 110 patients (96.5%) and APACHE II scores for 108 patients (94.7%). Missing data for these severity scores were handled using complete case analysis for the multivariable models.

STATISTICAL ANALYSIS

Continuous variables were assessed for normality using visual inspection and appropriate statistical tests and were reported as mean ± standard deviation or median with interquartile range as appropriate. Categorical variables were presented as counts and percentages. Comparisons between groups were performed using the Student's t-test or Mann–Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical

Table 1. Baseline Demographic and Clinical Characteristics (n=114)

Variable	Value
Age (years), IQR	65 [52-78]
Male sex	59 (51.8%)
Sepsis / Septic shock	41 (36.0%)
Mechanical ventilation	67 (58.8%)
Vasopressor use (≤6 h)	49 (43.0%)
$Lactate_0$ (mmol/L)	3.82 ± 2.14
$Lactate_6$ (mmol/L)	3.05 ± 2.01
Lactate clearance (%)	18.7 ± 21.3
SOFA score	7.1 ± 3.4
APACHE II	19.6 ± 6.3
ICU length of stay (days)	8.4 ± 5.6
In-hospital mortality	42 (36.8%)

IQR, interquartile range; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; $Lactate_0$, baseline lactate level; $Lactate_6$, lactate level at 6 hours.

variables. To evaluate the independent association between early lactate clearance and in-hospital mortality, multivariable logistic regression analysis was performed. Clinically relevant variables and those with $p<0.10$ in univariable analyses were entered into the multivariable model, including age, baseline lactate level, vasopressor use, and severity scores. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Model discrimination was assessed using the area under the receiver operating characteristic curve (AUC), and calibration was evaluated using the Hosmer–Lemeshow goodness-of-fit test. A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA).

Table 2. In-Hospital Mortality According to Lactate Clearance Categories

Lactate Clearance	n	Mortality n (%)
≥20% (High)	44	7 (15.9%)
10–19% (Intermediate)	28	8 (28.6%)
<10% (Low)	42	27 (64.3%)

RESULTS

Study Characteristics

A total of 114 adult patients met the inclusion criteria during the 2018–2019 study period. The cohort consisted of 59 males (51.8%) and 55 females (48.2%), with a median age of 65 years (interquartile range [IQR], 52–78 years; range, 18–94 years). The age distribution was non-normal based on the Shapiro-Wilk test. Overall in-hospital mortality was 36.8% (n=42), while ICU mortality was 33.3% (n=38). The mean ICU length of stay was 8.4 ± 5.6 days. Invasive mechanical ventilation was required in 67 patients (58.8%), and vasopressors were administered within the first 6 hours in 49 patients (43.0%). Baseline clinical and laboratory characteristics are presented in **Table 1**. The most common admission diagnosis was sepsis or septic shock (36.0%), followed by pneumonia without septic shock (16.7%) and acute exacerbation of chronic obstructive pulmonary disease (12.3%). The mean baseline lactate ($Lactate_0$) was 3.82 ± 2.14 mmol/L, and the mean 6-hour lactate ($Lactate_6$) was 3.05 ± 2.01 mmol/L. The mean early lactate clearance was 18.7 ± 21.3%. The mean SOFA score at admission was 7.1 ± 3.4, and the mean APACHE II score was 19.6 ± 6.3.

Patients were stratified according to predefined lactate clearance categories. Mortality differed significantly across clearance groups ($p<0.001$). Patients with low clearance (<10%) had markedly higher mortality compared to those achieving ≥20% clearance (64.3% vs. 15.9%) (**Table 2**).

Table 3 presents the comparative analysis between survivors and non-survivors. Non-survivors were significantly older and exhibited higher baseline lactate levels, lower lactate clearance, higher SOFA scores, and a greater need for vasopressor support and mechanical ventilation. The mean lactate clearance was 4.8 ± 16.9% in non-survivors, compared with 26.4 ± 19.8% in survivors ($p < 0.001$).

In multivariable logistic regression analysis adjusting for age, baseline lactate, SOFA score, and vasopressor

Table 3. Comparison of Survivors and Non-Survivors

Variable	Non-Survivors (n=42)	Survivors (n=72)	p-value
Age (years), IQR	71 [60-82]	61 [48-74]1	0.048
$Lactate_0$ (mmol/L)	4.91 ± 2.41	3.12 ± 1.67	<0.001
Lactate clearance (%)	4.8 ± 16.9	26.4 ± 19.8	<0.001
SOFA score	9.2 ± 3.6	5.8 ± 2.9	<0.001
Vasopressor use	30 (71%)	19 (26%)	<0.001
Mechanical ventilation	34 (81%)	33 (46%)	0.002
APACHE II score	22.4 ± 5.8	17.9 ± 6.1	<0.001
ICU length of stay (days)	10.5 ± 6.8	7.2 ± 4.3	0.003
Acute kidney injury	24 (57%)	15 (21%)	<0.001

Table 4. Multivariable Logistic Regression for In-Hospital Mortality

Variable	Adjusted OR	95% CI	p-value
Lactate clearance (per 10%)	0.78	0.67–0.91	0.002
Baseline lactate	1.31	1.09–1.57	0.004
SOFA score	1.24	1.11–1.39	<0.001
Age	1.02	1.00–1.04	0.061
Vasopressor use	2.18	1.01–4.69	0.047

use, early lactate clearance remained independently associated with reduced in-hospital mortality. Each 10% increase in lactate clearance was associated with a 22% relative reduction in the odds of death (adjusted OR 0.78; 95% CI 0.67–0.91; p=0.002) (**Table 4**). Baseline lactate and SOFA score were also independent predictors.

Model discrimination was strong, with an area under the ROC curve (AUC) of 0.87. The Hosmer–Lemeshow test indicated good calibration (p=0.62).

Receiver operating characteristic analysis demonstrated that lactate clearance alone had an AUC of 0.81 for predicting in-hospital mortality. The optimal cut-off value identified was 12%, yielding a sensitivity of 76% and specificity of 72%.

Secondary outcome analysis showed that patients with low lactate clearance had significantly longer ICU stays (10.2 ± 6.1 vs. 6.3 ± 4.2 days, p=0.001), longer duration of mechanical ventilation (7.8 ± 5.4 vs. 4.1 ± 3.6 days, p=0.003), and higher incidence of acute kidney injury (52% vs. 21%, p=0.004).

Overall, early lactate clearance demonstrated a strong and independent association with mortality and other clinically relevant outcomes in this secondary-care medical ICU population.

DISCUSSION

In this retrospective cohort of patients admitted to a secondary-care medical ICU, early lactate clearance demonstrated a significant and independent association with in-hospital mortality, supporting the role of dynamic metabolic monitoring in critical care prognostication. Our findings align with a substantial body of literature suggesting that serial lactate measurements and derived indices such as lactate clearance offer greater prognostic insight than single static measurements. Multiple studies have shown that dynamic changes in lactate are closely linked to outcomes in critical illness, with higher clearance generally associated with improved survival and lower clearance indicating persistent tissue hypoperfusion or inadequate resuscitation (6,10,13).

Several observational studies in sepsis populations have reinforced the value of lactate kinetics (9–11). For example, highlight that dynamic lactate indices, including lactate clearance over time, predict mortality more accurately than static lactate levels, emphasizing the importance of serial measurements in the first hours of ICU care (1,7,13,15). In a large retrospective study focused on septic shock patients, lactate clearance at 6 hours correlated with 28-day mortality, though lactate level itself often demonstrated equal or superior predictive performance (12,16). These findings partially mirror our results, where lactate clearance remained an independent predictor in multivariable analysis while also complementing severity scores such as SOFA.

Mechanistically, lactate clearance reflects the balance between production (often driven by tissue hypoxia, adrenergic stimulation, or impaired mitochondrial utilization) and elimination (primarily hepatic and renal metabolism) (13,17,18). Reviews on lactate biology underscore that elevated lactate may arise not solely from anaerobic metabolism but also from aerobic glycolysis in the context of systemic inflammation, which complicates the interpretation of a single measurement (7,9,10). Thus, the trajectory of lactate over time integrates both the severity of the underlying insult and the patient's physiological response to resuscitation, making it a more dynamic biomarker.

The Cut-off points for lactate clearance correspond with ranges identified in other cohorts. For instance, optimal 6-hour clearance thresholds such as <10–24% have been linked with worse outcomes in sepsis studies, although exact values and performance characteristics vary across populations and baseline disease burden (16,21). This variability highlights that while a universal threshold may be elusive, the trend of lactate decline matters clinically and should be interpreted alongside other markers of severity and hemodynamic status.

It is worth noting that some reports suggest that absolute lactate levels at subsequent time points may outperform clearance in certain contexts (6,9,13,22). For example, a study by Lee et al. found that 6-hour lactate values showed slightly better discrimination for 30-day mortality than clearance itself (23). This observation underscores the nuanced relationship between lactate dynamics and outcomes: a high 6-hour lactate may reflect unresolved shock despite an apparent relative decline, and both absolute levels and clearance should be considered in risk stratification models.

Although most evidence comes from sepsis or septic shock populations, our findings in a general medical ICU cohort suggest that the prognostic relevance of lactate clearance extends beyond isolated disease categories. A study conducted in a lower-middle-income country reported similar associations between lactate kinetics

and outcomes in broader critically ill populations, reinforcing the global applicability of dynamic lactate assessment (24). Furthermore, emerging research on early lactate trajectories and phenotype clustering in diverse critical care settings supports the concept that lactate changes over time may identify distinct risk profiles relevant to tailored interventions.

Several limitations of lactate-based prognostication warrant attention. Clearance may be influenced by non-perfusion factors such as hepatic dysfunction, adrenergic state, and metabolic alterations that are not directly addressed by standard resuscitation protocols. This complexity underscores the importance of integrating lactate kinetics with clinical context, organ failure scores, and other metabolic parameters, rather than relying on lactate clearance in isolation.

CONCLUSION

In this retrospective cohort of adult patients admitted to a secondary-care medical intensive care unit, early lactate clearance within the first 6 hours of admission was strongly and independently associated with in-hospital mortality. Patients with poor lactate clearance demonstrated significantly higher mortality rates, longer ICU stays, and greater need for organ support compared to those achieving adequate early metabolic improvement. Importantly, lactate clearance retained its prognostic value even after adjustment for baseline lactate levels, severity of illness scores, and vasopressor requirement, indicating that dynamic metabolic response provides incremental information beyond static measurements alone. These findings support the integration of early serial lactate assessment into routine ICU practice, particularly in resource-constrained or heterogeneous secondary-care settings where rapid and accessible risk stratification tools are essential. While lactate clearance should not replace comprehensive clinical evaluation, it may serve as a practical and physiologically meaningful adjunct to established scoring systems. Prospective multicenter studies are warranted to validate optimal clearance thresholds and to determine whether lactate-guided resuscitation strategies can translate into improved clinical outcomes.

DECLARATIONS

Ethics Committee Approval: This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Yenimahalle Training and Reserach Hospital Institutional Ethics Committee of the participating hospital (IRB No: E-2026-19). Given the retrospective design and the use of anonymized routinely collected clinical data, the ethics committee waived the requirement for written informed consent. All patient data were de-identified before analysis, and no directly identifiable personal information was accessed during the study process.

Consent to Participate: The manuscript does not contain any individual patient identifiers, images, or personal data that require separate consent for publication. The study has a retrospective desgin.

Availability of Data and Materials: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing Interests: The authors declare that they have no competing interests.

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Authors' Contributions: All authors contributed to the conception and design of the study. Data collection and analysis were performed by the authors. All authors contributed to the interpretation of the results and the preparation of the manuscript. All authors read and approved the final manuscript.

Use of Artificial Intelligence: Artificial intelligence (AI) tools were used solely for language editing and improvement of the manuscript. No AI tools were used in the study design, data collection, data analysis, or interpretation of the results. The authors take full responsibility for the content of the manuscript.

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Case Report

Familial Nephrocalcinosis Associated With Heterozygous SLC34A1 and TRPV5 Variants Presenting With Elevated 1,25-Dihydroxyvitamin D

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Abstract
Nephrocalcinosis is frequently associated with inherited disturbances of calcium-phosphate metabolism and renal tubular transport. Variants affecting renal phosphate reabsorption or distal tubular calcium handling may result in hypercalciuria, nephrolithiasis, and progressive renal calcification. The SLC34A1 gene encodes the sodium-phosphate cotransporter NaPi-IIa in the proximal tubule, and loss-of-function variants can cause renal phosphate wasting with inappropriate activation of 1α-hydroxylase, leading to elevated 1,25-dihydroxyvitamin D. The TRPV5 gene encodes a calcium-selective channel in the distal nephron and is essential for transcellular calcium reabsorption. We report a familial nephrocalcinosis phenotype in a 30-year-old woman and her 2-year-old daughter. The mother presented with bilateral flank pain, dysuria, palpitations, and fatigue. Laboratory evaluation demonstrated suppressed parathyroid hormone (PTH 9.6 pg/mL), serum calcium at the upper limit of normal (9.7 mg/dL), normal phosphate (3.1 mg/dL), chronically low 25-hydroxyvitamin D (24 ng/mL), and elevated 1,25-dihydroxyvitamin D, suggesting PTH-independent calcitriol excess. Nephrocalcinosis had previously been detected in the child. Targeted next-generation sequencing revealed a heterozygous splice-region variant in SLC34A1 (NM_003052.5:c.644+5G>C) and a heterozygous missense variant in TRPV5 (NM_019841.7:c.1849G>A; p.Gly617Arg) in both individuals. This case is presented as a hypothesis-generating report. Although both variants are classified as variants of uncertain significance, the shared genotype and characteristic biochemical profile suggest a potential disturbance of renal phosphate and calcium handling that may contribute to familial nephrocalcinosis and PTH-independent elevation of active vitamin D. However, definitive causal inferences cannot be established without additional evidence including segregation analysis in extended family members, functional studies, and comprehensive biochemical characterization.

Keywords: Nephrocalcinosis, Hypercalciuria, Vitamin D, Sodium-Phosphate Cotransporter Proteins (SLC34A1)

INTRODUCTION

Nephrocalcinosis refers to the deposition of calcium salts within the renal parenchyma and is associated with disorders affecting renal calcium and phosphate handling. In pediatric and familial cases, monogenic defects affecting tubular transport or vitamin D metabolism represent an important etiologic group (1-3). Genetic causes include abnormalities in renal phosphate transporters, epithelial calcium channels, and enzymes involved in vitamin D metabolism.

SLC34A1 encodes the sodium-dependent phosphate cotransporter NaPi-IIa located in the proximal renal tubule. This transporter mediates a major fraction of renal phosphate reabsorption (1). Loss-of-function variants in SLC34A1 reduce tubular phosphate reabsorption, resulting in renal phosphate wasting. Reduced phosphate availability stimulates renal 1α-hydroxylase activity and increases production of 1,25-dihydroxyvitamin D (1,2). Increased calcitriol enhances intestinal calcium absorption and contributes to hypercalciuria (2,3). This mechanism has been described in idiopathic infantile hypercalcemia type 2 and related phenotypes characterized by nephrolithiasis and nephrocalcinosis (2,3).

TRPV5 encodes a calcium-selective epithelial channel expressed in the distal convoluted tubule and connecting tubule. This channel mediates the apical calcium entry step of distal tubular transcellular calcium reabsorption and is therefore a biologically plausible determinant of urinary calcium excretion and calcium stone risk (4).

Variants in SLC34A1 are recognized causes of disorders

of renal phosphate handling. The clinical significance of combined variants involving SLC34A1 and TRPV5 in familial nephrocalcinosis has not been well defined. The present report describes a mother-child pair with nephrocalcinosis and a biochemical pattern characterized by suppressed parathyroid hormone and increased 1,25-dihydroxyvitamin D in whom heterozygous variants in SLC34A1 and TRPV5 were detected.

CASE

A 30-year-old woman was evaluated in a nephrology outpatient clinic because of bilateral flank pain, dysuria, palpitations, and fatigue. She had no previous diagnosis of nephrolithiasis, endocrine disease, chronic kidney disease, or granulomatous disease. She reported no use of vitamin D supplementation or calcium preparations.

Laboratory evaluation demonstrated suppressed parathyroid hormone (PTH 9.6 pg/mL). Serum calcium was 9.7 mg/dL, corresponding to the upper limit of the reference range. Serum phosphate was 3.1 mg/dL. The concentration of 25-hydroxyvitamin D was 24 ng/mL, whereas the active metabolite 1,25-dihydroxyvitamin D was elevated. This biochemical profile was compatible with PTH-independent calcitriol excess. Other routine biochemical parameters, including serum creatinine and electrolytes, were within reference ranges. The coexistence of suppressed PTH and increased 1,25-dihydroxyvitamin D prompted evaluation for disorders associated with extrarenal calcitriol production. Granulomatous diseases such as sarcoidosis were initially considered. During the clinical evaluation, it was noted that the patient's 2-year-old daughter had previously been diagnosed with nephrocalcinosis during pediatric assessment. The presence of nephrocalcinosis in a first-degree relative, as seen the case, suggested a possible hereditary disorder affecting mineral metabolism (**Figure 1A and Figure 1B**).

Genetic analysis was performed using next-generation sequencing with a targeted hypercalcemia gene panel that included 85 genes associated with calcium and phosphate metabolism. Genomic DNA extracted from peripheral blood samples of both the mother and the child was analyzed for variants in coding regions and exon-intron boundaries. The analysis detected a heterozygous splice-region variant in SLC34A1 (NM_003052.5:c.644+5G>C; rs1420848876) in both individuals. According to American College of Medical Genetics and Genomics criteria, this variant was classified as a variant of uncertain significance. In addition, both individuals carried a heterozygous missense variant in TRPV5 (NM_019841.7:c.1849G>A; p.Gly617Arg).

The presence of the same variants in both affected individuals suggested a possible association with the clinical phenotype. The biochemical profile was consistent with a disturbance of renal calcium-phosphate metabolism characterized by increased renal 1α-hydroxylase activity, elevated 1,25-dihydroxyvitamin D, suppressed parathyroid hormone levels, and episodic hypercalcemia.

Vitamin D supplementation was avoided because of the risk of aggravating hypercalciuria. The patient was advised to maintain adequate hydration and to avoid excessive dietary calcium intake. Neutral phosphate

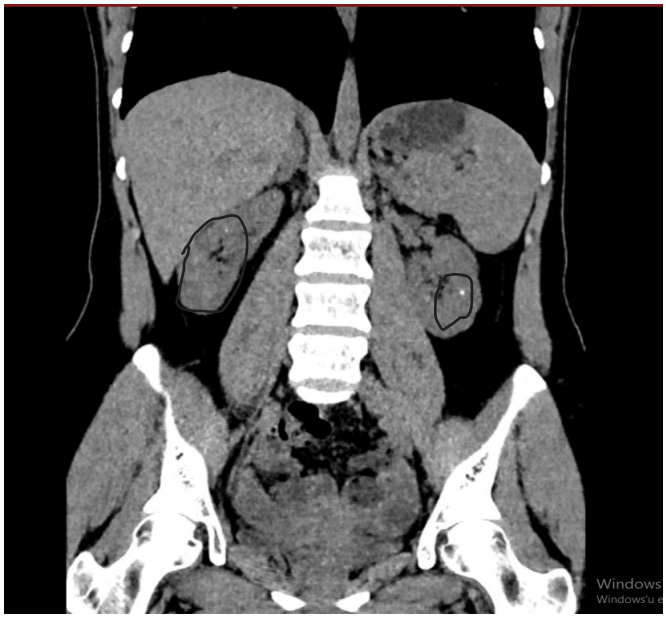

Figure 1A. Both kidneys demonstrate multiple corticomedullary calcifications.

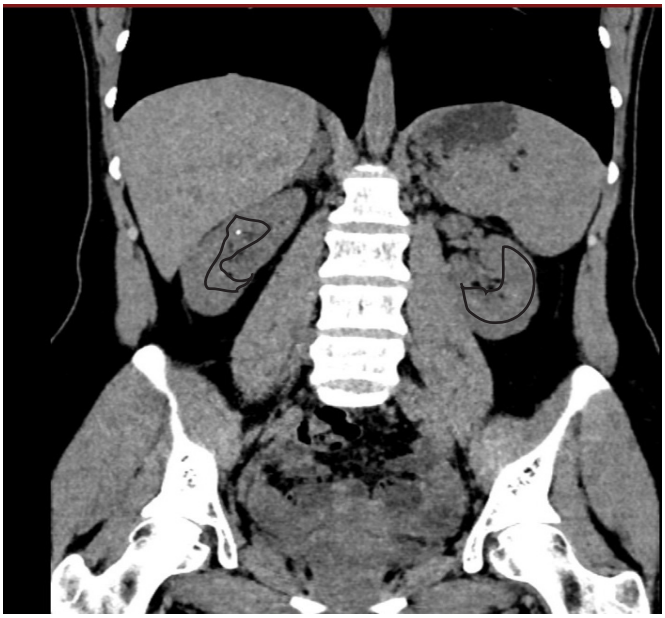

Figure 1B. Both kidneys demonstrate multiple corticomedullary calcifications.

therapy was initiated using a compounded phosphate solution consisting of $NaH_2PO_4 \cdot H_2O$ (18.2 g) and $Na_2HPO_4 \cdot 7H_2O$ (145 g) dissolved in 1000 mL of distilled water. The prescribed dose was 15 mL 3 times daily.

Follow-up evaluation was planned to monitor serum calcium, phosphate, parathyroid hormone, vitamin D metabolites, urinary calcium excretion, and renal imaging findings. Genetic counseling was recommended for the family. Additional segregation analysis involving other family members was considered to further evaluate the potential clinical significance of the identified variants.

While genetic analysis revealed identical variants in both the mother and child, segregation analysis involving additional family members was not performed. Furthermore, key biochemical parameters, including urinary calcium excretion and phosphate transport indices (TmP/GFR), were not assessed. These limitations restrict our ability to fully characterize renal calcium and phosphate handling and to establish a robust genotype–phenotype correlation. A detailed pedigree encompassing both affected and unaffected family members would be essential to determine the inheritance pattern and penetrance. These limitations are acknowledged and discussed in detail below.

DISCUSSION

Nephrocalcinosis is a radiologic and pathologic finding characterized by calcium salt deposition within the renal parenchyma and is commonly associated with disorders of calcium-phosphate metabolism, renal tubular transport defects, or dysregulation of vitamin D metabolism. In pediatric or familial presentations, monogenic causes should be actively considered (1-3).

Variants affecting renal phosphate transport represent an established cause of nephrocalcinosis and hypercalciuria. Among these, pathogenic alterations in SLC34A1, which encodes the sodium-dependent phosphate cotransporter NaPi-IIa located in the proximal tubule, have been associated with idiopathic infantile hypercalcemia type 2 (1-3). Reduced function of this transporter results in renal phosphate wasting and decreased tubular phosphate reabsorption capacity, which in turn stimulates renal 1α-hydroxylase activity and increases synthesis of 1,25-dihydroxyvitamin D (1,2). Elevated calcitriol increases intestinal calcium absorption and promotes hypercalciuria, which contributes to nephrocalcinosis and nephrolithiasis (2,3).

SLC34A1-related disease most commonly presents during infancy with hypercalcemia, suppressed parathyroid hormone, hypercalciuria, and nephrocalcinosis (2). However, phenotypic variability has been increasingly recognized, and milder or later-onset phenotypes, including cases with monoallelic variants or partial loss of transporter function, have been reported (3,5). These patients may present with isolated hypercalciuria, nephrolithiasis, or nephrocalcinosis without severe hypercalcemia (3,5).

The biochemical profile observed in the present case (suppressed PTH, elevated 1,25-dihydroxyvitamin D, and relatively normal serum calcium) supports a mechanism involving increased renal calcitriol synthesis rather than primary hyperparathyroidism or vitamin D intoxication. Similar biochemical patterns have been reported in mild idiopathic infantile hypercalcemia and related phosphate-wasting phenotypes (3).

Another established genetic cause of nephrocalcinosis associated with increased calcitriol levels is CYP24A1 deficiency. CYP24A1 encodes vitamin D 24-hydroxylase, the enzyme responsible for inactivation of active vitamin D metabolites. Loss-of-function mutations lead to accumulation of calcitriol and symptomatic hypercalcemia with nephrocalcinosis, and vitamin D exposure may accentuate the phenotype (6). However, CYP24A1 variants were not detected in the present patient using a targeted hypercalcemia gene panel, making this mechanism unlikely.

In the present report, both the mother and the child carried the same heterozygous splice-region variant in SLC34A1 (c.644+5G>C). According to ACMG criteria, this variant is currently classified as a variant of uncertain significance. Nevertheless, several observations support its possible clinical relevance. First, the variant segregated with the phenotype in two affected family members. Second, the biochemical profile was compatible with a disturbance in phosphate-dependent regulation of calcitriol synthesis. Third, the clinical presentation was consistent with previously reported mild SLC34A1-related phenotypes. Heterozygous SLC34A1-associated presentations with renal calcification and relatively subtle biochemical abnormalities have been documented in recent cohorts (3,5).

In addition to the SLC34A1 variant, both individuals also carried a heterozygous missense variant in TRPV5. TRPV5 encodes a calcium-selective epithelial channel located in the distal convoluted tubule and connecting tubule and represents the rate-limiting apical entry step in distal tubular calcium reabsorption (4). Recent human genetic evidence indicates that loss of TRPV5 function can cause renal calcium-wasting hypercalciuria, thereby supporting TRPV5 as a biologically plausible contributor to hypercalciuric kidney disease (7).

However, because the strongest current human evidence for TRPV5-related disease involves biallelic loss-of-

function, the contribution of a single heterozygous TRPV5 variant in the present family remains uncertain (7). The detected variant should therefore be interpreted cautiously, and a modifier effect rather than a definitively causal role is more appropriate at present.

The heterozygous TRPV5 missense variant (c.1849G>A; p.Gly617Arg) detected in this family warrants particularly cautious interpretation. The strongest and most robust human genetic evidence for TRPV5-related disease involves biallelic loss-of-function mutations, which cause autosomal recessive renal calcium-wasting hypercalciuria. In contrast, heterozygous TRPV5 variants have not been well-characterized in the literature, and their contribution to disease phenotypes remains uncertain. The present heterozygous missense variant may act as a phenotypic modifier that exacerbates the effects of the SLC34A1 variant, rather than serving as a primary causal determinant. Alternatively, this variant may be a benign polymorphism with no functional consequence. Functional studies such as patch-clamp electrophysiology to assess calcium permeability or cellular transport assays to measure TRPV5-mediated calcium uptake would be essential to determine whether this variant impairs channel function. Without such evidence, the role of the TRPV5 variant in the present case must be considered speculative.

Although the TRPV5 variant detected in our case was heterozygous, the coexistence of rare variants affecting proximal tubular phosphate transport (SLC34A1) and distal tubular calcium handling (TRPV5) offers a mechanistically coherent explanation for the observed phenotype. A proximal tubular defect may increase calcitriol production and intestinal calcium absorption, while a distal tubular defect may impair calcium reabsorption and increase urinary calcium loss. The combined effect of these mechanisms could enhance hypercalciuria and promote renal calcification. Similar additive effects of rare variants in more than one renal phosphate transport gene have been described in digenic disease (8).

The coexistence of heterozygous variants in both SLC34A1 and TRPV5 raises the possibility of digenic or oligogenic inheritance, wherein variants in two or more genes contribute additively or synergistically to the phenotype. A proximal tubular defect affecting phosphate reabsorption could increase calcitriol production and intestinal calcium absorption, while a concurrent distal tubular defect affecting calcium reabsorption could increase urinary calcium loss, thereby amplifying hypercalciuria and promoting renal calcification. This model is mechanistically plausible and is supported by precedent in the literature, as similar additive effects of rare variants in multiple renal phosphate transport genes have been described in digenic disease. However, this model remains speculative in the present case. To test this hypothesis, the following evidence would be necessary: (1) functional demonstration that both variants impair their respective protein functions; (2) segregation analysis showing that the phenotype correlates with the presence of both variants rather than either variant alone; (3) measurement of key biochemical parameters (urinary calcium, TmP/GFR) to confirm the proposed mechanism; and (4) evaluation of additional family members to establish inheritance pattern and penetrance. Without such evidence, the combined contribution of these variants cannot be confirmed.

Another feature supporting a genetic mechanism in the present case is the familial occurrence of nephrocalcinosis. The presence of the same variants in both the mother and the child suggests segregation of a genetic predisposition.

While the presence of identical variants in both the mother and child suggests familial segregation of a genetic predisposition, this observation alone is insufficient to establish causality or to determine the inheritance pattern. To properly evaluate familial segregation, a comprehensive pedigree including both affected and unaffected family members would be essential. Such a pedigree would allow assessment of: (1) whether the phenotype segregates with the genotype across multiple generations; (2) the inheritance pattern (autosomal dominant, autosomal recessive, X-linked, or complex); (3) penetrance and expressivity; and (4) whether other family members carry the variants but remain unaffected (incomplete penetrance) or whether unaffected family members lack the variants (supporting segregation). In the present case, segregation analysis involving extended family members was not performed, which represents a meaningful limitation. Therefore, while the familial occurrence of nephrocalcinosis in a mother-child pair is suggestive of a genetic mechanism, it does not constitute definitive proof of causality without broader segregation analysis.

From a clinical perspective, recognition of this mechanism has implications for management. In disorders characterized by calcitriol excess, vitamin D supplementation may aggravate hypercalcemia or hypercalciuria (6). In SLC34A1/SLC34A3-related disease, phosphate supplementation has been used, but recent cohort data suggest that biochemical improvement may be incomplete and that treatment should be individualized with careful longitudinal monitoring (5).

The present report has several limitations that should be considered. First, the detected variants are currently

classified as variants of uncertain significance, and functional studies were not performed to confirm pathogenicity. Second, segregation analysis involving additional family members was not available at the time of writing. Third, urinary calcium measurements and phosphate transport indices such as TmP/GFR (tubular maximum reabsorption of phosphate to glomerular filtration rate) were not reported in this case.

The central mechanistic hypothesis of this case (that the SLC34A1 variant causes renal phosphate wasting leading to increased calcitriol synthesis) is not directly supported by biochemical measurements. Specifically, urinary calcium excretion and phosphate transport indices such as TmP/GFR (tubular maximum reabsorption of phosphate to glomerular filtration rate) were not measured. These parameters are essential for characterizing the renal handling of calcium and phosphate and for confirming the proposed mechanism. Without urinary calcium measurements, we cannot quantify the degree of hypercalciuria or assess whether it is truly elevated relative to the degree of serum calcium elevation. Without TmP/GFR, we cannot directly assess the efficiency of tubular phosphate reabsorption or confirm that phosphate wasting is occurring. The absence of these measurements represents not merely a minor limitation but a meaningful restriction on the ability to establish a robust mechanistic link between the identified variants and the clinical phenotype. Future follow-up of this patient should include comprehensive biochemical characterization including 24-hour urinary calcium excretion, serum and urinary phosphate, and calculation of TmP/GFR to better define the renal handling defects

Despite these limitations, several findings support a mechanistic link between the identified variants and the clinical phenotype. These include familial occurrence, biochemical evidence of calcitriol excess with suppressed PTH, and genetic alterations affecting both proximal phosphate transport and distal calcium handling.

CONCLUSION

This report describes a familial nephrocalcinosis phenotype in a mother and her child associated with heterozygous variants in SLC34A1 and TRPV5 and accompanied by suppressed parathyroid hormone and elevated 1,25-dihydroxyvitamin D levels. The biochemical pattern suggests dysregulation of renal phosphate handling and calcium transport leading to increased calcitriol activity and hypercalciuria. Although the detected variants are currently classified as variants of uncertain significance, their segregation in affected family members and the compatible biochemical phenotype support a potential contribution to the observed disorder of mineral metabolism. This case highlights the importance of considering inherited tubular transport disorders in patients with unexplained nephrocalcinosis and atypical vitamin D metabolism. Recognition of such mechanisms has clinical implications for diagnostic evaluation, avoidance of inappropriate vitamin D supplementation, and implementation of genetic counseling and long-term renal monitoring.

DECLARATIONS

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Conflict of Interest: The authors declare that they have no conflicts of interest related to this work.

Data Availability: All data supporting the findings of this study are included in the article. Additional information may be available from the corresponding author upon reasonable request.

Author Contributions: O.J. and F.G. conceived the study, supervised the clinical evaluation, and contributed to manuscript preparation. E.Ç. contributed to the clinical interpretation, literature review, and drafting of the manuscript. All authors reviewed and approved the final version of the manuscript.

Ethics Statement: This study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent for publication of clinical information was obtained from the patient and the patient's legal guardian for the child. Institutional ethical approval was not required for this single case report according to local regulations.

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Case Report

Dysphagia and Refractory Gastroesophageal Reflux Due to Antral Web: A Case Report

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Abstract

Gastric antral web is a rare congenital or acquired condition that may remain undiagnosed until adulthood and typically presents with nonspecific upper gastrointestinal symptoms. In adults, it may mimic functional dyspepsia, gastroesophageal reflux disease, or cardiac conditions, leading to diagnostic delay. Impaired antral peristalsis and delayed gastric emptying increase intragastric pressure and contribute to dysphagia and refractory reflux symptoms. Endoscopic evaluation plays a key role in diagnosis, while management ranges from medical therapy to endoscopic interventions such as balloon dilation, needle-knife incision, and surgery in selected cases. In this case, the patient was treated with proton pump inhibitors and showed clinical improvement. This case highlights the need to consider antral web in the differential diagnosis of patients with dysphagia and refractory gastroesophageal reflux symptoms.

Keywords: Gastroesophageal Reflux, Endoscopy, Gastrointestinal, Hernia, Hiatal

INTRODUCTION

Gastric antral web is an uncommon anatomical abnormality characterized by a thin membranous structure partially obstructing the distal stomach. While it is typically diagnosed during infancy due to feeding intolerance or gastric outlet obstruction, adult cases are rare and frequently present with nonspecific upper gastrointestinal symptoms. These symptoms may resemble gastroesophageal reflux disease (GERD), functional dyspepsia, or even cardiac conditions, leading to diagnostic delay. Due to its subtle endoscopic appearance, the antral web may be overlooked unless carefully inspected. We present an adult case of dysphagia and refractory reflux symptoms in which an antral web was detected during upper gastrointestinal endoscopy.

CASE

A 39-year-old male presented with dyspepsia, epigastric pain, bloating, indigestion, dysphagia characterized by a sensation of food sticking during swallowing, chest tightness, and retrosternal burning sensation exacerbated by meals. The patient reported that these symptoms had been present intermittently but had significantly worsened over the last two weeks. He had no history of diabetes mellitus, hypertension, or coronary artery disease.

Given the chest-related symptoms, a comprehensive cardiac evaluation was performed. Electrocardiography demonstrated normal sinus rhythm at 102 beats per minute, and blood pressure was 120/70 mmHg. Transthoracic echocardiography revealed a left ventricular ejection fraction of 65%. Carotid Doppler ultrasonography and exercise stress testing were unremarkable. After exclusion of cardiac pathology, the patient was referred for gastroenterology department.

Physical examination revealed a soft, non-tender abdomen without guarding, rebound tenderness, or organomegaly. Laboratory investigations showed normal liver function tests and serum calcium levels. Abdominal ultrasonography demonstrated no pathological findings.

Upper gastrointestinal endoscopy revealed linear erosions exceeding 5 mm in the distal esophagus, consistent with Grade B esophagitis. The Z-line was located at 36 cm, and the diaphragmatic hiatus was crossed at 39 cm, indicating a hiatal hernia. The lower esophageal sphincter appeared loose. The fundus and corpus were hyperemic, and biopsies were obtained. The

antrum was hyperemic, and an antral web was identified in the prepyloric region (**Figure 1**). The pylorus, duodenal bulb, and second portion of the duodenum were normal. Histopathological evaluation of gastric biopsies revealed no evidence of Helicobacter pylori infection or mucosal atypia.

Based on these findings, the patient was diagnosed with Grade B esophagitis, hiatal hernia, lower esophageal sphincter laxity, superficial pangastritis, and antral web. Medical treatment with proton pump inhibitors (PPIs) was initiated. During follow-up, the patient reported significant clinical improvement, particularly a reduction in dysphagia and reflux symptoms.

DISCUSSION

Gastric antral web is a rare condition, most commonly congenital, and typically diagnosed in early childhood due to obstructive symptoms. However, in cases of partial obstruction, symptoms may remain mild and nonspecific, allowing the condition to remain undetected until adulthood (1).

Adult patients with antral web most commonly present with refractory gastroesophageal reflux, dyspepsia, epigastric pain, and dysphagia rather than classical gastric outlet obstruction. Morales et al. reported that most adult antral webs are non-obstructive and incidentally detected during endoscopic evaluation for persistent reflux symptoms (2). The clinical findings in our case are consistent with these observations(3).

The pathophysiology of symptoms in such patients is multifactorial. Impaired antral peristalsis and delayed gastric emptying increase intragastric pressure, thereby exacerbating reflux symptoms. However, in this patient, the presence of a hiatal hernia and lower esophageal sphincter laxity likely played a primary role in gastroesophageal reflux, while the antral web contributed as an additional aggravating factor. Similar findings have been reported in previous adult case reports, emphasizing the importance of thorough endoscopic examination of the prepyloric region (4).

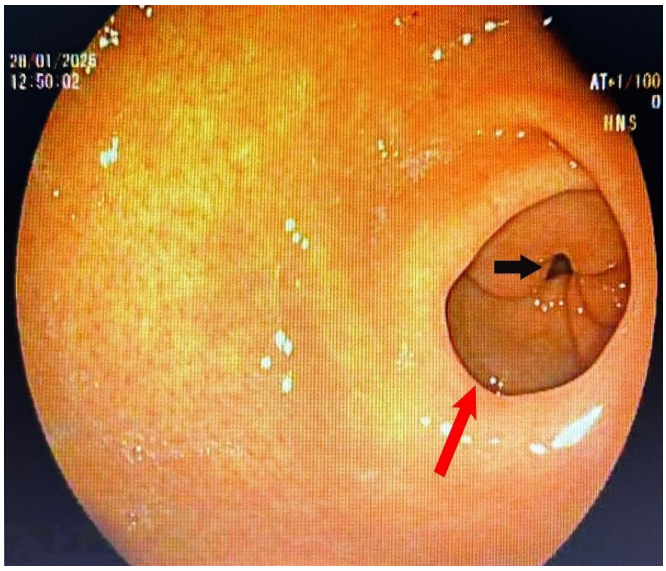

Figure 1. Upper gastrointestinal endoscopy showing a membranous antral web in the prepyloric antrum (red arrow) adjacent to the pylorus (black arrow).

Management of gastric antral web depends on the degree of obstruction and symptom severity. In mildly symptomatic or non-obstructive cases, medical therapy with proton pump inhibitors may be sufficient. In patients with persistent or severe symptoms, endoscopic treatment options such as balloon dilation or needle-knife incision have been reported to be safe and effective. Surgical intervention is rarely required and is generally reserved for refractory cases (5-7).

In the present case, the patient responded well to medical therapy alone, supporting the notion that not all antral webs require invasive treatment. Recognition of this condition and appropriate patient selection for intervention are essential for optimal management

CONCLUSION

Gastric antral web is a rare but clinically execarbating factor of dysphagia and refractory gastroesophageal reflux in adults. Its nonspecific presentation and coexistence with other reflux-promoting conditions may delay diagnosis. Careful endoscopic evaluation of the prepyloric region is essential in patients with persistent symptoms. Early recognition and appropriate management can result in significant symptom resolution and improved patient outcomes.

DECLARATIONS

Ethics Committee Approval: Ethics committee approval was not required for this case report in accordance with institutional policies. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Consent to Participate: Written informed consent was obtained from the patient for participation in this case report.

Availability of Data and Materials: All relevant data are included in the article. Additional data are available from the corresponding author upon reasonable request.

Competing Interests: The authors declare that they have no competing interests.

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Authors' Contributions: All authors contributed to the conception and design of the study. Data collection and analysis were performed by the authors. All authors contributed to the interpretation of the results and the preparation of the manuscript. All authors read and approved the final manuscript.

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Letter to Editor

Comment on "Gout: Evaluation and Management"

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Dear Editor,

In the review titled "Gout: Evaluation and Management" presented by Huzmeli, the topic is summarized in a comprehensive, clear, and fluent manner (1). As highlighted by Huzmeli, among urate-lowering therapy (ULT) agents used in the management of hyperuricemia and gout, allopurinol has long served as the first-line treatment. However, in recent years, strong evidence has demonstrated that febuxostat is more effective, particularly in achieving target serum uric acid levels. Furthermore, the renal elimination of allopurinol poses certain limitations in patients with chronic kidney disease (CKD), while the frequency of adverse effects remains a clinical concern. These factors collectively increase the relevance of febuxostat in patients with CKD.

Randomized controlled trials such as FACT and APEX have shown that febuxostat achieves target serum uric acid levels at a higher rate than allopurinol in patients both with normal renal function and with CKD (2,3). In CKD, the dose of allopurinol needs to be reduced due to its renal excretion. Therefore, the use of effective doses may be limited, which could compromise treatment efficacy. In contrast, febuxostat is primarily metabolized in the liver, allowing its administration at therapeutic doses without the need for dose adjustment in patients with impaired renal function. This characteristic is of particular importance in preventing inflammation, crystal deposition, and renal disease progression associated with uric acid accumulation.

On the other hand, the CARES trial raised concerns about a possible association between febuxostat and cardiovascular mortality (4). The fact that the patients in this trial already had a history of cardiovascular disease may have influenced the results. Indeed, the FAST trial did not confirm these findings and showed that febuxostat did not increase cardiovascular risk (5). Therefore, treatment decisions should be individualized based on cardiovascular risk assessment.

In conclusion, although allopurinol still retains its status as a first-line drug in guidelines, current literature indicates that febuxostat provides more effective serum uric acid control than allopurinol, particularly in patients with CKD. When used in appropriate patients with appropriate cardiovascular monitoring, febuxostat should be considered an important therapeutic option in nephrology practice.

DECLARATIONS

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