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Hipertansiyon Diyaliz ve Transplantasyon Vakfı

Journal of European Internal Medicine Professionals (JEIMP)

Dear Readers,

We are pleased to present the October 2025 issue of the Journal of European Internal Medicine Professionals (JEIMP), which offers a diverse selection of studies spanning nephrology, cardiology, neurology, genetics, and clinical pharmacology. This issue features original research exploring NT-proBNP as a predictor of chronic kidney disease progression, peritoneal transport and arterial stiffness in dialysis patients, clopidogrel resistance testing, and the clinical impact of prenatal exome sequencing in low-risk pregnancies. A comprehensive review on recent pharmacological advances in neurological diseases further enriches the content with insights into emerging therapies in Alzheimer's disease, Parkinson's disease, and multiple sclerosis.

In addition, two rare and instructive case reports highlight Dandy–Walker malformation presenting with hyponatremia and euglycemic ketoacidosis associated with prolonged malnutrition. The issue concludes with a thoughtful letter discussing the evolving role of finerenone in diabetes treatment.

We thank all authors, reviewers, and readers for their continued support of JEIMP and for contributing to its mission of fostering multidisciplinary scientific exchange.

The Editors
Mehmet Deniz Aylı, Mehmet Emin Demir, Özant Helvacı
The Journal of European Internal Medicine Professionals (JEIMP)

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Hipertansiyon Diyaliz ve Transplantasyon Vakfı

JEIMP
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Original Article

NT-proBNP as a Predictor of Chronic Kidney Disease Progression

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Abstract

Background: N-terminal pro–B-type natriuretic peptide (NT-proBNP) is a cardiac biomarker with emerging relevance in chronic kidney disease (CKD). While elevated NT-proBNP levels are commonly attributed to cardiac dysfunction, recent evidence suggests they may also reflect renal pathology and predict CKD progression. This single-center study aimed to evaluate the predictive role of NT-proBNP in CKD progression independent of structural heart disease.

Methods: We enrolled 24 patients with stage 3–5 CKD, all with normal cardiac function confirmed by echocardiography (normal ejection fraction and left ventricular indices). Baseline NT-proBNP and comprehensive metabolic parameters (renal function, lipids, glycemic markers, inflammatory markers, nutritional indicators) were measured and repeated at 24 weeks. Changes in NT-proBNP were correlated with changes in renal function (creatinine clearance) and other variables. Statistical significance was set at $p<0.05$. We also considered advanced analyses (ROC curve and multivariate regression) to further assess NT-proBNP's prognostic performance.

Results: NT-proBNP levels rose significantly over 24 weeks ($p<0.001$) as renal function declined (creatinine clearance decreased, $p<0.001$). There was an inverse correlation between the change in NT-proBNP and the change in creatinine clearance ($r = –0.437$, $p<0.05$), even after excluding patients with heart failure or other cardiac abnormalities. Baseline NT-proBNP correlated negatively with serum albumin and total protein ($r = –0.525$ and $–0.414$, respectively), and these correlations persisted at follow-up ($r = –0.577$ and $–0.483$; $p<0.01$). Subgroup analysis showed the NT-proBNP–renal function relationship was more pronounced in diabetic CKD patients ($r = –0.638$, $p<0.05$) than in non-diabetics. NT-proBNP changes were not significantly associated with body mass index, blood pressure, lipid profile, or HbA1c. High-sensitivity C-reactive protein (hs-CRP) levels increased during follow-up; however, the change in hs-CRP did not correlate with the change in NT-proBNP.

Conclusion: NT-proBNP levels increased in tandem with CKD progression, suggesting NT-proBNP is a promising marker for monitoring renal deterioration independent of heart function. Its strong association with nutritional status (albumin/protein levels) implies a multifactorial biomarker role. Larger prospective studies and advanced statistical analyses (e.g., threshold determination via ROC, multivariate models) are warranted to validate NT-proBNP's prognostic value and to integrate it into clinical decision-making for CKD..

Keywords: N-Terminal pro-B-Type Natriuretic Peptide, Kidney Diseases, Chronic, Disease Progression, Biomarkers, Nutrition; Inflammation, Prognosis

INTRODUCTION

Chronic kidney disease (CKD) is a progressive disorder characterized by a gradual decline in renal function and is a significant global health challenge (1). Its prevalence is rising worldwide, driven by severe complications and substantial healthcare costs (1,2). Major clinical consequences include progression to end-stage renal disease (ESRD), CKD-related complications, and a heightened risk of cardiovascular disease (CVD) regardless of etiology (3). Early detection and intervention are essential to slow disease progression and prevent adverse outcomes, underscoring the need for improved biomarkers and timely diagnostic strategies.

CKD patients face a markedly higher risk of cardiovascular death than the general population, and indeed many succumb to cardiac events before reaching ESRD (3,4). Reduced kidney function itself is a major risk factor for cardiovascular complications (3-5). Left ventricular hypertrophy (LVH), often stemming from long-standing hypertension and anemia, is common in advanced CKD and strongly predicts mortality. Even subtle cardiac alterations can emerge early in CKD, highlighting the intertwined nature of cardiac and renal health (3-5).

Natriuretic peptides play a key role in cardiovascular assessment and fluid homeostasis (6,7). B-type natriuretic peptide (BNP) and its N-terminal fragment NT-proBNP are well-established biomarkers for diagnosing and managing heart failure, and guidelines recommend their measurement in that context (7). Unlike BNP, which is cleared by enzymes and has a short half-life, NT-proBNP is primarily eliminated by the kidneys via glomerular filtration (8). Consequently, NT-proBNP levels are more closely related to glomerular filtration rate (GFR) than BNP levels (8,9). As GFR declines, NT-proBNP tends to accumulate due to reduced renal clearance, even in the absence of overt heart failure. This dependency on renal excretion means CKD can elevate NT-proBNP levels per se, which historically led clinicians to discount elevated NT-proBNP in CKD patients without heart failure. However, several studies show that in patients without heart failure, higher NT-proBNP is still strongly prognostic for adverse outcomes, including cardiovascular events and kidney function decline (10,11). Elevated NT-proBNP may reflect chronic neurohormonal activation and venous congestion that contribute to CKD progression, rather than just reduced clearance (12).

Beyond cardiovascular implications, natriuretic peptides have been linked to renal outcomes. Early observations in the 2000s indicated that BNP/NT-proBNP levels rise as CKD advances and might predict progression to ESRD (13,14). Spanaus et al. reported that higher baseline BNP predicted faster CKD progression in non-diabetic CKD patients (13). Carr et al. similarly demonstrated prognostic value for N-terminal BNP in predialysis CKD: in a cohort of 83 CKD stage 4 patients without heart failure, elevated NT-proBNP was associated with a markedly increased risk of mortality or cardiovascular events, and higher baseline levels trended with progression to ESRD (15).

Although kidney dysfunction clearly influences NT-proBNP concentrations, the relationship between NT-proBNP and CKD progression has not been fully elucidated. Many prior investigations did not rigorously exclude cardiac disease, leaving open the question of whether elevated NT-proBNP was simply a marker of subclinical heart failure in CKD patients. To address this gap, the present study focused on CKD patients with normal cardiac structure and function, verified by echocardiography, thereby isolating the renal contributions to NT-proBNP levels. By excluding confounding cardiac abnormalities, we aimed to objectively evaluate NT-proBNP's role in renal function decline. The primary aim was to determine whether NT-proBNP correlates with CKD progression toward ESRD, independent of cardiac dysfunction.

METHODS

Study Design and Participants

This single-center prospective study was conducted at the Nephrology Clinic of Ankara Education and Research Hospital. A total of 24 patients with CKD stage 3–5 (pre-dialysis) were enrolled. All participants had a history of hypertension, and 13 had diabetes mellitus. Key inclusion criteria were age ≥18 years, CKD stage 3–5 (estimated GFR <60 mL/min/1.73 m²) not yet on renal replacement therapy, and the absence of symptomatic heart disease. To ensure cardiac health, each patient underwent a comprehensive echocardiographic evaluation; only those with normal left ventricular ejection fraction (LVEF), normal left ventricular mass index (LVMI), and normal right ventricular size/function were included. This stringent inclusion criterion was intended to eliminate confounding by overt structural heart disease.

Exclusion Criteria

We excluded patients with any condition that could independently influence NT-proBNP or renal outcomes aside from CKD. Specifically, exclusion criteria were: (1) acute or chronic infections, (2) chronic liver disease or active malignancy, (3) uncontrolled volume overload (edema unresponsive to diuretics), (4) any history of solid organ transplantation or current immunosuppressive therapy, (5) known heart failure or prior diagnosis of cardiomyopathy, (6) known coronary artery disease or prior myocardial infarction, and (7) pregnancy. Patients under evaluation for any of these conditions were also excluded. All participants provided written informed consent. The study protocol was approved by the local Ethics Committee (Ankara Education and Research Hospital, Approval No. 0291-2153) prior to commencement.

Data Collection and Measurements

Baseline demographics (age, sex) and clinical data (comorbidities such as diabetes, blood pressure, medications) were recorded. A physical examination was performed including measurements of height and weight to calculate body mass index (BMI = kg/m²). Blood pressure was measured with a standard sphygmomanometer after a 15-minute rest. Fasting venous blood samples were obtained in the morning (after an overnight 12-hour fast) at baseline and at the 24-week follow-up. The following laboratory

parameters were measured at both time points using standard automated techniques: serum NT-proBNP, urea, electrolytes, fasting glucose, glycated hemoglobin (HbA1c), lipid profile [total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C)], albumin, total protein, transferrin, ferritin, high-sensitivity C-reactive protein (hs-CRP), hemoglobin, and hematocrit. Proteinuria was assessed by spot urine protein or 24-hour protein excretion, as available. Renal function was assessed using the Cockcroft–Gault formula to estimate creatinine clearance (mL/min). The term 'creatinine clearance' is used consistently throughout the study to reflect this calculation method. All laboratory analyses were performed in the hospital's central lab using standardized methods. NT-proBNP levels were measured in pg/mL using an electrochemiluminescence immunoassay (Elecsys, Roche Diagnostics). For interpretability, NT-proBNP values were analyzed on a continuous scale and also categorically in some analyses (e.g., by median or clinically relevant cut-offs).

Follow-up

Participants were followed for 24 weeks (~6 months). At the end of follow-up, clinical data and the same laboratory measurements were repeated. The primary outcome was the change in renal function over 24 weeks, assessed by change in creatinine clearance (or creatinine clearence). We also noted whether any patient progressed to a more advanced CKD stage or required dialysis during this short follow-up. Secondary outcomes included changes in NT-proBNP and their associations with changes in other parameters (e.g., fluid/nutritional markers and metabolic measures).

STATISTICAL ANALYSIS

Continuous variables are presented as mean ± standard deviation or median [interquartile range] as appropriate to their distribution. Categorical variables are summarized as counts and percentages. We used the Shapiro-Wilk test to assess normality of continuous data. Changes in biochemical parameters from baseline to 24 weeks were evaluated using paired t-tests for normally distributed variables or Wilcoxon signed-rank tests for non-normal data. Correlations between changes in NT-proBNP and changes in other variables (e.g., creatinine clearance, albumin, etc.) were analyzed using Spearman's rank correlation coefficients (since NT-proBNP and some clinical variables showed skewed distributions). For baseline cross-sectional correlations, Pearson or Spearman correlation was applied as appropriate. A two-tailed p-value <0.05 was considered statistically significant for all analyses.

Given the limited sample size, formal multivariable modeling was not initially performed in the original analysis. However, to enhance analytical robustness, we developed exploratory strategies for advanced statistical analysis. We planned a receiver operating characteristic (ROC) curve analysis to assess the discriminatory ability of baseline NT-proBNP for predicting renal function decline. Specifically, we considered defining "CKD progression" as a ≥20% decline in creatinine clearance at 24 weeks and then evaluating the area under the ROC curve (AUC) for baseline NT-proBNP to predict this outcome. Additionally, we contemplated a multivariate regression model (logistic or linear regression, depending on outcome distribution) to adjust for potential confounders (age, sex, baseline GFR, diabetes status, blood pressure, etc.) and test whether NT-proBNP is an independent predictor of kidney function decline. All statistical analyses were performed using IBM SPSS Statistics (Version 22.0, Armonk, NY).

RESULTS

The study cohort included 24 patients with chronic kidney disease (CKD) stages 3–5 (15 women [62.5%] and 9 men [37.5%]). Thirteen patients (54%) had diabetes

Table 1. Demographic and clinical characteristics of patients

Parameter	Total (n=24)	Patients with DM (n=13)	Patients without DM (n=11)
Gender, Female/male	15 (62.5%) / 9 (37.5%)	7 (46.7%) / 6 (66.7%)	8 (53.3%) / 3 (33.3%)
Age (years)	50.6 ± 14.3	–	–
BMI (kg/m²)	26.5 ± 4	–	–
Systolic BP (mmHg)	129.7 ± 18	–	–
Diastolic BP (mmHg)	81.8 ± 11.3	–	–
Diabetes Mellitus	13 (54.2%)	–	–
Stage 3 CKD	6 (25%)	–	–
Stage 4 CKD	16 (66.7%)	–	–
Stage 5 CKD	2 (8.3%)	–	–
Ejection Fraction (%)	62 ± 5.1	–	–
LVMI	80.8 ± 23.2	–	–

BMI: Body Mass Index; BP: Blood Pressure; CKD: Chronic Kidney Disease; LVMI: Left Ventricular Mass Index; DM: Diabetes Mellitus.

Table 2. Biochemical parameters of all patients at baseline and 24 weeks

Parameter	Baseline	24th Week	p value
Creatinine (mg/dL)	3.1 ± 0.9	3.7 ± 1.0	0.001
Creatinine clearance (mL/min)	24.9 ± 9.06	21.6 ± 7.3	0.001
NT-proBNP (pg/mL)	75.5 ± 66.4	131.8 ± 121.3	0.001
Glucose (mg/dL)	116.5 ± 40.3	115.5 ±76.8	>0.05
Urea (mg/dL)	102.7 ± 31	120.4 ± 25.3	<0.01
Uric acid (mg/dL)	6.5 ± 1.6	5.7 ± 1.0	>0.05
Total protein (g/dL)	7 ± 0.9	7 ± 0.7	>0.05
Albumin (g/dL)	3.8 ± 0.5	3.9 ± 0.5	>0.05
Total cholesterol (mg/dL)	198.7 ± 54.3	183.6 ± 55	>0.05
Triglyceride (mg/dL)	154.8 ± 75.6	157.7 ± 101	>0.05
HDL-cholesterol (mg/dL)	46.8 ± 14.0	49.5 ± 16.3	>0.05
LDL- cholesterol (mg/dL)	116.8 ± 49.1	105.6 ± 44.3	>0.05
Magnesium (mmol/L)	0.8 ± 0.1	0.8 ± 0.1	>0.05
Transferrin (g/L)	1.9 ± 0.3	2.1 ± 0.3	>0.05
Hemoglobin (g/dL)	11.4 ±1.7	11.0 ± 1.2	<0.05
Hematocrit (%)	32.4 ± 4.8	32.1 ± 3.6	>0.05
Ferritin (ng/mL)	155.2 ± 134.4	128.5 ± 112.2	<0.05
HbA1c (%)	7.0 ± 2.0	6.6 ± 2.4	<0.05
24-hour urine protein (g/day)	3.3 ± 2.8	2.6 ± 3.3	<0.05
hs-CRP (mg/L)	1.8 ± 2.3	2.4 ± 2.1	<0.05

HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; hs-CRP: High-sensitivity C-reactive protein.

mellitus (DM), and all had a history of hypertension. The gender and diabetes distribution are presented in **Table 1**, showing that 7 of 13 patients with DM (46.7%) were female, while 6 (66.7%) were male; among non-diabetics, 8 (53.3%) were female and 3 (33.3%) were male.

At baseline, the mean age was 50.6 ± 14.3 years, BMI was 26.5 ± 4 kg/m², and mean systolic and diastolic blood pressures were 129.7 ± 18 mmHg and 81.8 ± 11.3 mmHg, respectively. Most patients were in stage 4 CKD (66.7%), with smaller proportions in stage 3 (25%) and stage 5 (8.3%). Echocardiographic evaluation confirmed normal cardiac function in all participants, with a mean left ventricular ejection fraction (LVEF) of 62 ± 5.1% and left ventricular mass index (LVMI) of 80.8 ± 23.2 g/m². Detailed demographic and clinical data are summarized in **Table 1.**

Changes in Renal Function and NT-proBNP

Over the 24-week follow-up period, there was a statistically significant deterioration in renal function accompanied by an increase in NT-proBNP levels. Serum creatinine rose from 3.1 ± 0.9 mg/dL to 3.7 ± 1.0 mg/dL ($p < 0.001$), while creatinine clearance declined from 24.9 ± 9.1 mL/min to 21.6 ± 7.3 mL/min ($p < 0.001$). In parallel, NT-proBNP increased from 75.5 ± 66.4 ng/mL at baseline to 131.8 ± 121.3 ng/mL ($p < 0.001$), as shown in **Table 2.**

No patients developed clinical or echocardiographic evidence of heart failure during follow-up, confirming that the observed NT-proBNP elevation was not attributable to new cardiac dysfunction. Other parameters showing statistically significant changes over 24 weeks included urea ($p < 0.01$), hemoglobin ($p < 0.05$), ferritin ($p < 0.05$), HbA1c ($p < 0.05$), 24-hour urine protein ($p < 0.05$), and hs-CRP ($p < 0.05$), indicating mild progression of uremic and inflammatory status. Lipid profile and serum albumin remained stable, with no significant differences between baseline and week 24 values (**Table 2**).

Subgroup Analysis by Diabetic Status

In subgroup analyses, patients with diabetes exhibited a more pronounced renal decline and NT-proBNP increase. In the diabetic group, creatinine clearance dropped from 30.3 ± 8.0 mL/min to 25.3 ± 6.8 mL/min ($p < 0.005$), whereas the non-diabetic group showed a smaller, non-significant change (18.6 ± 5.3 → 17.2 ± 5.4 mL/min, $p > 0.05$). Similarly, NT-proBNP rose significantly among diabetics (76.4 ± 70.8 → 127.9 ± 90.1 ng/mL, $p < 0.01$), while the increase among non-diabetics did not reach significance (74.5 ± 64.1 → 136.5 ± 155.2 ng/mL, $p = 0.06$) (**Table 3 and 4**).

Other biochemical variables (glucose, lipid profile, albumin, and magnesium) remained statistically unchanged in both subgroups ($p > 0.05$), suggesting that NT-proBNP variation was predominantly related to renal function changes rather than metabolic differences between diabetic and non-diabetic CKD.

Correlation Analyses

Correlation analyses further clarified the relationship between NT-proBNP and renal parameters. As shown in **Table 6**, the change in NT-proBNP (ΔNT-proBNP) was positively correlated with ΔCreatinine ($r = 0.585$, $p < 0.005$) and negatively correlated with ΔCreatinine

Table 3. Biochemical parameters of patients with diabetes mellitus at baseline and 24 weeks

Parameter	Baseline	24th Week	p value
Creatinine (mg/dL)	2.7 ± 0.7	3.3 ± 1.0	<0.005
Creatinine clearance (mL/min)	30.3 ± 8.0	25.3 ± 6.8	<0.005
NT-proBNP (pg/mL)	76.4 ± 70.8	127.9 ± 90.1	<0.01
Glucose (mg/dL)	136.6 ± 45.0	138.5 ± 99.9	>0.05
Urea (mg/dL)	96.3 ± 29.2	115.1 ± 28.8	<0.05
Uric acid (mg/dL)	6.6 ± 1.46	6.0 ± 1.0	>0.05
Total protein (g/dL)	7.1 ± 0.8	7.1 ± 0.5	>0.05
Albumin (g/dL)	3.7 ±0.5	3.9 ± 0.3	>0.05
Total cholesterol (mg/dL)	202.3 ± 60.3	180.0 ± 47.1	>0.05
Triglyceride (mg/dL)	171.4 ± 81.6	183.5 ± 122.9	>0.05
HDL-cholesterol (mg/dL)	46.6 ± 16.5	47.9 ± 19.8	>0.05
LDL cholesterol (mg/dL)	113.8 ± 57.3	100.1 ± 34.8	>0.05
Magnesium (mmol/L)	0.8 ± 0.08	0.8 ± 0.1	>0.05
Transferrin (g/L)	2.0 ± 0.2	2.2 ± 0.45	>0.05
Hemoglobin (g/dL)	11.4 ± 1.6	11.0 ± 1.4	>0.05
Hematocrit (%)	32.6 ± 4.7	32.0 ± 4.3	>0.05
Ferritin (ng/mL)	138.7 ± 112.8	128.5 ± 122.7	>0.05
HbA1c (%)	8.3 ± 1.8	7.6 ± 2.7	>0.05
24-hour urine protein (g/day)	3.4 ± 2.3	3.1 ± 4	>0.05
hs-CRP (mg/L)	1.8 ± 2.3	2.7 ± 2.5	>0.05

HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; hs-CRP: High-sensitivity C-reactive protein.

clearance ($r = –0.437$, $p < 0.05$), confirming that greater renal decline was accompanied by larger NT-proBNP elevations.

No significant associations were found between ΔNT-proBNP and changes in glucose, lipid fractions, HbA1c, hs-CRP, proteinuria, blood pressure, or BMI (all $p > 0.05$). These findings indicate that the biomarker's variation was largely independent of metabolic or inflammatory parameters (**Table 5**).

When patients were analyzed by diabetes status, these correlations were markedly stronger in the diabetic subgroup. In diabetics, ΔNT-proBNP correlated positively with ΔCreatinine ($r = 0.664$, $p < 0.05$) and negatively with ΔCreatinine clearance ($r = –0.638$, $p < 0.05$), whereas non-diabetic patients exhibited weaker and non-significant associations ($r = 0.319$ and $r = –0.165$, respectively; $p > 0.05$) (**Table 6**). Neither Δhs-CRP nor Δ24-hour urine protein showed significant correlation with NT-proBNP in either subgroup, though a mild positive trend between Δhs-CRP and ΔNT-proBNP was noted in non-diabetics ($r = 0.506$, $p > 0.05$).

Table 4. Biochemical parameters of patients without diabetes mellitus at baseline and 24 weeks

Parameter	Baseline	24th Week	p value
Creatinine (mg/dL)	3.7 ± 0.97	4.3 ± 1	<0.005
Creatinine clearance (mL/min)	18.6 ± 5.3	17.2 ± 5.4	>0.05
NT-proBNP (pg/mL)	74.5 ± 64.1	136.5 ± 155.2	=0.06
Glucose (mg/dL)	92.6 ± 12.4	88.2 ± 8.9	>0.05
Urea (mg/dL)	110.4 ± 32.6	126.7 ± 20.0	<0.05
Uric acid (mg/dL)	6.3 ± 1.9	5.4 ± 1.1	>0.05
Total protein (g/dL)	7.0 ± 1.0	7.0 ± 0.8	>0.05
Albumin (g/dL)	3.8 ± 0.6	3.8 ± 0.6	>0.05
Total cholesterol (mg/dL)	194.4 ± 48.8	187.9 ± 65.2	>0.05
Triglyceride (mg/dL)	135.2 ± 66.1	127.1 ± 59.0	>0.05
HDL-cholesterol (mg/dL)	47.0 ± 11.1	51.3 ± 11.6	<0.05
LDL-cholesterol (mg/dL)	120.3 ± 39.6	111.0 ± 53.3	>0.05
Magnesium (mmol/L)	0.8 ± 0.1	0.9 ± 0.1	<0.05
Transferrin (g/L)	1.7 ± 0.4	2.0 ± 0	>0.05
Hemoglobin (g/dL)	11.3 ± 2.06	10.9 ± 0.9	>0.05
Hematocrit (%)	32.1 ± 5.1	32.3 ± 2.5	>0.05
Ferritin (ng/mL)	174.7 ± 159.7	128.6 ± 104.2	>0.05
HbA1c (%)	5.4 ± 0.3	5.2 ± 0.3	<0.05
24-hour urine protein (g/day)	3.1 ± 3.4	2.0 ± 2.3	>0.05
hs-CRP (mg/L)	1.7 ± 2.5	2.0 ± 1.5	>0.05

Table 5. Correlation between changes in NT-proBNP and other parameters (general population)

Parameter	p-value	Correlation coefficient (r)
Δ Creatinine	< 0.005	0.585
Δ Creatinine clearance	< 0.05	-0.437
Δ Glucose	> 0.05	0.251
Δ Total protein	> 0.05	-0.110
Δ Albumin	> 0.05	0.236
Δ Total cholesterol	> 0.05	-0.137
Δ Triglyceride	> 0.05	0.080
Δ LDL-cholesterol	> 0.05	-0.099
Δ HbA1c	> 0.05	0.250
Δ 24-hour urine protein	> 0.05	-0.127
Δ hs-CRP	> 0.05	0.003
Δ Systolic BP	> 0.05	0.103
Δ Diastolic BP	> 0.05	-0.051
Δ BMI	> 0.05	-0.078

Table 6. Correlation between changes in NT-proBNP and other parameters in diabetic and non-diabetic patients

Parameter	Diabetic (p-value and r)	Non-diabetic (p-value and r)
Δ Creatinine	**< 0.05 / 0.664**	**> 0.05 / 0.319**
Δ Creatinine clearance	**< 0.05 / -0.638**	**> 0.05 / -0.165**
Δ 24-hour urine protein	**> 0.05**	**> 0.05**
Δ hs-CRP	**> 0.05**	**> 0.05**

Table 7. Correlation Between NT-proBNP and Nutritional Parameters at Baseline and 24 Weeks

Parameter	Baseline r and p value	24th Week r and p value
Albumin (g/dL)	–0.525 / < 0.001	–0.577 / <0.005
Total Protein (g/dL)	–0.414 / <0.05	–0.483 / <0.005
Transferrin (g/L)	–0.298 / >0.05	–0.214 / >0.05

As shown in **Table 7**, NT-proBNP demonstrated significant inverse correlations with nutritional parameters, including serum albumin ($r = –0.53$, $p < 0.01$) and total protein ($r = –0.41$, $p < 0.05$) at baseline, and these relationships strengthened at 24 weeks (albumin $r = –0.58$, $p < 0.005$; total protein $r = –0.48$, $p < 0.05$).

DISCUSSION

In this study of CKD patients without confounding cardiac dysfunction, we found that NT-proBNP increased significantly as renal function declined, supporting its role as a marker of CKD progression. BNP and NT-proBNP are classically secreted by the cardiac ventricles in response to wall stress, promoting natriuresis, diuresis, and vasodilation. They are established cardiac biomarkers, and elevated levels have been linked to mortality even in individuals without overt heart failure. Our findings expand on this concept by demonstrating NT-proBNP's prognostic signal in the renal arena. The observed inverse relationship between NT-proBNP and creatinine clearance is consistent with earlier studies and highlights that NT-proBNP can reflect kidney dysfunction severity. Importantly, because we excluded patients with any significant cardiac impairment, we believe that the NT-proBNP elevations largely reflect non-cardiac factors.

Previous work by Spanaus et al. and Carr et al. suggested that higher natriuretic peptide levels predict faster CKD progression in predialysis patients (13,15). Our results align with these and more recent observations. Ascher et al. analyzed longitudinal data from the SPRINT trial and reported that participants with ≥25% increases in NT-proBNP over one year had significantly faster subsequent creatinine clearence decline and higher odds of a ≥30% drop in GFR, compared to those with stable NT-proBNP; notably, this was true even after accounting for baseline kidney function, and was most pronounced in those with CKD at baseline (16). Likewise, Sasaki et al. showed in a 10-year community cohort that individuals in the highest NT-proBNP quartile (≥300 pg/mL) had a nearly doubled risk of developing CKD and a more rapid annual GFR loss relative to those in the lowest quartile (14). In that study, adding NT-proBNP to traditional risk factor models improved prediction of incident CKD, underscoring NT-proBNP's independent value. These large-scale data corroborate our single-center findings and strengthen the evidence that NT-proBNP is not merely a bystander in CKD but a potential predictive biomarker.

Unlike many prior investigations that assessed cardiac status only via history or rudimentary exams, we rigorously excluded patients with any echocardiographic abnormalities. This approach reinforces that the NT-proBNP increases observed in our patients were attributable to renal deterioration rather than occult heart failure. In other words, even with well-preserved cardiac function, CKD progression led to rising NT-proBNP, indicating the biomarker's utility beyond heart failure contexts. Our study design therefore offers a clearer interpretation of NT-proBNP as a renal risk indicator, supporting its cardiac-independent predictive power.

Our analysis also provides insight into mechanistic links between NT-proBNP, nutrition, and fluid status in CKD. We found strong inverse correlations between NT-proBNP and serum albumin, total protein, and transferrin. Malnutrition and hypoalbuminemia are common in CKD due to decreased intake, inflammation, and protein loss, and they are closely tied to worse outcomes (17,18). Satyan et al. previously reported that NT-proBNP was not associated with albumin in asymptomatic hemodialysis patients (suggesting volume status as a bigger driver in that setting), but our pre-dialysis cohort did show such an association (19). The discrepancy may stem from differences in patient populations or sample size. Our findings suggest that poor nutritional status (low albumin/protein) accompanies higher NT-proBNP, potentially because malnutrition often coexists with fluid overload in CKD (the malnutrition-inflammation

complex). Hypoalbuminemia can lead to reduced plasma oncotic pressure and edema, which in turn increases cardiac wall stress and NT-proBNP release. Indeed, other studies have observed NT-proBNP to be inversely related to nutritional markers and positively related to inflammation in CKD. In a recent study, NT-proBNP was inversely associated with serum albumin and prealbumin (and BMI) and directly associated with CRP; furthermore, NT-proBNP levels were significantly higher in patients meeting criteria for protein-energy wasting (19). Our data are in line with this pattern (NT-proBNP ↔ low albumin, high CRP trend), although our CRP correlation did not reach significance. The interplay between NT-proBNP and the malnutrition-inflammation-atherosclerosis (MIA) syndrome is a topic of interest. It appears NT-proBNP may serve as an integrative marker reflecting not only cardiac stress but also volume status and nutritional/inflammatory status in CKD. Clinicians should recognize that an elevated NT-proBNP in a CKD patient without heart failure might be a surrogate for volume overload or poor nutrition rather than a "false-positive" cardiac alarm.

We also examined other factors that could influence NT-proBNP. Obesity can lower circulating natriuretic peptide levels due to increased clearance by adipose tissue receptors and decreased secretion (20). In our cohort, BMI was mostly in the normal range and we did not observe a NT-proBNP–BMI relationship, likely due to limited variability and the small sample. Prior research has noted an inverse NP–BMI relationship in the general population (natriuretic peptide levels tend to be lower in individuals with higher BMI), so in broader CKD cohorts one might need to account for obesity when interpreting NT-proBNP levels (20,21). Similarly, sex differences (higher NT-proBNP in females) have been reported in healthy adults, attributed to hormonal factors, but in our CKD patients these differences were not apparent, possibly overshadowed by CKD severity and volume status (22,23). Inflammation has been postulated to elevate NT-proBNP by cytokine-mediated myocardial strain or direct effects on myocytes (24,25). While we did not find a direct correlation in our data, inflammation likely still plays a role in the complex milieu of CKD that influences NT-proBNP. As noted, NT-proBNP correlates with CRP and other inflammatory markers in some CKD studies.

From a prognostic standpoint, NT-proBNP appears to have substantial value in CKD. It has been associated not only with progression to ESRD but also with cardiovascular outcomes and mortality in CKD populations. Previous studies reported that NT-proBNP was a significant predictor of both all-cause mortality and need for dialysis on follow-up (26,27). Gromadzinski et al. reported an optimal NT-proBNP cutoff of ~385 pg/mL for predicting the composite outcome of death or dialysis (sensitivity 70.8%, specificity 72.7%) (28). Moreover, NT-proBNP remained an independent predictor in multivariate analysis, with an adjusted odds ratio ~4.7 for mortality or RRT at that cutoff. These data suggest that even moderately elevated NT-proBNP levels (on the order of a few hundred pg/mL, well below the usual heart failure threshold) carry prognostic weight in CKD (28). In another study of advanced CKD (stages 4–5), baseline NT-proBNP >1345 ng/L predicted initiation of dialysis within 5 years, and baseline BNP >140 ng/L predicted 1-year dialysis risk, reinforcing that natriuretic peptides can stratify the timing of progression to ESRD (29). Our study was not powered to assess long-term outcomes like mortality or dialysis initiation, but the consistent association of NT-proBNP with short-term GFR decline hints at its broader prognostic significance, aligning with these findings.

Despite its strengths, our study has several limitations that should be considered when interpreting the findings. The most important limitations are the small sample size (n = 24) and the short follow-up period (6 months), which limit the statistical power and generalizability of the results. The relatively small cohort may have reduced the ability to detect weaker associations or to perform robust multivariate analyses. Additionally, the short observational window prevented the assessment of long-term renal outcomes such as initiation of dialysis, doubling of serum creatinine, or mortality.

Another limitation is that renal function was evaluated using creatinine clearance calculated by the Cockcroft–Gault formula, which, although practical and reproducible, may slightly differ from MDRD or CKD-EPI–based eGFR estimations. However, this method was consistently applied across all analyses. Furthermore, NT-proBNP measurements were performed at only two time points (baseline and week 24), which might not fully capture short-term fluctuations related to hydration or metabolic status. Finally, while we rigorously excluded patients with structural or functional heart disease to isolate renal effects, this design may limit extrapolation of the findings to CKD populations with concurrent cardiac comorbidities.

In conclusion, our findings indicate that NT-proBNP may serve as a promising biomarker for predicting renal outcomes, independent of heart failure. Its association with renal function decline, as well as volume and nutritional status, highlights its potential clinical relevance. Further large, multicenter prospective studies are needed to validate these findings and define standardized thresholds for clinical application in CKD management.

CONCLUSION

NT-proBNP may serve as a valuable adjunct marker

for tracking the progression of chronic kidney disease, even in the absence of overt cardiac dysfunction. In our single-center study, rising NT-proBNP levels paralleled declines in renal clearance over 6 months and were associated with indicators of malnutrition and volume status. These findings suggest that NT-proBNP captures key aspects of CKD progression risk that are not reflected by traditional measures alone. If confirmed in larger and longer-term studies, NT-proBNP could be integrated into clinical risk assessment to identify patients at higher risk of renal function loss and to tailor interventions accordingly. Until such data are available, NT-proBNP should be interpreted cautiously yet constructively in CKD: rather than dismissing an elevated NT-proBNP as a false alarm in a CKD patient without heart failure, clinicians should recognize it as a possible red flag for worsening renal and cardiovascular health. Ultimately, additional large-scale, long-term prospective studies with appropriate control groups are needed to validate NT-proBNP's prognostic utility and to determine whether interventions guided by this biomarker can improve clinical outcomes in CKD.

DECLARATIONS

Ethics Committee Approval: The study was approved by the Ankara Education and Research Hospital Ethics Committee (Approval No. 0291-2153) and conducted in accordance with the Declaration of Helsinki.

Data Availability: Datasets are available from the corresponding author upon reasonable request.

Competing Interests: The authors declare no competing interests.

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Original Article

Association Between Peritoneal Transport Changes and Arterial Stiffness Parameters in Peritoneal Dialysis Patients

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Abstract

Background: Alterations in peritoneal membrane transport characteristics are common in long-term peritoneal dialysis (PD) patients and may reflect underlying microvascular dysfunction. Such changes are commonly associated with peritonitis episodes, prolonged use of glucose-based dialysate, and microvascular injury to the peritoneal membrane, reflecting structural and functional deterioration of the peritoneum. Arterial stiffness, particularly measured via augmentation index (AIx) and pulse wave velocity (PWV), is a known morbidity and closely related to macro and microvascular disease in this population. However, the relationship between longitudinal changes in peritoneal transport and arterial stiffness remains unclear.

Methods: This retrospective observational cohort study included all adult patients who had initiated PD and underwent a baseline peritoneal equilibration test (PET), with a follow-up duration of at least two years. AIx and PWV were measured in all participants using a non-invasive method. Patients were categorized into two groups based on the stability of their PET classification: stable PET vs. changed PET. Demographic, clinical, laboratory, and arterial stiffness parameters (PWV and AIx) were compared between groups.

Results: There were no significant differences in age, sex, comorbidities, laboratory values, or dialysis and adequacy measures between the two groups. PWV values were comparable (9.3 ± 2.1 m/s vs. 9.3 ± 1.9 m/s; p = 0.90). However, the AIx was significantly higher in the changed PET group compared to the stable group (30.6 ± 10.2 vs. 23.0 ± 10.6; p = 0.02).

Conclusion: The findings indicate an associative relationship between peritoneal transport changes and increased small artery stiffness. AIx may serve as a sensitive, non-invasive indicator of microvascular alterations in PD patients. These associations should be interpreted cautiously, and prospective studies are warranted to confirm the temporal and mechanistic links.

Keywords: Peritoneal Dialysis, Peritoneal Equilibration Test (PET), Vascular Stiffness, Augmentation Index (AIx)

INTRODUCTION

Peritoneal dialysis (PD) is a home-based renal replacement therapy that provides hemodynamic stability and greater autonomy for patients with end-stage renal disease. The long-term efficacy of PD, however, largely depends on the maintenance of peritoneal membrane integrity, including solute transport and ultrafiltration capacity (1-3). Chronic exposure to glucose-based dialysates, persistent low-grade inflammation, and the accumulation of advanced glycation end-products (AGEs) can induce progressive structural alterations in the peritoneal membrane (4,5). These changes may not only compromise local peritoneal function but also contribute to systemic vascular dysfunction (6,7). All of these are causes that have been identified to date, but the cause of the change in peritoneal permeability has not yet been fully elucidated.

Arterial stiffness is a well-established predictor of cardiovascular morbidity and mortality (8-10). Non-invasive techniques such as pulse wave velocity (PWV) and augmentation index (AIx) have been widely employed for its assessment (13). Arterial stiffness arises from a combination of structural and cellular changes, including the replacement of elastic fibres in the arterial lamina with collagen, chronic low-grade inflammation within the arterial wall, endothelial dysfunction, phenotypic modulation of vascular

smooth muscle cells, and vascular calcification. These alterations collectively diminish arterial compliance, resulting in elevated systolic and reduced diastolic blood pressures, particularly during the early phases of disease progression. The consequent hemodynamic load on the left ventricle promotes left ventricular hypertrophy and contributes to the development of diastolic dysfunction (14-16). Non-invasive methods used to assess arterial stiffness include arterial tonometry, which plays an important role. In this context, PWV and AIx are prominent arterial tonometry techniques (17). PWV is calculated by dividing the time it takes for the pulse wave to travel between the arms and ankles by the distance between these points. AIx primarily reflects the stiffness of smaller and muscular arteries. Increased arterial stiffness leads to higher PWV, which in turn contributes to elevated AIx values through earlier wave reflections. Both PWV and AIx have been independently associated with adverse cardiovascular outcomes and increased all-cause mortality, particularly in patients undergoing dialysis (18-20). Numerous studies have demonstrated a significant positive correlation between arterial stiffness and inflammation in various patient populations, including those with chronic kidney disease (21). While increased AIx has been observed in PD patients with comorbid conditions such as metabolic syndrome, the relationship between temporal changes in peritoneal transport characteristics and systemic arterial stiffness remains poorly understood (22,23). There are no studies in the literature investigating the relationship between peritoneal permeability and arterial stiffness indices.

In this study, we aimed to investigate whether longitudinal changes in PET status are associated with alterations in arterial stiffness markers particularly PWV and AIx in a cohort of chronic PD patients.

METHODS

Study Design and Participants

This retrospective observational cohort study included 43 incident adult patients undergoing PD who were followed between 2020 and 2024 at the Peritoneal Dialysis Unit, Department of Nephrology, Dokuz Eylül University Hospital. The inclusion criteria were as follows: age ≥18 years, PD duration of at least 24 months, and the availability of both a baseline and at least two consecutive annual PET results. Patients with active infections, malignancies, recent cardiovascular events, or without a baseline PET were excluded from the study.

Peritoneal Equilibration Test (PET)

PET is a standardized method used to evaluate the permeability of the peritoneal membrane to small solutes. Based on the dialysate/plasma (D/P) creatinine ratio typically measured at the 4th hour patients are classified into four peritoneal transport categories: high (D/P ≥ 0.81), high-average (0.65–0.80), low-average (0.50–0.64), and low transporters (D/P ≤ 0.49). When the PET classification remains unchanged over time, it is defined as "stable PET," while increase or decrease at least one categoric is considered a "PET change."

Grouping According to PET Changes

According to the change in PET classification category, patients were divided into two groups: the "stable PET" group consisting of patients with stable PET categories over time (n=25) and the "changed PET" group consisting of patients with ≥1 category change in PET classification (n=18).

Assessment of Arterial Stiffness

Arterial stiffness parameters were assessed using a validated oscillometric pulse wave analysis device (Mobil-O-Graph; IEM GmbH, Germany). Measurements were performed on the brachial artery under standardized resting conditions. Three consecutive readings were obtained, and the mean values were used in the analysis. PWV was measured to evaluate large artery stiffness, while AIx served as an indicator of small artery stiffness.

Additional Clinical Parameters and Ethical Approval

Additional clinical parameters included blood pressure, ejection fraction, hemogram indices, serum biochemical values, mineral metabolism markers, and peritonitis history. The study was approved by the Non-Interventional Clinical Research Ethics Committee of Dokuz Eylul University Faculty of Medicine and conducted in accordance with the principles outlined in the Declaration of Helsinki. This study was approved by the Non-Interventional Clinical Research Ethics Committee of Dokuz Eylul University Faculty of Medicine (Approval No: 2024/23-05).

STATISTICAL ANALYSIS

Continuous variables were presented as means with standard deviations or as medians with interquartile ranges, depending on their distribution. All clinical and demographic data were retrieved from the hospital's electronic medical record system. Comparisons between groups were performed accordingly. Statistical analyses were conducted using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 26.0; IBM Corp., Armonk, NY, USA). Parametric variables were analyzed using the Student's t-test, non-parametric variables using the Mann–Whitney U test, and categorical variables using the chi-square test. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 43 patients were included in the analysis and categorized into two groups based on temporal changes in their PET classification: the stable PET group (n=25) and the changed PET group (n=18). Baseline

Table 1. Baseline characteristics of study participants

Parameter	Stable PET (n = 25)	Changed PET (n = 18)	p-value
Age (years, mean ± SD)	63.4 ± 13.9	61.6 ± 9.5	0.63
Sex, F/M, n (%)	11 (44%) / 14 (56%)	11 (61.1%) / 7 (38.8%)	0.26
BMI (kg/m², mean ± SD)	27.8 ± 5.0	27.3 ± 4.3	0.81
Diabetes Mellitus, n (%)	8 (32%)	3 (16.6%)	0.25
Hypertension, n (%)	15 (60%)	13 (72.2%)	0.40
Cardiovascular disease, n (%)	4 (16%)	1 (5.5%)	0.29
Baseline PET category, n (%)			0.92
Low	1 (4%)	1 (5.5%)	
Low-average	6 (24%)	3 (16.6%)	
High-average	15 (60%)	11 (61.1%)	
High	3 (12%)	3 (16.6%)	
Dialysis modality (CAPD/APD), n (%)	21 (84%) / 4 (16%)	14 (77.7%) / 4 (22.3%)	0.60
Dialysis duration (months, median, IQR)	36 (12–32)	24 (12–108)	0.28
Ejection fraction (%), mean ± SD	61.2 ± 2.3	60.0 ± 2.0	0.25
Systolic BP (mmHg, mean ± SD)	142.8 ± 15.8	139.8 ± 22.3	0.74
Diastolic BP (mmHg, mean ± SD)	83.5 ± 11.7	86.0 ± 13.8	0.67
Residual renal function (mL/day, median, IQR)	1500 (750–3000)	1400 (0–3000)	0.39
Peritonitis episodes (median, IQR)	1 (0–5)	0.5 (0–7)	0.55

BMI ; Body Mass Index, PET; Peritoneal Equilibration Test, CAPD; Continuous Ambulatory Peritoneal Dialysis, APD; Automated Peritoneal Dialysis, BP; Blood Pressure, SD; Standard Deviation, IQR; Interquartile Range

demographic and clinical characteristics, including age, sex, body mass index (BMI), presence of diabetes or hypertension, cardiovascular disease history, dialysis modality continuous ambulatory peritoneal dialysis (CAPD) vs. automatic peritoneal dialysis (APD), peritonitis frequency, and total dialysis duration, did not significantly differ between the groups (Table 1).

Laboratory parameters such as baseline serum sodium, potassium, albumin, hemoglobin, calcium, phosphorus, bicarbonate, parathyroid hormone levels, and ejection fraction were comparable between the groups. Systolic and diastolic blood pressure values were also similar (Table 2).

Regarding arterial stiffness parameters, mean PWV values were similar between the groups (stable PET: 9.3 ± 2.1 m/s vs. changed PET: 9.3 ± 1.9 m/s; p = 0.90). The mean AIx was significantly higher in the changed PET group compared to the unchanged group (30.6 ± 10.2 vs. 23.0 ± 10.6; p = 0.02) (Table 3).

DISCUSSION

This study examined the relationship between longitudinal changes in peritoneal membrane transport characteristics and arterial stiffness parameters in patients undergoing peritoneal dialysis. Our findings demonstrate that patients who experienced a change in their PET classification exhibited significantly higher AIx values compared to those with stable transport status. In contrast, PWV, which reflects large artery stiffness, did not differ significantly between the groups. These results suggest that dynamic changes in peritoneal transport properties may reflect systemic processes rather than being solely attributable to local peritoneal alterations.

Over time, various factors contribute to alterations in peritoneal membrane permeability. Pathophysiological mechanisms such as the accumulation of AGEs due to prolonged exposure to glucose-based dialysate, chronic

Table 3. Pulse Wave Analysis Results

Parameter	Stable PET (n = 25)	Changed PET (n = 18)	p value
PWV (m/s)	9.3 ± 2.1	9.3 ± 1.9	0.90
AIx (%)	23.0 ± 10.6	30.6 ± 10.2	*0.02*

Table 2. Laboratory Parameters of the Study Population

Parameter	Stable PET (n = 25)	Changed PET (n = 18)	p-value
Sodium (mmol/L)	139.3 ± 3.3	137.2 ± 4.6	0.29
Potassium (mmol/L)	5.0 ± 0.4	5.0 ± 0.6	0.95
Albumin (g/dL)	3.8 ± 0.3	3.5 ± 0.4	0.12
Hemoglobin (g/dL)	10.8 ± 2.1	9.8 ± 1.4	0.25
Calcium (mg/dL)	9.1 ± 0.8	9.1 ± 0.7	0.82
Phosphorus (mmol/L)	5.1 ± 1.7	5.1 ± 1.1	0.99
Alkaline phosphatase (U/L)	83.3 ± 28.0	82.0 ± 29.6	0.92
Bicarbonate (mmol/L)	24.3 ± 2.4	22.6 ± 2.6	0.19
PTH (pg/mL, median, IQR)	255.8 (111.7–710.6)	278.7 (29.9–1005.4)	0.96

PET, peritoneal equilibration test; SD, standard deviation; IQR, interquartile range; PTH, parathyroid hormone.

peritoneal inflammation, neoangiogenesis, vascular sclerosis, peritoneal sclerosis and fibrosis, activation of cytokines including transforming growth factor-beta (TGF-β) and vascular endothelial growth factor (VEGF), as well as peritoneal microcalcification, have all been implicated (24-26). In addition, clinical and treatment-related factors such as a history of peritonitis, long-term peritoneal dialysis (particularly beyond five years), and poor glycaemic control also play a significant role in the progression of membrane alterations. It should be considered whether factors long accepted as local consequences of peritoneal involvement might in fact reflect underlying systemic pathophysiological mechanisms.

The accumulation of advanced glycation end products (AGEs) induces the release of proinflammatory mediators, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), contributing to systemic inflammation and endothelial dysfunction. A study has shown that longitudinally high levels of high-sensitive C-reactive protein (hs-CRP) is associated to increased peritoneal permeability (27). These results are consistent with the hypothesis that changes in peritoneal permeability may be driven, at least in part, by systemic mechanisms.

Chronic inflammation, glucose-based solutions, hypoxia, and other stimuli increase the expression of angiogenic mediators such as vascular endothelial growth factor (VEGF). VEGF-A increases endothelial cell proliferation and vascular permeability. Angiopoietin and hypoxia-induced factor (HIF-1α) support angiogenesis. As a result, small water-soluble molecules, such as urea, creatinine, and glucose, diffuse more rapidly into the peritoneal cavity. Ultrafiltration is impaired because glucose is rapidly reabsorbed as the osmotic gradient is lost. In one study, higher VEGF levels were detected in patients using solutions containing high glucose, and increased peritoneal permeability was also demonstrated in these patients (24). In another study, increased HIF-1α was associated with pathological changes in permeability (28).

Chronic glucose exposure increases TGF-beta release. Fibroblast activation leads to extracellular matrix accumulation. As a result, submesothelial fibrosis, basal membrane thickening, and capillary wall sclerosis occur. Solute transport becomes irregular, and the transcapillary permeability of the peritoneum increases pathologically. A study has demonstrated a close association between TGF-beta release and peritoneal fibrosis (25,26).

Peritoneal calcification is one of the histomorphological consequences of long-term PD (29). In a study where peritoneal tissue samples were taken, peritoneal microcalcification was observed in 12 of 18 patients who had undergone long-term PD (30). There are limited studies that propose whether peritoneal calcification frequently observed in patients undergoing peritoneal dialysis is a causative factor in peritoneal membrane injury or merely a consequence of ongoing structural damage. However, a study has shown that high Ca×P levels are associated with increased permeability (31).

The strengths of our study include the use of consecutive annual PET assessments, simultaneous measurement of arterial stiffness parameters using a validated device, and long follow-up duration. These features allow for a more robust temporal evaluation of both peritoneal and vascular changes. However, several limitations should be acknowledged. First, the retrospective nature of PET data collection and the relatively small sample size reduce the statistical power and limit the generalizability of our findings. A formal a priori or post hoc power analysis was not feasible due to the retrospective design and limited cohort size; however, the observed effect size for AIx was consistent with previously published data, suggesting that the study was sufficiently sensitive to detect clinically meaningful differences. Second, the absence of direct endothelial or inflammatory biomarkers restricts our ability to validate the proposed mechanistic link between peritoneal transport alterations and vascular stiffness. Since the study was designed retrospectively based on existing clinical and dialysis records, data on circulating inflammatory or endothelial markers (such as hs-CRP, IL-6, or VEGF) were not uniformly available and thus could not be included in the analysis. Future prospective studies incorporating these biomarkers may provide a more comprehensive understanding of the systemic processes contributing to both peritoneal and vascular changes.

CONCLUSION

In conclusion, our findings indicate an associative relationship between longitudinal changes in peritoneal membrane transport characteristics and increased small artery stiffness, as reflected by higher AIx values. No significant difference was observed in PWV, suggesting that large artery stiffness may be less influenced by peritoneal transport dynamics. These results imply that AIx may serve as a sensitive, non-invasive marker for early detection of microvascular alterations in peritoneal dialysis patients. However, the present data do not establish causality, and the observed associations should be interpreted with caution. Future prospective studies with larger sample sizes and biomarker-based endothelial assessments are warranted to clarify the underlying mechanisms and temporal relationships.

DECLARATIONS

Ethics Committee Approval: The study was approved by the Non-Interventional Clinical Research Ethics Committee of Dokuz Eylul University Faculty of Medicine, Izmir, Turkey (Approval No: 2024/23-05). All procedures were conducted in accordance with the ethical standards of the institutional research committee and with the principles outlined in the Declaration of Helsinki.

Data Availability: The datasets generated and analyzed during the current study are available from the corresponding author, Dr. Ilker Atay (email: ilkeratayy@gmail.com), upon reasonable request.

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

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Informed Consent: Not applicable, as this study was based on retrospective analysis of anonymized clinical and dialysis records.

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Original Article

Retrospective Analysis of Clopidogrel Resistance Tests

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Abstract

Background: Clopidogrel binds to P2Y12 and inhibits platelet aggregation. Clopidogrel resistance can be categorized into two main categories: laboratory clopidogrel resistance and clinical clopidogrel resistance. Laboratory clopidogrel resistance refers to the inadequate in vitro antiplatelet effects of clopidogrel. In the present study, we aimed to evaluate the clopidogrel resistance test results from the perspective of laboratory specialists.

Methods: All clopidogrel resistance test results from the Bilkent City Hospital laboratory information system, between February 1, 2019, and May 31, 2025, were collected. Clopidogrel resistance tests were performed using the adenosine diphosphate-induced platelet aggregation method using an aggreometer device (Stago Chrono-Log Model 700). Data were expressed as mean, minimum, and maximum levels, numerically and as percentages. The Chi-square test was performed a categorical data comparison between the created groups. IBM SPSS Statistics performed statistical analyses for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA).

Results: A total of 285 clopidogrel resistance test results were included. Negative and positive clopidogrel test results were as follows: 95 (33.3 %) and 190 (66.7 %). The present study consisted of 98 (34.4 %) females, 187 (65.6 %) males' clopidogrel resistance tests. There were 107 (37.5%) clopidogrel resistance test results in the under 65 years old group, while there were 178 (62.5%) in the 65 and older years group. The neurology clinic requested clopidogrel resistance tests mostly (N:72, 62.5 %). No statistical differences were found in gender among age intervals ($p>0.05$), in clopidogrel resistance tests among gender ($p>0.05$), and in clopidogrel resistance tests among age intervals ($p>0.05$).

Conclusion: The most appropriate laboratory test to assess clopidogrel resistance has not yet been determined. The present study, evaluated from a laboratory perspective, may be useful for future research; however, prospective studies combining laboratory and clinical findings may be more effective.

Keywords: Platelet Aggregation, Thrombosis, Blood Coagulation

INTRODUCTION

The formation of a blood clot within a blood vessel is thrombosis (1). Normal hemostasis involves sensitive interactions between the coagulation and fibrinolytic systems. Deviations in the normal hemostasis/blood clotting system cause thrombosis (2). Thrombosis occurs through three basic steps: platelet adhesion, platelet activation, and platelet aggregation (3). In platelet adhesion, interactions occur between the GP Ib/V/IX receptor complex located on the surface of platelets and the collagen and von Willebrand factor (vWF) and its receptor when exposed to the site of vascular injury (1).

Adenosine diphosphate (ADP) interacts with the platelet membrane ADP receptor (P2Y12), which is involved in ADP-induced activation of the glycoprotein IIb/IIIa receptor. Activation of the glycoprotein IIb/IIIa receptor leads to increased platelet degranulation and thromboxane production, as well as prolonged platelet aggregation (4).

Blocking P2Y12 is a potent pharmacological antiplatelet strategy for the treatment of arterial thrombosis caused

by coronary atherosclerosis and the prevention of thrombosis. Platelet adhesion, activation, and aggregation are important in atherothrombosis. Intracoronary atherothrombosis is one of the most common causes of acute coronary syndrome; it plays a role in complications associated with percutaneous coronary intervention, including recurrent acute coronary syndrome, procedure-related myocardial infarction, or stent thrombosis (5,6).

Clopidogrel binds to P2Y12 and inhibits platelet aggregation (7). Clopidogrel, the P2Y12 inhibitor, is a second-generation thienopyridine (8). Clopidogrel is a prodrug and does not have a direct effect on antiplatelet activity. The antiplatelet effect occurs through oxidation of the active clopidogrel metabolite by cytochrome P450 enzymes. After oral administration, the drug is absorbed with approximately 50% bioavailability (9). The highest level of platelet inhibition due to clopidogrel occurs within 2 to 5 hours after a single dose of 400 mg. The same level of inhibition is achieved after 3 to 7 days with daily use of 75 mg of clopidogrel (10). Clopidogrel has a role in reducing fibrinogen levels, and it also inhibits erythrocyte aggregation (11,12). Clopidogrel, which has been widely used in recent years, has bleeding and hematological complications, but considering its hematological side effects, it is still one of the safest drugs in the thienopyridine class (13).

Clopidogrel and aspirin inhibit platelet aggregation through different pathways. Combining antiplatelet therapy offers additional and complementary benefits compared with either drug alone (14,15). The CAPRIE study, conducted in a selected patient population, demonstrated significant benefits of clopidogrel therapy compared with aspirin alone (16). The combined use of clopidogrel and aspirin is the gold standard for reducing platelet activation and aggregation in patients with acute coronary syndromes and those undergoing stent placement (14,15).

However, despite dual antiplatelet therapy, recurrent ischemic events are common in patients with acute coronary syndromes and those undergoing percutaneous coronary intervention. Stent thrombosis, in particular, can have serious consequences. The antiplatelet activity of clopidogrel varies among individuals (17). Some individuals experience recurring cardiovascular events despite the use of potent antiplatelet drugs such as aspirin and clopidogrel. This has led to the emergence of the concept of unresponsiveness or resistance to antiplatelet drugs (18). Gruber et al. stated that the definition of unresponsiveness or resistance to an antiplatelet drug is the failure of the antiplatelet drug to inhibit its target of action (15).

Clopidogrel resistance can be categorized into two main categories: laboratory clopidogrel resistance and clinical clopidogrel resistance. Laboratory clopidogrel resistance refers to the inadequate in vitro antiplatelet effects of clopidogrel. Clinical clopidogrel resistance refers to treatment failure, and patients experience cardiovascular events despite clopidogrel use (19). Laboratory and clinical resistance are not the same. Not every patient with laboratory resistance will experience a cardiovascular event. Clinical resistance is associated with inadequate treatment. Laboratory resistance does not occur in every patient receiving antiplatelet drug therapy. Sometimes, laboratory and clinical clopidogrel resistance coexist (20).

In the present study, we aimed to evaluate clopidogrel resistance test results retrospectively from the perspective of laboratory specialists and share the data with the existing literature.

METHODS

Study Design and Data Collection

The research was conducted at Bilkent City Hospital. Clopidogrel resistance test results recorded in the hospital's laboratory information system between February 1, 2019, and May 31, 2025, were retrospectively reviewed. For each patient, only the first available test result was included in the analysis to avoid duplication and ensure data consistency

Laboratory Analysis

Clopidogrel resistance testing was performed in an external reference laboratory contracted with Bilkent City Hospital. The analysis was based on adenosine diphosphate (ADP)–induced platelet aggregation, measured using an aggregometer device (Stago Chrono-Log Model 700).

Ethical Approval

This study received ethical approval from the Ethics Committee of Bilkent City Hospital (Approval No: TABED 2-25-1352; Date: June 25, 2025).

STATISTICAL ANALYSIS

Continuous variables were summarized as mean, minimum, and maximum values, whereas categorical variables were expressed as frequencies and percentages. Differences between categorical variables across the study groups were assessed using the Chi-square test. A p-value < 0.05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Study Population

A total of 285 clopidogrel resistance test results were included in the final analysis. Study groups were stratified according to gender, age, and clopidogrel resistance test results.

Table 1. Distribution of Clopidogrel Resistance Test Results by Demographic and Clinical Characteristics

Variable	N	%
Female	98	34.4
Male	187	65.6
Under 65 years	107	37.5
65 years and older	178	62.5
Clopidogrel Resistance Test Results		
Negative	95	33.3
Positive	190	66.7
Requesting Clinics		
Neurology	178	62.5
Neurosonology	79	27.7
Neurosurgery	9	3.2
Rehabilitation	5	1.8
Cardiovascular Surgery	4	1.4
Cardiology	3	1.1
Infectious Diseases	1	0.4
Interventional Radiology	1	0.4
Chest Diseases	1	0.4
Internal Diseases	1	0.4
Nephrology	1	0.4
Neuromuscular Diseases	1	0.4
Organ Transplantation Intensive Care	1	0.4

Gender Distribution

Among all participants, 98 (34.4%) were female and 187 (65.6%) were male. The Neurology Clinic accounted for the majority of clopidogrel resistance test requests (n = 72; 62.5%) (Table 1).

Age Distribution

The mean age of participants younger than 65 years was 56.2 years (range: 37–64), while the mean age in the ≥65 years group was 73.9 years (range: 65–92). There were 107 (37.5%) test results in individuals under 65 years and 178 (62.5%) in those aged 65 years or older.

Clopidogrel Resistance Results

Overall, 95 (33.3%) of the tests were negative, while 190 (66.7%) were positive for clopidogrel resistance. The distribution of clopidogrel resistance across subgroups is detailed in the following comparisons.

Comparative Analyses

Gender and Age: The gender distribution across age intervals is summarized in Table 2 (p = 0.559).

Clopidogrel Resistance and Gender: The relationship between clopidogrel resistance and gender is presented in Table 3 and Figure 1 (p = 0.659).

Clopidogrel Resistance and Age: The comparison of clopidogrel resistance across age intervals is shown in Table 4 and Figure 2 (p = 0.484).

DISCUSSION

Antiplatelet drugs play a pivotal role in reducing the risk of thromboembolic events, particularly in patients with cerebrovascular diseases or those undergoing neurovascular stent placement (21). By inhibiting platelet aggregation, these agents aim to prevent ischemic complications. However, in a subset of patients, the expected therapeutic response is not achieved, a condition first described in the 1980s and referred to as antiplatelet therapy resistance (22). Among the commonly used agents, clopidogrel resistance has been associated with recurrent ischemic events, particularly in high-risk populations (20).

Reported prevalence rates of clopidogrel resistance

Table 2. Gender Distribution Among Age Intervals

Age Interval	Female n (%)	Male n (%)	p value*
<65 years	37 (34.6)	70 (65.4)	0.559
65 years and older	61 (34.3)	117 (65.7)	

Chi-square test was used for comparison.

Table 3. Clopidogrel Resistance Tests by Gender

Clopidogrel Resistance Status	Gender	n	%	p value*
Negative	Female	31	32.6	0.659
	Male	64	67.4	
Positive	Female	67	35.3	
	Male	123	64.7	

Table 4. Clopidogrel Resistance Tests by Age Intervals

Clopidogrel Resistance Status	Age Group	n	%	p*
Negative	Under 65 years	35	36.8	0.484
	65 years and older	60	63.2	
Positive	Under 65 years	72	37.9	
	65 years and older	118	62.1	

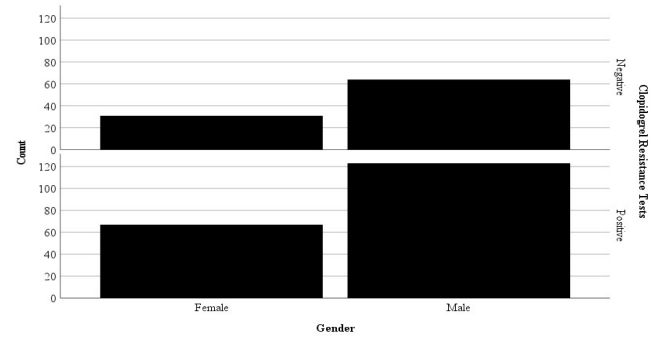

Figure 1. Clopidogrel Resistance Tests Among Genders

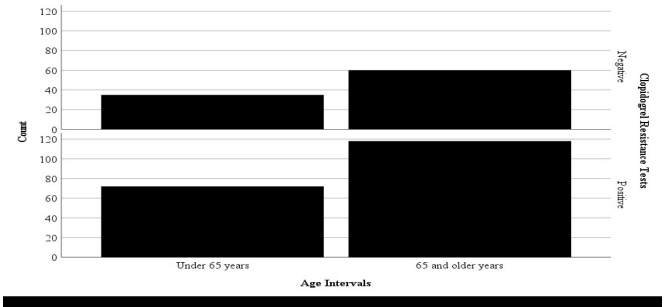

Figure 2. Clopidogrel Resistance Test Results Among Age Intervals

vary widely across studies. In a review by Nguyen et al., the prevalence was found to range between 4% and 30% (23). İyigündoğdu et al. reported a rate of 17.2% among patients followed for carotid artery stenting in neurology clinics (24). Similarly, a separate study involving patients with carotid stents documented a 19.0% resistance rate, while Müller-Schunk et al. reported 28% in patients with supra-aortic stents (25,26). In the present study, the prevalence of clopidogrel resistance was notably higher, at 66.7%. This discrepancy may be attributable to the inclusion of all laboratory clopidogrel resistance test data, independent of patients' underlying diagnoses or clinical settings. Such inclusion likely captures a broader patient spectrum, potentially inflating the observed rate compared with disease-specific cohorts.

Prabhakaran et al. identified a significant association between advancing age and reduced platelet inhibition, suggesting that diminished cytochrome P450 3A4 activity with age may impair clopidogrel metabolism and activation (27). However, other studies, including those by Ryu et al., Kim et al., and İyigündoğdu et al., found no significant age-related difference in clopidogrel responsiveness (21,24,28). Consistent with these findings, our study, which divided participants into two groups (<65 years and ≥65 years), demonstrated no statistically significant difference in clopidogrel resistance between the two age categories.

Previous investigations by Kim et al., Ryu et al., and Atasoy et al. similarly reported no significant gender differences in clopidogrel resistance (21,28,29). The present study supports these observations, finding no statistical difference between males and females. Nonetheless, some reports have suggested a higher prevalence of resistance among females, potentially reflecting pharmacokinetic and hormonal differences affecting clopidogrel absorption and metabolism (24,30). These conflicting results highlight the need for larger, well-controlled studies to clarify the influence of gender on clopidogrel response.

The mechanisms underlying clopidogrel resistance are multifactorial. Genetic polymorphisms affecting cytochrome P450 isoenzymes, reduced drug bioavailability, interindividual variability in baseline platelet reactivity, and accelerated platelet turnover have all been implicated (31). Although pre-procedural clopidogrel resistance testing may offer potential value in predicting thromboembolic risk, randomized controlled trials are still required to confirm its clinical utility and to define management strategies for resistant patients. Furthermore, the lack of standardized testing methods, including differences in agonists, assay platforms, and cutoff definitions, complicates cross-study comparisons. Despite the growing body of literature, a consensus on the clinical interpretation and management of clopidogrel resistance has yet to be reached (24).

The present study was conducted at Bilkent City Hospital, one of the largest tertiary healthcare centers in Türkiye, and utilized an extensive dataset comprising clopidogrel resistance test results collected between February 1, 2019, and May 31, 2025. The inclusion of a large sample size over a prolonged study period provides a robust overview of the real-world prevalence and demographic distribution of clopidogrel resistance. This comprehensive dataset strengthens the reliability of the observed patterns and enhances the generalizability of the findings within similar clinical settings.

Several limitations should be acknowledged. First, the retrospective design of the study restricted the ability to control for preanalytical factors that may influence clopidogrel resistance testing. Second, detailed clinical information regarding patients' concurrent medications, comorbidities, or treatment adherence was unavailable, which may have confounded the interpretation of resistance rates. Lastly, the data were analyzed primarily from a laboratory-based perspective, without incorporating direct clinical outcomes, which limits causal inferences regarding the association between laboratory resistance results and thromboembolic events.

CONCLUSION

Platelet function testing plays a crucial role in the management of cardiovascular and cerebrovascular diseases; however, the relationship between in vivo platelet activity and ex vivo laboratory test results remains uncertain [20]. At present, no single laboratory method has been universally accepted as the gold standard for assessing clopidogrel resistance (32). The present study, conducted from a laboratory-based perspective, provides valuable real-world insight into the prevalence and distribution of clopidogrel resistance. Nevertheless, prospective, multicenter studies that integrate laboratory findings with clinical outcomes are needed to better elucidate the mechanisms and clinical implications of clopidogrel resistance and to guide individualized antiplatelet therapy in the future.

DECLARATIONS

Ethics Committee Approval: The study was approved by the Non-Interventional Clinical Research Ethics Committee of Bilkent City Hospital, Ankara, Türkiye (Approval No: TABED 2-25-1352; Date: June 25, 2025). All procedures were conducted in accordance with the ethical standards of the institutional research committee and with the principles outlined in the Declaration of Helsinki.

Data Availability: The datasets generated and 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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Informed Consent: Not applicable, as this study was based on the retrospective analysis of anonymized laboratory data.

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Original Article

Clinical Outcomes and Counseling Impact of Exome Sequencing in a Low-Risk Prenatal Cohort

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Abstract

Background: Prenatal exome sequencing (pES) is recommended mainly for fetuses with major or multiple structural anomalies when conventional karyotyping and chromosomal microarray are non-diagnostic. Outside these indications, its clinical value is uncertain.

Methods: We retrospectively reviewed 10 fetuses tested with pES at our center (2016–2025) despite lacking guideline-based indications. Indications included advanced maternal age (n=1), sex-chromosome anomalies (n=5), parental gonadal mosaicism risk (n=2), and isolated soft ultrasonographic marker (n=2). All cases had karyotype and/or chromosomal microarray (CMA) before pES.

Results: One fetus carried a pathogenic *SETD5* (NM_001080517.3) c.1541del, p.(Lys514Argfs*2) variant, along with 45,X/46,XY mosaicism and transient ascites/pleural effusion. The *SETD5* variant was considered incidental in the prenatal context, though it influenced management and led to medical termination. A second fetus had a maternally inherited heterozygous NSD1 (NM_022455.4) c.2410C>T, p.(Pro804Ser) variant of uncertain significance supporting pregnancy continuation, but the pregnancy was terminated in an external center. One other fetus was lost to follow-up; all other live-born infants appeared normal on postnatal examination.

Conclusion: In this small "out-of-indication" series, pES was management-changing in one pregnancy and created uncertainty in another, which complicated the family's decision-making process. The latter finding aligns with current recommendations discouraging pES in low-risk antenatal settings due to its limited yield. Nonetheless, in select situations involving unresolved diagnostic ambiguity, pES may still uncover variants with potential relevance to counseling and management.

Keywords: Exome sequencing, Chromosome Aberrations, Genetic Counseling, Genomics

INTRODUCTION

Prenatal genetic diagnosis has evolved from cytogenetic karyotyping to chromosomal microarray analysis (CMA) and, more recently, to genome-scale sequencing capable of detecting single-nucleotide and small indel variants. These technological advances have markedly improved diagnostic rates for fetuses with structural anomalies and have become integral to prenatal counseling and pregnancy management (1). Following a normal CMA, whole-exome sequencing (WES) provides an additional diagnostic yield of approximately 10–30% in fetuses with structural anomalies, with the highest rates observed in fetuses with skeletal dysplasia findings, while the yield falls below 2% in those with isolated increased nuchal translucency (2-4). Exome sequencing, despite its diagnostic power in anomaly-selected fetal cases, provides minimal (0.6-2.7%) incremental yield in fetuses without malformations (5-7). This contrast underpins current recommendations for selective use with major guidelines uniformly emphasizing that prenatal exome sequencing (pES) should be reserved for fetuses with one or more major structural anomalies that remain unexplained after standard genetic analyses (8-10). Moreover, pathogenic variants identified with antenatal

exome analysis are not always clinically actionable in the prenatal period, as many associated phenotypes display variable expressivity, reduced penetrance or age-related penetrance (11).

Despite this, clinicians encounter requests for prenatal exome sequencing (pES) outside anomaly-based selection. A common scenario is pES driven by parental anxiety after invasive testing performed for reasons other than fetal structural anomalies, such as advanced maternal age, increased risk in aneuploidy screening, or isolated soft markers. Another occurs when sex-chromosome abnormalities or CNVs of uncertain significance are detected, prompting pES to exclude additional monogenic findings that could influence counseling and decision-making. In these settings, decisions must balance the modest potential for meaningful findings against the risks of uncertainty, anxiety, and unnecessary follow-up. Thorough pre- and post-test counseling and clear reporting criteria help mitigate these challenges.

This study describes a single-center retrospective series of 10 fetuses that underwent pES without anomaly-based indications. We report indications, molecular results and fetal/postnatal outcomes, and outline how individual results influenced counseling and management. The goal is to provide pragmatic information for clinicians who face similar requests in low-risk settings and to illustrate when pES added value, when it did not, and how uncertainty was handled. Although our data come from the prenatal setting, the clinical questions it raises about the balance of diagnostic yield, psychological impact, and downstream decision-making resonate across many clinical application domains of genomic testing ranging from internal medicine and oncology to reproductive genetics. This is a systemic challenge that the wider medical community is beginning to face: how to integrate powerful genomic tools into routine practice without overextending their use, and how to support patients when the answers provided are uncertain or incidenta.

METHODS

Study Design and Setting

We conducted a retrospective review of all prenatal exome sequencing (pES) cases performed between January 2016 and June 2025 at the Medical Genetics Department of our tertiary referral center. Written informed consent for testing and secondary analysis of anonymized data was obtained from all couples before invasive sampling. Clinical and follow-up data were retrieved from institutional medical records. This study was approved by the Institutional Review Board of Koç University (IRB No: 2025.462.IRB2.215).

Inclusion and Exclusion Criteria

The inclusion criterion was performance of pES outside guideline-based indications. Cases tested under standard indications, including fetal structural or multisystem malformations, amniotic fluid or placental abnormalities, and growth or fluid regulation anomalies were excluded. Cases with a fetal chromosomal anomaly that explained the observed fetal findings were also included.

Cohort Description

The final cohort comprised ten fetuses: one with advanced maternal age, five with numerical sex-chromosome abnormalities, two with parental gonadal mosaicism risk due to a previously affected child, and two with isolated soft ultrasound markers (nasal bone hypoplasia). The decision to perform pES was made upon the family's request for comprehensive testing once fetal material was already available and after detailed pre-test counseling regarding the expected yield and interpretive limitations.

Sample Collection and Laboratory Methods

Samples were obtained by amniocentesis or chorionic villus sampling (CVS) using standard procedures. All cases underwent karyotype and/or chromosomal microarray (CMA) prior to sequencing. Exome sequencing was performed in accredited diagnostic laboratories using validated capture platforms and next-generation sequencing pipelines. All exome analyses achieved a mean coverage of at least >94% at ≥20x depth and >97% at ≥10x depth. Reads were aligned to the human reference genome (GRCh37 or GRCh38), and variants were annotated using population databases (gnomAD, 1000 Genomes) and disease databases (ClinVar, OMIM, HGMD). Variants were classified according to ACMG/AMP 2015 guidelines as pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, or benign (12). Parental confirmation was performed with Sanger sequencing in peripheral blood DNA to determine inheritance and phase.

Follow-up and Outcomes

One family was lost to follow-up in the prenatal period due to transfer of care. In the rest, pregnancy outcomes were obtained from obstetric and pediatric records. For live births, postnatal evaluations were made or reviewed for growth, structural anomalies, or developmental concerns. For one terminated pregnancy, clinical and radiological postmortem examinations were performed.

STATISTICAL ANALYSIS

Given the descriptive and retrospective nature of the study, no formal statistical analyses were performed. Data were compiled and analyzed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) for tabulation and summarization. Because of the small cohort size (n=10) and the absence of a control group, no inferential or quantitative statistics were applied.

RESULTS

Molecular Findings

Of the ten fetuses, one carried a pathogenic *SETD5* (NM_001080517.3): c.1541del, p.(Lys514Argfs*2) variant and one had a variant of uncertain significance in *NSD1* (NM_022455.4): c.2410C>T, p.(Pro804Ser). The remaining eight showed no reportable sequence variants (**Table 1**).

Cytogenetic Findings

Among the ten cases, five fetuses had sex-chromosome aneuploidies: one with 47,XXX; one with 47,XXY (Klinefelter syndrome); one with 47,XYY; one with 45,X/46,XX mosaic Turner syndrome; and one with 45,X/46,XY mosaicism consistent with mixed gonadal dysgenesis. In four of these cases, the indication for invasive testing was an increased risk for sex-chromosome aneuploidy detected on noninvasive prenatal testing (NIPT). Only in the fetus with mixed gonadal dysgenesis, the invasive procedure was performed due to the presence of ambiguous genitalia with ascites and pericardial effusion, that were detected to be transient on follow-up.

Chromosomal Microarray (CMA) Results

All chromosomal microarray (CMA) results were consistent with the karyotype findings, except in Case 8, where CMA revealed two small deletions of uncertain significance: one on chromosome 2q13, encompassing the *NPHP1* gene, and another on 16p12.2, partially overlapping the *OTOA* gene. Both were considered carrier states for the respective autosomal recessive conditions; the *NPHP1*-related ciliopathies (MIM# 609583, #256100, #266900) and *OTOA*-related deafness (MIM#607039). In this case, pES was additionally performed to rule out possible inherited or de novo pathogenic variants that could result in disease expression when in trans.

Case 8: SETD5 Variant and Phenotypic Correlation

Case 8 with ambiguous genitalia exhibited 45,X/46,XY mosaicism and transient ascites and pleural effusion that resolved by the late second trimester. While hydropic findings in 45,X/46,XY mosaicism are recognized but uncommon, exome sequencing was pursued to explore whether the transient hydrops phenotype could be better explained by a single-gene disorder (13). Exome analysis and familial studies revealed a de novo heterozygous frameshift *SETD5* variant, classified as likely pathogenic and compatible with a molecular diagnosis of autosomal dominant Intellectual Developmental Disorder 23 (MRD23, MIM# 615761) (14).

Antenatal phenotypes related to *SETD5* pathogenic variants are not well characterized; however, increased nuchal translucency has been reported in one fetus (15). While *SETD5* could have theoretically contributed to the fetal findings, the absence of a well-described prenatal phenotype made a causal link uncertain, and the variant was therefore considered incidental in this context. The *SETD5* finding greatly influenced counseling: as *SETD5* pathogenic variants are associated with intellectual disability and behavioral anomalies, the family opted for medical termination at 24 weeks following detailed counselling.

Case 3: NSD1 Variant

Case 3 with a 47,XYY karyotype underwent pES and was found to carry a missense *NSD1* variant initially classified as a VUS. Segregation analysis demonstrated maternal inheritance from a clinically unaffected mother, supporting reclassification to likely benign. Although the family was informed that the prenatal phenotype was not expected to be associated with neurodevelopmental impairment, they opted for termination of the pregnancy at an external center.

Summary of Remaining Cases and Outcomes

No pathogenic or likely pathogenic variants were identified in the remaining eight fetuses through pES. Among all pregnancies, one was lost to follow-up, while the remaining seven resulted in live births. All infants were clinically normal on neonatal and early postnatal examinations, with no structural malformations or growth abnormalities.

DISCUSSION

This retrospective series illustrates the complex realities of performing pES outside established indications, and both the potential value and pitfalls of such testing. The small size of this cohort reflects the rarity of out-of-indication prenatal exome sequencing in routine clinical practice. Over nearly a decade, fewer than ten such cases were encountered at our tertiary center, underscoring both the limited demand and the cautious clinical attitude toward testing beyond guideline recommendations. Even small, carefully documented series like this can contribute valuable real-world data for future reviews addressing the clinical utility and ethical implications of pES in low-risk settings.

Case 8 with the *SETD5* variant demonstrates that actionable, or at least management-influencing findings can occasionally arise in low-yield settings and help families make decisions. Conversely, Case 3 with 47,XYY and the *NSD1* variant differs in that it represents emotional challenges and confusion for the family and misguided parental decisions. The family with the *SETD5*-positive fetus initially planned to continue the pregnancy, as the detected 45,X/46,XY mosaicism and genital findings were not considered absolute indications for termination. Their decision changed after learning that *SETD5*-related disorders are associated with intellectual disability and behavioral impairment. Conversely, the family of the fetus with 47,XYY remained undecided about termination until the *NSD1*

Table 1. Clinical and laboratory findings of fetuses with low-risk indications undergoing pES.

	GA (weeks) / Consanguinity	Indication for invasive procedure	Cytogenetic / Array findings (GRCh37)	Fetal USG findings & WES results	Outcome
1	16 / No	Advanced maternal age (41)	46,XY .arr(1–22)x2,(XY)x1	Normal; No variant detected	Healthy newborn
2	16 / No	Increased risk for sex-chromosome anomaly on NIPT	47,XXX .arr(X)x3	Normal; No variant detected	Healthy newborn
3	19 / No	Increased risk for sex-chromosome anomaly on NIPT	47,XYY .arr(X)x1,(Y)x2	Normal; Maternal het VUS in *NSD1* (NM_022455.4): c.2410C>T p.(Pro804Ser)	ToP
4	19 / No	Increased risk for sex-chromosome anomaly on NIPT	47,XXY .arr(X)x1,(Y)x2	Normal; No variant detected	Lost to follow-up
5	17 / No	Increased risk for sex-chromosome anomaly on NIPT	mos 45,X/46,XX [21/39] .arr(X) x1[0.3]	Normal; No variant detected	Healthy newborn
6	23 / No	Ambiguous genitalia, ascites, and pericardial effusion	mos 45,X/46,XY [17/3] .arr(X) x1,(Y)x0[0.6]	Transient ascites and effusion; De novo het LP variant in *SETD5* (NM_001080517.3): c.1541del p.(Lys514Argfs*2)	ToP
7	23 / No	Soft ultrasound marker on anomaly screening	46,XY .arr(1–22)x2,(XY)x1	Normal; No variant detected	Healthy newborn
8	22 / No	Isolated small nasal bone	46,XX .arr 2q13(110874327_111388468)x1; 16p12.2(21405328_21737414)	Small NB; No variant detected	Healthy newborn
9	21 / –	1% gonadal mosaicism risk for *COMP* (NM_000095.2): c.1417_1419del, p.(Asp473del)	46,XY .arr(1–22)x2,(XY)x1	Normal; No variant detected	Healthy newborn
10	13 / No	1% gonadal mosaicism risk for *IQSEC2* (NM_001111125.2): c.2983C>T, p.(Arg995Trp)	46,XX .arr(1–22,X)x2	Normal; No variant detected	Healthy newborn

GA, gestational age (weeks); NIPT, noninvasive prenatal testing; USG, ultrasonography; arr, chromosomal microarray result; mos, mosaic; het, heterozygous; LP, likely pathogenic; VUS, variant of uncertain significance; ToP, termination of pregnancy; NB, nasal bone

variant of uncertain significance was reported. Although segregation analysis confirmed maternal inheritance and the variant was interpreted as likely benign, and the family was counseled in detail that the prenatal phenotype was not expected to be associated with severe outcomes, the additional information increased parental anxiety and contributed to the decision to terminate the pregnancy (Table 1).

These examples show that pES outside standard indications can alter management even when variants are incidental or uncertain, sometimes by shifting parental perception of risk. At the same time, they highlight the potential for harm through anxiety, overinterpretation, and decisional pressure, which are amplified when testing is not phenotype-driven.

Our diagnostic yield (1/10) is higher than expected for such unselected cases, but this reflects the small sample size rather than a trend. Larger meta-analyses report <2% incremental yield when pES is applied in low-risk or structurally normal fetuses. Thus, the key message is not the yield itself but the interpretive and counseling demands that follow. Every pathogenic variant or VUS requires thoughtful multidisciplinary discussion and careful communication with the family. The medical implications for the family must be addressed during pre-test counseling, particularly when residual uncertainty is likely to persist even after testing.

Lastly, although the *SETD5*-positive fetus also had mixed gonadal dysgenesis, the detailed postmortem examination provided valuable clinical information that may contribute to understanding the prenatal phenotype associated with *SETD5*-related disorders. Findings such as clinodactyly and distal phalangeal hypoplasia of the second and fifth fingers, in addition to mild craniofacial and genital anomalies, enrich the limited phenotypic data available for *SETD5* in the antenatal period. These observations, though confounded by the coexisting karyotypic abnormality, highlight the importance of thorough postmortem assessment in expanding knowledge of prenatal genotype-phenotype correlations. Future multicenter studies with standardized inclusion criteria, systematic follow up, and consideration of cost-effectivity issues are needed to better define the clinical value of pES in low-risk pregnancies or fetal cases where chromosomal anomalies already explain the phenotype. These studies may ultimately guide the balanced integration of "out-of-indication" pES into clinical practice.

This study is limited by its retrospective design and relatively small sample size, which may restrict the generalizability of the findings. Additionally, deep phenotyping information was incomplete except for one case, and long-term postnatal outcomes were not systematically assessed.

CONCLUSION

In this small "out-of-indication" cohort, pES provided additional information in only one pregnancy but created diagnostic uncertainty in another, ultimately influencing

both families' decisions. In the first family, sequencing clarified prognosis and guided decision-making, whereas in the second, it complicated the process. This shows that pES remains a powerful tool capable of generating management-influencing data, but its use outside guideline-based indications should remain selective and purpose-driven. Careful counseling before and after testing, transparent communication of uncertainty, and multidisciplinary interpretation are essential to balance potential benefits against emotional and ethical costs. Lastly, our findings contribute valuable postmortem data to the limited body of knowledge on prenatal SETD5-related phenotypes, revealing features such as clinodactyly and distal phalangeal hypoplasia of the second and fifth fingers. These observations may help refine future understanding of early *SETD5*-associated manifestations. .

DECLARATIONS

Ethics Committee Approval: This study was approved by the Institutional Review Board of Koç University (IRB No: 2025.462.IRB2.215). All procedures were conducted in accordance with the principles of the Declaration of Helsinki.

Data Availability: The datasets generated and 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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Informed Consent: Written informed consent was obtained from all participants or their legal guardians at the time of sample collection, covering both diagnostic analyses and the use of de-identified clinical data and biological materials for research purposes, in accordance with institutional policy

Author Contributions: UA: Conceptualization, provision of clinical and molecular data, formal analysis, methodology, investigation, visualization, original draft preparation, and writing, editing. EÇ, TSS, AY: Clinical evaluation, and provision of clinical data. HK: Supervision, provision of clinical and molecular data, conceptual guidance, validation, interpretation of results, and critical review of the manuscript.

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Review

Novel Pharmacological Approaches to Neurological Diseases: A Review of Recent Clinical Breakthroughs

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Abstract

Neurological diseases present significant global health challenges due to their high prevalence, substantial disability burden, and previously limited therapeutic options. Recent breakthroughs in neuropharmacology and precision medicine have dramatically advanced treatment paradigms, ushering in targeted medications that alter disease progression, alleviate symptoms, and improve patient quality of life. This review systematically examines recent pharmacological innovations across Alzheimer's disease, Parkinson's disease, and multiple sclerosis (MS). For AD, landmark disease-modifying therapies such as aducanumab and lecanemab targeting amyloid pathology, and the introduction of transdermal donepezil, have expanded therapeutic possibilities. In PD, novel formulations like opicapone and sublingual apomorphine provide enhanced control of motor fluctuations. For MS, oral sphingosine-1-phosphate receptor modulators (ozanimod, ponesimod), home-administered B-cell therapies (ofatumumab), novel fumarate formulations (monomethyl fumarate), and optimized monoclonal antibodies (ublituximab) represent significant therapeutic advancements. This review provides clinicians and researchers with comprehensive, structured insights into these novel pharmacotherapies, highlighting their clinical efficacy, dosing considerations, and safety profiles, thereby facilitating informed clinical decision-making and promoting precision medicine in neurology.

Keywords: Neurology, Pharmacotherapy, Alzheimer's Disease, Parkinson's Disease, Multiple Sclerosis

INTRODUCTION

Neurological diseases constitute a major global health challenge due to their high prevalence, disability burden, and limited therapeutic options historically available (1). Until recently, many neurological conditions lacked targeted treatments, relying heavily on supportive and symptomatic care. However, the rapid evolution of neuropharmacology and precision medicine in the recent years has transformed therapeutic approaches significantly, providing clinicians and patients with a spectrum of new medications that alter disease courses, reduce symptom burden, and enhance quality of life (2,3).

Each section provides detailed descriptions of newly approved drugs, their mechanisms of action, clinical efficacy based on pivotal trials, recommended dosing regimens, routes of administration, and critical safety considerations. Organized tables accompany the text to facilitate concise comparisons and practical application. Furthermore, the review emphasizes emerging trends in precision medicine, particularly the increased use of targeted monoclonal antibodies, antisense oligonucleotides, and transformative gene therapies.

By synthesizing comprehensive and systematically structured evidence on emerging pharmacotherapies, this narrative review, grounded in PubMed and FDA/EMA database analyses, seeks to provide neurologists, clinicians, researchers, and healthcare professionals with an up-to-date overview of current therapeutic options and their translational relevance to clinical practice.

METHODS

This narrative review was conducted through a structured literature search of the PubMed, FDA, and EMA databases covering publications and regulatory

Table 1. Key Recent Drug Approvals in Alzheimer's Disease (2020–2024)

Drug (Brand)	Year	Indication	Mechanism	Key Efficacy Results	Dosing	Major Side Effects	Clinical Importance
Aducanumab (Aduhelm)	2021	Early Alzheimer's (MCI/mild)	Anti-amyloid antibody	Modest slowing of cognitive decline (controversial)	IV every 4 weeks	ARIA (edema, bleeding), headache	First amyloid-clearing therapy
Lecanemab (Leqembi)	2023	Early Alzheimer's (MCI/mild)	Anti-amyloid antibody	~27% slower cognitive decline	IV every 2 weeks	ARIA, infusion reactions, headache	Proven clinical benefit, slows AD progression
Donepezil (Adlarity patch)	2022	Mild–severe Alzheimer's	Acetylcholinesterase inhibitor	Equivalent efficacy to oral form	Weekly transdermal patch	Skin irritation, less GI upset	Improved compliance and tolerability

approvals between January 2020 and June 2025. The search combined keywords including neurology, pharmacotherapy, Alzheimer's disease, Parkinson's disease, multiple sclerosis, novel drug approval, monoclonal antibody, and gene therapy. Priority was given to peer-reviewed clinical trials, meta-analyses, and regulatory summaries describing newly approved or late-phase pharmacological agents. Reference lists of relevant articles were also screened to identify additional studies. Data were synthesized qualitatively to highlight mechanisms of action, efficacy outcomes, dosing, and safety profiles of recent therapeutic advances in neurology.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) saw the first disease-modifying therapies reach clinical use in 2021–2023. Aducanumab was approved in 2021 for early AD (mild cognitive impairment or mild dementia stage) (4,5). It is a monoclonal antibody targeting aggregated beta-amyloid, designed to clear amyloid plaques from the brain. In clinical trials, a high dose of aducanumab modestly slowed cognitive decline in one Phase III study, though a parallel study was negative (4,5). The FDA granted approval based on the surrogate outcome of plaque reduction (6). Aducanumab is administered via intravenous infusion every four weeks. Major side effects include amyloid-related imaging abnormalities (ARIA), such as cerebral edema or microhemorrhages seen on MRI in about one-third of patients (often asymptomatic, but occasionally causing headache or confusion) (7). Despite controversy over its unclear clinical benefit, aducanumab's approval was significant as the first therapy aimed at AD's underlying pathology (4-7) (Table 1).

Lecanemab (Leqembi), approved in 2023, is another anti-amyloid monoclonal antibody for early-stage AD (8). Lecanemab binds soluble amyloid protofibrils, facilitating clearance of amyloid. In the Phase III CLARITY-AD trial, lecanemab treatment led to a statistically significant slowing of cognitive and functional decline (approximately 25–30% less decline on a clinical dementia rating scale at 18 months compared to placebo) (9). This provided the first clear evidence of clinical benefit with amyloid removal. Lecanemab is given by IV infusion every two weeks. Its safety profile also features ARIA (incidence ~12% for edema, higher in APOE4 gene carriers), plus infusion-related reactions (10). While ARIA requires monitoring, most cases are mild (10). Lecanemab's approval (first under accelerated status, then full approval) marked a milestone as a therapy that both reduces amyloid burden and demonstrates a measurable, albeit modest, clinical benefit in AD (8-10).

In addition, a new formulation of an existing AD drug was introduced during this period. Donepezil transdermal patch (Adlarity) was approved in 2022 for mild to severe AD dementia (11,12). This once-weekly patch provides continuous delivery of the acetylcholinesterase inhibitor donepezil. It offers similar cognitive symptomatic benefits as oral donepezil but with improved adherence (weekly dosing) and reduced gastrointestinal side effects (since the transdermal route avoids high peak oral dosing). The most common adverse effects of the patch are application-site reactions and mild cholinergic effects. This formulation provides an alternative option for patients who have difficulty with daily oral medications (12).

PARKINSON'S DISEASE

While no cures emerged, new therapies addressed motor fluctuations in Parkinson's disease (PD) between 2020 and 2024. Opicapone (Ongentys), approved in 2020, is an add-on therapy for PD patients experiencing "off" episodes while on levodopa (13). Opicapone is a catechol-O-methyltransferase (COMT) inhibitor that prevents peripheral breakdown of levodopa, thereby increasing levodopa's availability to the brain. In clinical trials, opicapone (25–50 mg once daily) significantly reduced daily "off" time and increased "on" time (periods of good motor control) by about 1 hour on average, comparable to the older COMT inhibitor entacapone (13). Unlike entacapone, which must be taken with each levodopa dose, opicapone's long duration allows for once-daily dosing. Its side effect profile mainly reflects enhanced levodopa effects: dyskinesias (involuntary

Table 2. Key Recent Drug Approvals in Alzheimer's Disease (2020–2024)

Drug (Brand)	Year	Indication in PD	Mechanism	Key Results	Dosing	Major Side Effects	Clinical Importance
Opicapone (**Ongentys**)	2020	Add-on for levodopa "off" episodes	COMT inhibitor	~1 hour less daily "off" time	Oral, once daily at bedtime	Dyskinesia, insomnia, constipation, hypotension	Simplifies dosing, improves levodopa effectiveness
Apomorphine sublingual film (**Kynmobi**)	2020	Acute treatment of "off" episodes	Dopamine agonist	Rapid symptom relief within ~15 min	Sublingual, as needed (up to 5× daily)	Nausea, oral irritation, hypotension, sedation	Non-injectable, rapid rescue from sudden "off" episodes

COMT: catechol-O-methyltransferase

movements) were the most common adverse effect as higher levodopa levels can cause them. Other side effects include insomnia, constipation, low blood pressure, and vivid dreams. Opicapone's once-daily dosing and potent COMT inhibition offer a convenient way to manage motor fluctuations in advanced PD (13,14).

Apomorphine sublingual film (Kynmobi) was approved in 2020 as an acute rescue therapy for intermittent "off" episodes in PD (15) (**Table 2**). Apomorphine is a fast-acting dopamine agonist that can rapidly alleviate Parkinsonian symptoms when oral medications have temporarily lost effect. Previously available as a subcutaneous injection (Apokyn), apomorphine was often underused due to injection burden (15,16). The sublingual film formulation allows patients to place a strip under the tongue at the start of an off episode. In Phase III trials, sublingual apomorphine produced a clinically meaningful improvement in motor function within 15–30 minutes, with significantly more patients converting from an "off" state to an "on" state (improved mobility) compared to placebo (17). Doses are titrated (10–30 mg) based on effect, and up to 5 doses per day may be used as needed. Side effects are notable: nausea and vomiting can be prominent (antiemetic pre-treatment is recommended, though 5-HT3 antagonist antiemetics are contraindicated due to severe hypotension risk). Other common adverse effects include dizziness, orthostatic hypotension, oral mucosal irritation or ulceration (from the film), somnolence, and potential hallucinations. In clinical studies a substantial proportion of patients discontinued due to side effects like nausea or mouth irritation. Despite these challenges, the sublingual film provides a non-invasive, rapid-onset option to rescue patients from disabling off off episodes states, improving daily functioning and independence (17).

MULTIPLE SCLEROSIS

Several innovative disease-modifying therapies for multiple sclerosis (MS) were introduced in 2020–2024, expanding treatment options for relapsing forms of MS. Ozanimod (Zeposia), approved in 2020, is an oral sphingosine-1-phosphate (S1P) receptor modulator (18) (**Table 3**). It selectively binds S1P_1 and S1P_5 receptors, trapping lymphocytes in lymph nodes and preventing them from entering the CNS to cause inflammation. In Phase III trials (SUNBEAM and RADIANCE), ozanimod significantly lowered the annualized relapse rate and reduced new brain MRI lesions compared to interferon beta-1a (19). For example, the high-dose ozanimod group had an ARR of ~0.18 per year versus ~0.35 on interferon, nearly a 50% reduction. Ozanimod is taken once daily orally. Its safety profile is similar to fingolimod but with greater selectivity: most common side effects are nasopharyngitis, headache, elevated liver

Table 3. New Multiple Sclerosis Drugs (2020–2024)

Drug (Brand)	Year	Indication	Mechanism	Key Outcomes	Dosing	Side Effects	Clinical Importance
Ozanimod (**Zeposia**)	2020	Relapsing MS	S1P receptor modulator	~45% relapse reduction, fewer MRI lesions	Oral once daily	Headache, elevated liver enzymes, bradycardia, infection risk	Oral convenience with high efficacy, improved safety over older S1P agents
Ponesimod (**Ponvory**)	2021	Relapsing MS	$S1P_1$ receptor modulator	~30–35% relapse reduction vs teriflunomide	Oral once daily (14-day titration)	Bradycardia, hypertension, infections	Short half-life allows quick reversal if therapy interrupted
Ofatumumab (**Kesimpta**)	2020	Relapsing MS	Anti-CD20 (B-cell depletion)	~50% relapse reduction, ~90% fewer new MRI lesions	Monthly subcutaneous injection	Injection reactions, flu-like symptoms, infections	First at-home injectable anti-CD20 therapy
Monomethyl fumarate (**Bafiertam**)	2020	Relapsing MS	Nrf2 pathway activator (fumarate)	Similar efficacy as dimethyl fumarate (50% relapse reduction)	Oral capsule twice daily	Flushing, GI upset, lymphopenia, rare PML risk	Potentially improved GI tolerability compared to dimethyl fumarate
Ublituximab (**Briumvi**)	2022	Relapsing MS	Anti-CD20 antibody	~60% relapse reduction, ≥90% fewer MRI lesions	IV infusion every 24 weeks	Infusion reactions, infections, rare serious infections	Short infusion duration, extended dosing interval; potent B-cell therapy

MS, Multiple Sclerosis; S1P, Sphingosine-1-phosphate; $S1P_1$, Sphingosine-1-phosphate receptor subtype 1; CD20, Cluster of Differentiation 20; Nrf2, Nuclear factor erythroid 2–related factor 2; GI, Gastrointestinal; PML, Progressive Multifocal Leukoencephalopathy; IV , Intravenous; ARR, Annualized Relapse Rate.

enzymes, and mild first-dose bradycardia (thus a dose-escalation starter pack is used). It has no required genetic testing. Ozanimod offers a convenient oral alternative for relapsing MS with efficacy comparable to injectables (19,20).

Ponesimod (Ponvory), approved in 2021, is another oral S1P_1 receptor modulator for relapsing MS (21). In the head-to-head Phase III OPTIMUM trial against teriflunomide, ponesimod showed superior efficacy: about a one-third lower relapse rate (ARR ~0.19 vs 0.29) and significant reductions in MRI lesion activity (22). Ponesimod is taken once daily, with a 14-day titration at initiation. A distinguishing feature is its relatively short half-life (~33 hours), if therapy is stopped, immune effects wear off within a week, allowing quicker lymphocyte recovery than fingolimod. This can be advantageous if therapy must be interrupted (e.g. for infection or pregnancy). Side effects of ponesimod include dose-dependent transient bradycardia (on first doses), hypertension, elevated liver enzymes, and other S1P-class effects like macular edema and respiratory slight declines (22,23). The option to rapidly eliminate the drug makes ponesimod an appealing choice for some patients concerned about reversibility of immune suppression.

Ofatumumab (Kesimpta) was approved in 2020 as the first B-cell therapy for relapsing MS that patients can self-administer at home (24,25). Ofatumumab is a fully human monoclonal antibody targeting CD20 on B-lymphocytes, similar to ocrelizumab, but delivered via subcutaneous injection rather than IV infusion. In the Phase III ASCLEPIOS I and II trials, monthly ofatumumab injections were superior to oral teriflunomide: annual relapse rates were reduced by ~50% (ARR ~0.1 vs 0.2), and ofatumumab significantly slowed disability progression and cut MRI lesion counts. Dosing is 20 mg subcutaneously; after initial loading doses at weeks 0, 1, and 2, it's given monthly (26). The safety profile showed mostly mild injection-related reactions (local redness, flu-like symptoms) and a risk of infections (e.g. upper respiratory infections) due to B-cell depletion, comparable to other anti-CD20 therapies. Unlike IV therapies, there were no infusion reactions and no requirement for premedication. Ofatumumab's key value is offering highly effective B-cell–mediated suppression of MS disease activity in a convenient at-home injection, lowering barriers to accessing potent therapy (24-26).

Monomethyl fumarate (Bafiertam) gained approval in 2020 as a novel fumarate formulation for relapsing MS. Bafiertam contains the active metabolite of dimethyl fumarate (Tecfidera) (27). It activates the Nrf2 pathway to reduce neuroinflammation and oxidative stress. Bafiertam was approved via demonstration of bioequivalence to dimethyl fumarate, and thus yields similar efficacy in reducing relapses and delaying progression. The advantage is in tolerability: Bafiertam uses a lower starting dose and may cause fewer gastrointestinal side effects (nausea, diarrhea) and vasodilatory effect-flushing, since it delivers the active metabolite directly, potentially reducing GI irritation from intermediate metabolites. The dosing is 95 mg capsules, two twice daily (after a one-week half-dose starter) (28). Side effects mirror Tecfidera overall: flushing, GI upset, decreased lymphocyte counts, and rare serious risks like PML (progressive multifocal leukoencephalopathy) in severely immunosuppressed patients. Bafiertam's introduction provided patients another oral fumarate option, with hopes of improved GI tolerability while maintaining the known benefits of this mechanism (28).

Ublituximab (Briumvi), approved in 2022, is a monoclonal antibody against CD20 for relapsing MS (29). Like ocrelizumab and ofatumumab, ublituximab depletes B-cells, but it is engineered (glycooptimized) to enhance antibody-dependent cytotoxicity (29,30). In the ULTIMATE I & II Phase III trials, ublituximab (given every 6 months IV) was superior to teriflunomide, cutting annual relapses by ~60% (ARR ~0.08 on ublituximab vs 0.19 on teriflunomide) and markedly reducing new MRI lesion formation (31). Notably, over 40% of ublituximab-treated patients had no evidence of disease activity. The dosing begins with an infusion split over day 1 and 15, then one infusion every 24 weeks. Infusion time can be as short as one hour after the first dose, making it a relatively quick administration. Adverse effects include infusion reactions (premedication is used to mitigate these), mild infections (nasopharyngitis, etc.), and laboratory abnormalities like low immunoglobulins with prolonged therapy. Overall safety and efficacy are in line with other B-cell therapies (31,32). Ublituximab's approval gives another high-efficacy option, and its shorter infusion duration and potential for flexible dosing schedules provide practical advantages in MS care.

LIMITATIONS

This comprehensive review has several limitations, including its focus on neurological medications approved specifically between 2020 and 2025, thus excluding earlier foundational treatments and therapies still under investigation. Additionally, regulatory approval status may vary across different regions (e.g., FDA versus EMA), limiting the global applicability of certain treatments. Given the rapidly evolving nature of neurological therapeutics, emerging developments after the preparation of this manuscript might not be included. Furthermore, due to the recent approval of many therapies, particularly gene therapies and biologics, long-term safety and efficacy data remain limited. Lastly, potential publication bias favoring positive trial outcomes may have influenced the overall interpretation

of clinical benefits. Readers should therefore interpret the summarized evidence in light of ongoing research and emerging clinical data.

CONCLUSION

The period from 2020 to 2025 has marked a remarkable advancement in the pharmacological management of neurological diseases, significantly expanding therapeutic options across Alzheimer's disease, Parkinson's disease, and multiple sclerosis. The introduction of novel targeted therapies, including disease-modifying antibodies, innovative small molecules, and optimized biologics, has shifted the therapeutic paradigm toward more precise, mechanism-based interventions.

While antisense oligonucleotides and gene therapies represent promising and rapidly advancing frontiers in neurotherapeutics, they remain emerging research areas and were therefore not discussed in detail in this review. As clinical experience with these modalities grows, future evidence is expected to clarify their long-term safety, efficacy, and applicability across different neurological disorders.

Ongoing research, vigilant post-marketing surveillance, and efforts to ensure equitable access to these innovative treatments will be essential to fully realize their potential and sustain the current momentum toward precision medicine in neurology.

DECLARATIONS

Ethics Approval and Consent to Participate: Not applicable. This manuscript is a literature review; no human or animal studies were performed.

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Availability of Data and Materials: Not applicable. This review utilized previously published data and publicly available information.

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Case Report

Euglycemic Ketoacidosis in a Patient with Prolonged Malnutrition Syndrome

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Abstract

We present the case of a 53-year-old woman admitted to the emergency department for vomiting and abdominal pain, ultimately diagnosed with euglycemic ketoacidosis. The patient had a history of severe malnutrition associated with depressive disorder, with almost exclusive fruit intake for at least 2 months. Evaluation revealed high anion gap metabolic acidosis, significant ketonemia, but normal blood glucose levels. Exogenous intoxication and diabetes mellitus were excluded. Fluid resuscitation and bicarbonate led to clinical and laboratory improvement. This case highlights the importance of considering malnutrition as a cause of ketosis and metabolic acidosis.

Keywords: Diabetic Ketoacidosis, Ketosis, Malnutrition, Acidosis, Metabolic, Malnutrition/complications, Anorexia

INTRODUCTION

Euglycemic ketoacidosis (EKA) is a rare subtype of high anion gap metabolic acidosis, characterized by elevated serum ketones in the absence of significant hyperglycaemia (blood glucose <250 mg/dL) [1]. Although frequently associated with sodium-glucose co-transporter 2 inhibitors (iSGLT2) [2], EKA may also arise in the context of prolonged fasting, malnutrition, pregnancy, alcoholism, or acute illness [3,4].

The pathophysiology of EKA involves reduced insulin activity and increased counter-regulatory hormones, leading to enhanced lipolysis and hepatic ketogenesis [1]. In malnourished individuals, depleted glycogen reserves and impaired gluconeogenesis may exacerbate ketosis and acid-base imbalance [4]. Because hyperglycaemia is absent, EKA may be misdiagnosed or delayed, hindering appropriate treatment.

We describe a case of EKA in a non-diabetic patient with severe dietary restriction due to depressive illness, highlighting the need to consider nutritional status when evaluating metabolic acidosis.

CASE

We present the case of a 53-year-old woman, previously independent in her activities of daily living, with a history of adjustment disorder with depressive features, thyroid nodules (with normal thyroid function), and breast nodules under surveillance. She had no known history of diabetes mellitus. Her regular medications included esomeprazole, atorvastatin, sertraline, trazodone, as-needed ethyl loflazepate, an oral contraceptive, and occasional paracetamol, which she denied having taken recently. The patient reported no regular alcohol consumption, smoking, or illicit drug use. She described a restrictive diet over the past five months, predominantly fruit-based, resulting in significant weight loss (~15 kg - BMI 22.4 kg/m^2 when admitted to the floor), in the context of anorexia linked to a depressive episode triggered by her partner's prolonged hospital admission. She presented in the emergency department with lower abdominal pain, nausea, and recurrent postprandial vomiting, accompanied by complete oral intolerance, beginning the previous day. She also reported a single episode of low-grade fever and altered bowel habits with soft stools, without other associated symptoms.

Table 1. Arterial blood gas and biochemical results indicating severe high–anion gap metabolic acidosis consistent with ketoacidosis.

Test	Reference Range	Patient Value
Arterial Blood Gas (ABG)		
pH	7.35 – 7.45	7.066
pCO_2 (mmHg)	35 – 45	12.6
HCO_3^- (mEq/L)	22 – 26	3.6
Anion Gap (mEq/L)	16 ± 4	27
Lactate (mmol/L)	0.5 – 2.5	0.3
K^+ (mEq/L)	3.5 – 5.3	5.4
Biochemistry		
Glucose (mg/dL)	<140	109
Creatinine (mg/dL)	<1.1	0.99
BUN (mg/dL)	6 – 20	25.43
iPhosphate (mg/dL)	2.5 – 4.5	1.8
AST (U/L)	<40	57
Additional Tests		
Ketonemia (mmol/L) (POCT)	<0.6	>3

ABG, Arterial Blood Gas, pCO_2; Partial pressure of carbon dioxide, HCO_3^-; Bicarbonate, K^+; Potassium, BUN; Blood Urea Nitrogen, iPhosphate; Inorganic Phosphate, AST Aspartate Aminotransferase, POCT; Point-of-Care Testing.

On examination, she was conscious, cooperative, and oriented, with no neurological deficits but clinical signs of dehydration. She was afebrile (36.2 ºC), normotensive (BP 118/82 mmHg), in sinus rhythm (HR 90 bpm), eupnoeic, and maintaining an oxygen saturation of 99% on room air. Abdominal examination revealed generalized tenderness without peritoneal signs.

Laboratory investigations showed a blood glucose level of 109 mg/dL, ketonemia >3 mmol/L (point-of-care testing taken hours after admission, once the possibility of de differential diagnosis of ketoacidosis, the initial value is supposed to be significantly higher), and urinary ketones of 150 mg/dL. Arterial blood gas analysis revealed severe metabolic acidosis with an increased anion gap: pH 7.066, HCO_3^- 3.6 mmol/L, pCO_2 12.6 mmHg, calculated anion gap of 27. There was no lactic acidosis (lactate 0.3 mmol/L). Renal function was preserved (creatinine 0.99 mg/dL), although blood urea nitrogen (BUN) was elevated at approximately 19.3 mg/dL (urea 54.5 mg/dL). She also had hypophosphatemia (1.8 mg/dL), mildly elevated potassium (5.4 mmol/L), and liver function tests were unremarkable, except for a mild increase in AST (57 U/L). Toxicology screening revealed negative levels for paracetamol and ethanol. Methanol and ethylene glycol were not measured due to a lack of clinical suspicion. Full blood count showed leucocytosis with neutrophilia (13.200/µL [normal range 4.000-11.000/µL]) and a haemoglobin level of 13.7 g/dL (normal range for adult females between 12.1-15.1g/dL). **Table 1** presents all relevant lab results, and **Figure 1** demonstrates the evolution of arterial blood gas parameters throughout our approach.

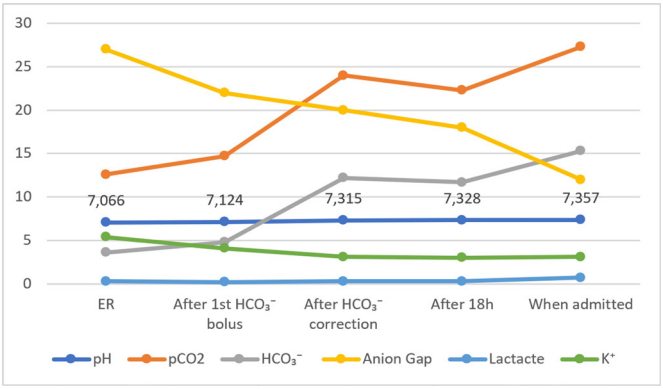

Figure 1. Evolution of arterial blood gas parameters

MANAGEMENT AND OUTCOME

Given the combination of significant ketonemia, severe metabolic acidosis with increased anion gap, and normoglycemia, a diagnosis of euglycemic ketoacidosis in the context of prolonged malnutrition was established. Treatment was initiated with intravenous solution 8.4% sodium bicarbonate (a total of 300 mL) to tamper the initial acidosis detected alongside targeted electrolyte correction (mild hyperkalemia [5.4 mmol/L] with no electrophisiologic repercussions, treated with inhaled salbutamol (2.5 mg nebulized every 4 hours) and intravenous insulin (2 units/hour) in 5% dextrose in normal saline to shift potassium intracellularly while preventing hypoglycemia. Potassium levels were monitored every 6 hours, and treatment was adjusted accordingly. Hypophosphatemia (1.8 mg/dL) detected in a second moment is a hallmark of refeeding syndrome and was .promptly corrected with intravenous potassium phosphate (0.08-0.16 mmol/kg infused over 6 hours). Phosphate levels were monitored every 6 hours during refeeding, with adjustments made to maintain levels above 2.5 mg/dL and prevent complications of severe hypophosphatemia, such as cardiac arrhythmias or respiratory failure, concomitantly with initiation of nutritional support. The patient was monitored by the Nutrition team that adjusted dietary supplements and diet troughout her stay. A psychiatric evaluation was requested to assess her psychopathologic state. Given the patient's history of adjustment disorder with depressive features and restrictive eating habits, the psychiatric evaluation focused on identifying potential underlying mood disorders or eating disorders that contributed to her malnutrition. The evaluation suggested IRSS as well as inclusion in a psychotherapy session for both grief support and eating disorders, recognizing that addressing these psychological factors is crucial for preventing relapse and promoting long-term recovery. Her symptoms improved within the first 18 hours, allowing the introduction of a light oral diet. She was discharged following metabolic stabilization, with referral for multidisciplinary follow-up in Nutrition and Psychiatry outpatient clinics.

DISCUSSION

Euglycemic ketoacidosis (EKA) is a rare and frequently underdiagnosed clinical entity, characterized by metabolic acidosis with increased anion gap, ketonemia or ketonuria, and normoglycemia (glucose <250 mg/dL) (1). While it is typically associated with sodium-glucose co-transporter 2 inhibitors (iSGLT2), it can also occur in prolonged fasting, malnutrition, alcoholism, pregnancy, or other catabolic states (2-5). Table 2 shows the causes for metabolic acidosis with elevated anion gap and Table 3 proposes a mnemonic for those causes.

In this case, the absence of diabetes or iSGLT2 suggests that EKA was not related to DM. The pathophysiology is similar to starvation ketoacidosis, where glucose restriction leads to increased lipolysis and hepatic ketogenesis, along with depletion of endogenous insulin (4). Normal glycaemia may delay recognition of the underlying acid-base disorder. In chronically malnourished individuals, reduced hepatic glycogen stores and hormonal imbalances can exacerbate the risk of ketosis (4).

The differential diagnosis of high anion gap metabolic acidosis includes potentially life-threatening causes such as toxic ingestions (methanol, ethylene glycol, salicylates, paracetamol), lactic acidosis, and renal failure (5). In this case, the absence of exposure history, preserved renal function, and negative toxicology results rendered these less likely. Normal lactate levels and haemodynamic stability ruled out type A lactic acidosis (6).

Current literature supports a structured approach to high anion gap acidosis using integrated diagnostic algorithms. Key elements include clinical history, calculation of the anion (and osmolar) gap, and selective toxicology screening (7). Management focuses on halting ketogenesis and correcting fluid and electrolyte disturbances. Administration of glucose and bicarbonate in more severe cases is effective in resolving EKA, as observed in this patient (8). Refeeding syndrome is a serious metabolic complication that can occur in these cases. It is characterized by rapid shifts in fluids and electrolytes, particularly phosphate, potassium, and magnesium, due to increased insulin secretion triggered by carbohydrate intake. These changes can lead to cardiac, respiratory, and neurologic complications (9,10).

Prevention involves identifying at-risk individuals, initiating refeeding with a low caloric intake, and closely monitoring and correcting electrolyte imbalances, especially phosphate. Thiamine should be administered before starting nutritional support (11,12). Additionally, a brief psychiatric evaluation during hospitalization is advisable in malnourished patients, particularly those with eating disorders or psychosocial stressors, to support comprehensive and multidisciplinary care (13).

This case underlines the importance of considering EKA in patients with non-specific symptoms, normoglycemia, and metabolic acidosis-especially in the context of malnutrition, prolonged fasting, or catabolic states. Ongoing nutritional and psychiatric follow-up are essential to prevent recurrence and support recovery.

Table 2. Causes for Metabolic acidosis with elevated Anion Gap

Mechanism	Elevated Anion Gap
Increase production	Lactic acidosis (and D-Lactic acidosis – produced by intestinal flora)
	Ketoacidosis
	Diabetes mellitus
	Malnutrion
	Alcohol (acute poisoning)
	Ingestion
	Methanol
	Ethylene glycol and diethylene glycol (antifreeze)
	Salicylates
	Toluene (only when impaired renal function)
	Propyleneglycol (perfumes)
	Pyroglutamic acid (5-oxoproline) (acetaminophen metabolite)
Diminished renal excretion	Severe renal insufficiency (eGFR <15 to 20 mL/min/1.73 m^2)

Table 3. Causes for Metabolic acidosis with elevated Anion Gap

	Toxin/Clinical disorder	Accumulated acids
G	Glycols (Ethylene glycol, diethylene glycol, and propylene glycol)	Multiple organic and inorganic acids
O	Oxyproline (associated with chronic acetaminophen use)	5-oxyproline (or Pyroglutamic acid)
L	Lactic acid	Lactic acid
D	D-Lactic acid	D-Lactic acid
M	Methanol	Formic acid
A	Aspirin	Multiple organic acids
R	Renal Failure (uraemia)	Multiple organic and inorganic acids
K	Ketoacidosis	β-hydroxybutyric acid and acetoacetic acid

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Case Report

Dandy Walker Malformation in a Patient Presenting with Hyponatremia

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Abstract

Hyponatremia is defined as a serum sodium concentration of less than 135 mmol/L and is a common electrolyte abnormality. The most common causes of hyponatremia following central nervous system disorders are syndrome of inappropriate antidiuretic hormone secretion (SIADH) and cerebral salt wasting (CSW). In this case report, we discuss the diagnosis and treatment of CSW in a 30-year-old male patient with recurrent episodes of hyponatremia, in the context of the literature. CSW develops after central nervous system disorders and is characterized by hypovolemia, low serum osmolality, high urine osmolality, and high urine sodium levels.

Keywords: Dandy-Walker Syndrome, Hyponatremia, Kidney Diseases

INTRODUCTION

Dandy-Walker syndrome, or Dandy-Walker malformation, is a developmental anomaly characterized by an enlarged posterior fossa, cystic enlargement of the fourth ventricle, hypoplasia, and upward rotation of the cerebellar vermis. Affected individuals may experience psychomotor retardation, ataxia, apnea episodes, muscle weakness, occasional muscle spasms, seizures, nystagmus, and macrocephaly (1). The most common central nervous system anomalies associated with Dandy-Walker syndrome include ventriculomegaly, agenesis of the corpus callosum, holoprosencephaly, and encephalocele. Common extracranial anomalies include congenital heart disease, polycystic kidneys, and facial clefts. Less frequently observed anomalies include limb and abdominal wall abnormalities, diaphragmatic hernia, ambiguous genitalia, and fetal growth restriction (2).

Hyponatremia, defined as a serum concentration of less than 135 mmol/L, is most commonly caused by SIADH and CSW in patients with central nervous system disorders. The most commonly reported trigger for CSW is aneurysmal subarachnoid hemorrhage. Conditions leading to SIADH and CSW include head trauma, intracranial or metastatic neoplasms, carcinomatosis or infectious meningitis, subarachnoid hemorrhage, and central nervous system surgery (3). However, in rare congenital CNS malformations such as Dandy-Walker syndrome, CSW may also develop due to altered hypothalamic and autonomic regulation of sodium and water balance.

CASE

A 30-year-old male patient was admitted to a district hospital with complaints of fatigue and was diagnosed with hyponatremia (sodium 123 mmol/L). After receiving treatment, he was discharged. The patient was referred to our clinic due to recurrent hyponatremia. His past medical history was unremarkable (a ventriculoperitoneal shunt had been proposed in childhood but was not performed), and he was married with two children. His brother had a shunt placed, but they were unaware of the diagnosis.

The patient's complaints included fatigue and intermittent seizures for the past 15 days, occurring once or twice a day. Physical examination revealed a blood pressure of 110/70 mmHg, pulse rate of 78 bpm, clear

Table 1. Laboratory findings

Parameter	Reference Range	Admission	Post-treatment
Serum Sodium (mmol/L)	135–145	125	135
Serum Potassium (mmol/L)	3.5–5.0	4.5	4.3
Serum Uric Acid (mg/dL)	3.4–7.0	3.6	4.2
Urine Sodium (mmol/L)	<20 (low volume)	114	58
Urine Osmolality (mOsm/kg)	300–900	High	Normal
Serum Osmolality (mOsm/kg)	275–295	Low	Normal

lung sounds, and no pretibial edema.

Laboratory results showed a serum sodium level of 125 mmol/L, potassium 4.5 mmol/L, glucose 134 mg/dL, uric acid 3.6 mg/dL, urine density 1025, and urine sodium 114 mmol/L. The presence of high urine sodium and osmolality with low serum osmolality suggested hypovolemic hyponatremia consistent with CSW. Brain natriuretic protein (BNP) was 11.2 ng/ml, renin and aldosterone levels were within normal limits, and antidiuretic hormone level was 6.4 pmol/L.

Brain CT showed marked dilation of the ventricular system. The septum pellucidum and corpus callosum were absent. The patient was diagnosed with Dandy-Walker syndrome. A neurology consultation was requested due to epileptic seizures, and the patient was started on levetiracetam. After treatment, no further seizures occurred. Neurosurgery confirmed Dandy-Walker syndrome but did not recommend surgery. Cardiology consultation revealed an ejection fraction of 60% and mild tricuspid insufficiency.

The patient received hydration, which normalized the serum sodium level. Improvement following isotonic saline therapy supported the diagnosis of CSW rather than SIADH. Due to frequent recurrence, sodium chloride tablets were recommended but unavailable; therefore, fludrocortisone 0.1 mg twice daily was initiated. On follow-up, serum sodium levels were found to be 135 mmol/L, and the patient remained asymptomatic under outpatient monitoring.

DISCUSSION

Hyponatremia is the most common electrolyte disorder, affecting approximately 5% of adults and up to 20% of individuals over 65. The onset of symptoms is closely related to the rate of sodium decline and is categorized as mild (130–135 mmol/L), moderate (125–129 mmol/L), or severe (<125 mmol/L). Symptoms range from mild, nonspecific complaints to life-threatening cerebral edema (4–6).

CSW is characterized by renal loss of sodium and water in the setting of normal kidney function, leading to extracellular volume depletion. The exact pathophysiology remains unclear; elevated BNP and atrial natriuretic peptide levels are frequently implicated in promoting natriuresis.

Both CSW and SIADH manifest with low serum osmolality, high urine osmolality, and high urine sodium. However, CSW differs by the presence of clinical hypovolemia, hemoconcentration, and positive response to isotonic saline, whereas SIADH patients remain euvolemic or hypervolemic and may worsen with fluid administration (7–10).

In Dandy-Walker malformation, hydrocephalus and hypothalamic dysfunction may contribute to dysregulated sodium handling, occasionally triggering CSW. Previous studies have described similar cases linking Dandy-Walker malformation and hyponatremia secondary to cerebral salt wasting (11–13).

Fludrocortisone acts by enhancing renal sodium reabsorption and plasma volume expansion. Recent trials (e.g., FLUSH SALT 2023) have shown improved sodium stabilization and reduced recurrence in neurocritical CSW patients treated with fludrocortisone (9).

CONCLUSION

In central nervous system disorders, the most common causes of hyponatremia are SIADH and CSW. Differentiating between them is challenging, but a favorable response to isotonic saline and evidence of hypovolemia strongly support CSW. In our case, a young patient presenting with hyponatremia was diagnosed with CSW related to Dandy-Walker syndrome. After treatment with fludrocortisone, no further hyponatremic episodes occurred. This case emphasizes the importance of evaluating sodium balance disturbances in congenital CNS malformations and considering CSW in the differential diagnosis.

DECLARATIONS

Ethics Approval and Consent to Participate: Not applicable.

Consent for Publication: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Availability of Data and Materials: Not applicable.

Competing Interests: The authors declare that they have no competing interests relevant to this manuscript.

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Letter to Editor

Comment on "What's Missing in Diabetes Treatment? A Novel Agent, Finerenone?"

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To the Editor,

PThe review article by Öztürk et al., titled "What's Missing in Diabetes Treatment? A Novel Agent, Finerenone?", successfully summarizes the anti-inflammatory and antifibrotic effects of finerenone in diabetic kidney disease, particularly within the context of the FIDELIO-DKD and FIGARO-DKD trials (1). However, new clinical data published in 2025 further expand finerenone's therapeutic potential, emphasizing its important role in patients with non-diabetic heart failure.

In a post-hoc subgroup analysis of FINEARTS-HF Vaduganathan et al. evaluated the effects of finerenone in heart failure patients both with and without concomitant SGLT2 inhibitor use. Regardless of baseline SGLT2 inhibitor therapy, finerenone reduced cardiovascular death and heart failure events. This study showed that finerenone and SGLT2 inhibitors act via different mechanisms and may provide additive protection when used together (2).

Interestingly, in a study published in The Lancet, the FINEARTS-HF diabetes post-hoc analysis found that finerenone treatment reduced the incidence of new-onset diabetes by 24% compared with placebo in patients with heart failure. Notably, despite higher SGLT2 inhibitor use in the placebo group, diabetes incidence was lower in the finerenone group. This suggests that the diabetes-preventive effect of finerenone is independent of SGLT2 inhibitor use. This unexpected metabolic benefit suggests that finerenone may play a potential role in diabetes prevention (3).

In diabetic kidney disease, finerenone has been shown to reduce albuminuria and progression to ESRD. However, findings from the CONFIDENCE trial, published in NEJM, are particularly striking (4). This randomized, double-blind clinical trial evaluated the effects of finerenone combined with empagliflozin in patients with type 2 diabetes and chronic kidney disease. Participants were randomized to finerenone, empagliflozin, or combination therapy. The combination achieved a significant reduction in urine albumin creatine ratio reaching 52% by day 180. Compared to finerenone alone, the combination achieved an additional 29% reduction, and compared to empagliflozin alone, an additional 32% reduction. This effect was observed as early as day 14 and reached 40% by day 90. Although albuminuria levels rebounded after treatment discontinuation, they remained below baseline. The combination of finerenone and empagliflozin was thus shown to reduce albuminuria more effectively than either agent alone, making it a valuable option for early and robust intervention in clinical practice.

Taken together, these studies highlight the evolving role of finerenone as not only a renoprotective agent but also as a pleiotropic drug providing cardiovascular and metabolic modulation. Integrating these findings into the original review would offer readers a more comprehensive and up-to-date perspective on finerenone's clinical benefits.

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