Turkish Journal of Diabetes and Obesity / *Türkiye Diyabet ve Obezite Dergisi*
Original Article / Özgün Araştırma

Assessment of the Effects of Metformin and DPP-4 Inhibitors on Electrolyte and Vitamin B12 Levels in Patients with Type 2 Diabetes: A Retrospective Study

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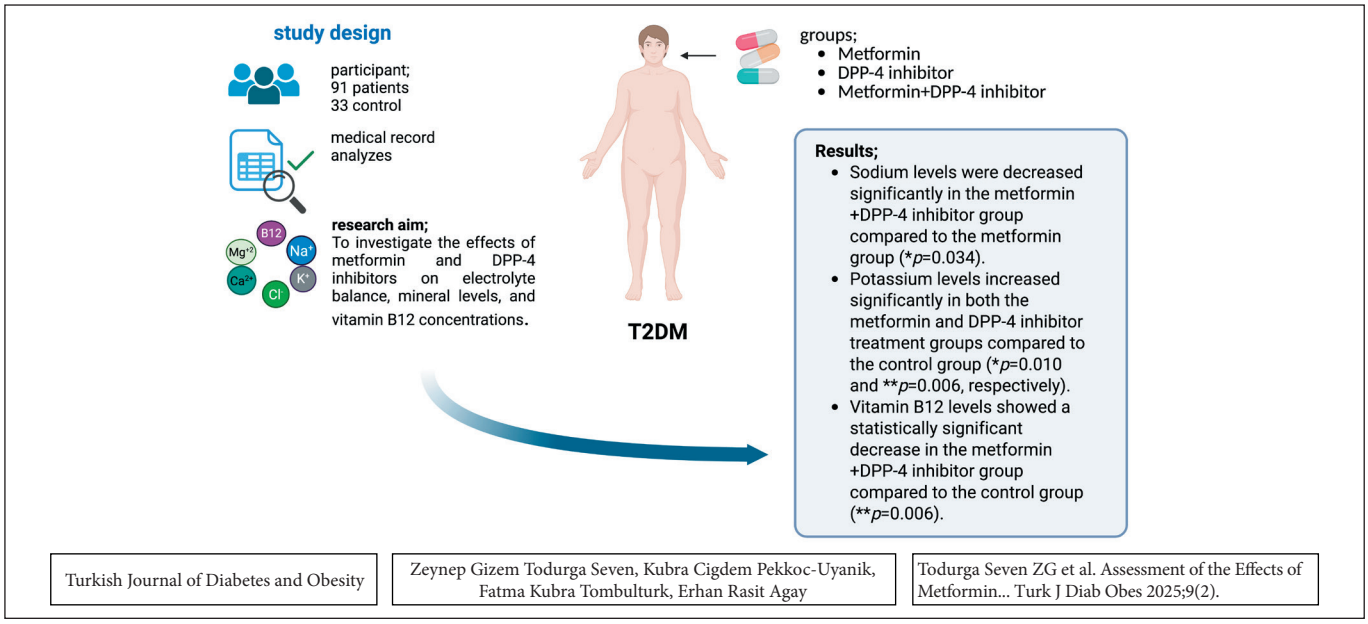
Cite this article as: Todurga Seven ZG et al. Assessment of the effects of metformin and DPP-4 inhibitors on electrolyte and vitamin B12 levels in patients with type 2 diabetes: A retrospective study. Turk J Diab Obes 2025; 9(2): 107-115.

GRAPHICAL ABSTRACT



ABSTRACT

Aim: Type 2 diabetes mellitus (T2DM) is commonly managed using metformin and DPP-4 inhibitors (vildagliptin, linagliptin) to improve glycemic control. However, their effects on electrolyte, mineral, and vitamin B12 levels remain unclear. The aim of this research was to evaluate the impact of metformin and DPP-4 inhibitors on electrolyte levels, as well as mineral and vitamin B12 levels.

Material and Methods: Electrolyte and mineral levels (including sodium, potassium, calcium, magnesium, and chloride), along with vitamin B12 concentrations, measured through standard laboratory methods in blood samples from T2DM patients receiving metformin and DPP-4 inhibitors, as well as healthy controls, were retrospectively obtained from medical records. The results were analyzed by comparing the control group with the treatment groups and the treatment groups with each other.

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DOI: 10.25048/tudod.1648392

Received / *Geliş tarihi* : 27.02.2025
Revision / *Revizyon tarihi* : 12.08.2025
Accepted / *Kabul tarihi* : 13.08.2025

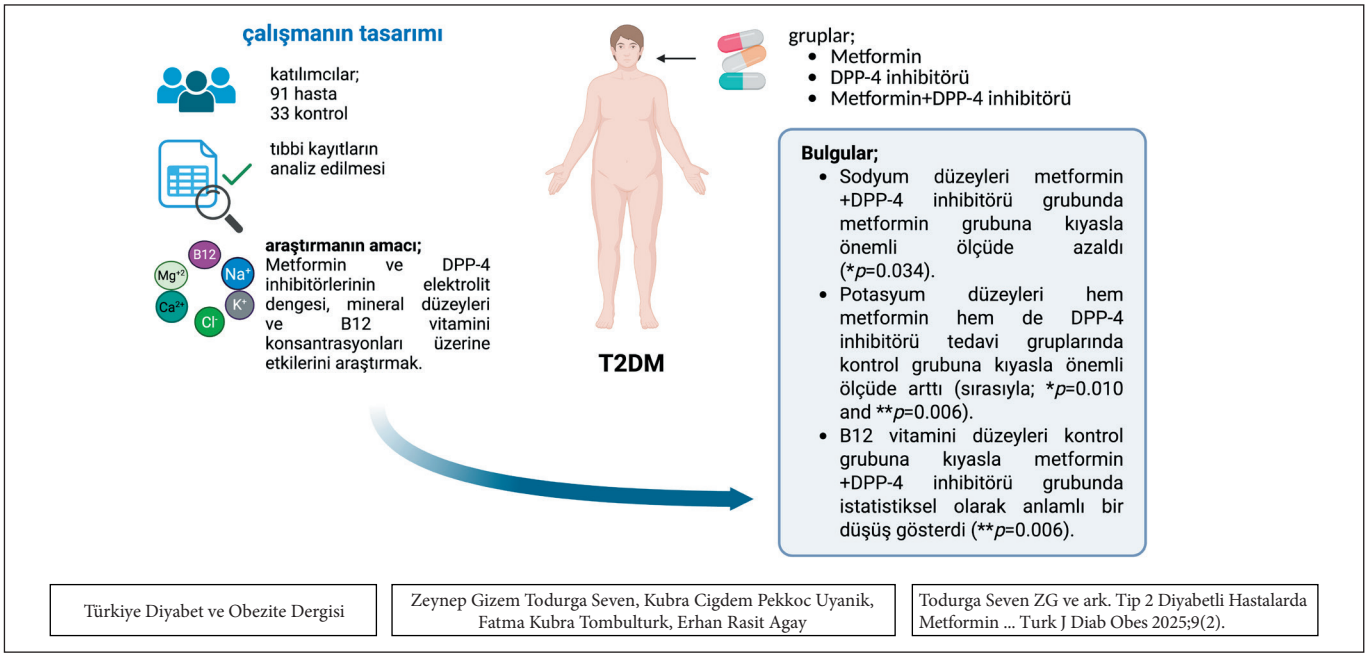
Results: Sodium levels were decreased significantly in the metformin+DPP-4 inhibitor group compared to the metformin group (p=0.034). Potassium concentrations were considerably elevated in both the metformin group and the DPP-4 inhibitor group than in the control group (p=0.010 and p=0.006, respectively). Vitamin B12 concentrations demonstrated a statistically significant reduction in the metformin+DPP-4 inhibitor group relative to the control group (p=0.006).

Conclusion: These findings highlight the potential impact of metformin and DPP-4 inhibitors on mineral and electrolyte homeostasis, emphasizing the importance of regular assessment of electrolyte levels and vitamin B12 status in individuals receiving these treatments.

Keywords: *T2DM, Metformin, DPP-4 inhibitor, Electrolyte, Vitamin B12*

Tip 2 Diyabetli Hastalarda Metformin ve DPP-4 İnhibitörlerinin Elektrolit ve Vitamin B12 Düzeyleri Üzerindeki Etkilerinin Değerlendirilmesi: Retrospektif Bir Çalışma

GRAFİKSEL ÖZET



ÖZ

Amaç: Tip 2 diabetes mellitus (T2DM) tedavisinde sık kullanılan metformin ve DPP-4 inhibitörleri (vildagliptin, linagliptin), glisemik kontrolü sağlamak için yaygın olarak kullanılmaktadır. Ancak, elektrolit, mineral dengesi ve B12 vitamini düzeyleri üzerindeki etkileri tam olarak bilinmemektedir. Bu çalışma, metformin ve DPP-4 inhibitörlerinin elektrolit dengesi, mineral düzeyleri ve B12 vitamini üzerindeki etkilerini incelemeyi amaçlamaktadır.

Gereç ve Yöntemler: Metformin ve DPP-4 inhibitörleri alan T2DM hastalarının ve sağlıklı katılımcıların standart laboratuvar teknikleriyle ölçülen kan örneklerindeki elektrolit/mineral (sodyum, potasyum, kalsiyum, magnezyum ve klorür) ve vitamin B12 seviyeleri geçmiş tıbbi kayıtlardan elde edildi. Sonuçlar, kontrol grubu ile tedavi grupları arasında ve tedavi grupları da kendi aralarında karşılaştırılarak analiz edildi.

Bulgular: Sodyum düzeyleri metformin grubuna kıyasla, metformin+DPP-4 inhibitörü grubunda belirgin şekilde azaldı (p=0.034). Potasyum düzeyleri kontrol grubuna kıyasla hem metformin hem de DPP-4 inhibitörü tedavi gruplarında belirgin şekilde arttı (sırasıyla p=0.010, p=0.006). Vitamin B12 düzeyleri kontrol grubuna kıyasla, metformin+DPP-4 inhibitörü grubunda istatistiksel açıdan önemli bir düşüş gösterdi (p=0.006).

Sonuç: Bu bulgular metformin ve DPP-4 inhibitörlerinin mineral ve elektrolit homeostazı üzerindeki potansiyel etkisini vurgulamakta ve bu tedavileri gören hastalarda elektrolit ve vitamin B12 düzeylerinin dikkatli bir şekilde izlenmesi gerektiğini vurgulamaktadır.

Anahtar Sözcükler: *T2DM, Metformin, DPP-4 inhibitorü, Elektrolit, Vitamin B12*

INTRODUCTION

Type 2 diabetes mellitus (T2DM) has emerged as a major global health challenge, driven by rising prevalence of excess body weight, sedentary lifestyles, and unhealthy eating patterns. The prevalence of diabetes has considerably increased in recent years, primarily because of the rising incidence of T2DM. Many people continue to suffer increasingly from this disease, which causes not only health-related difficulties but also economic and sociological challenges, as T2DM is defined by reduced insulin production by the pancreatic β-cells and the inability of insulin-sensitive tissues to properly respond to insulin (1,2). There is a wide range of antidiabetic medications available, which can be used either individually or in combination. There are currently ten classes of pharmacologic agents that can be taken orally to treat T2DM. These consist of sulfonylureas, biguanides, thiazolidinediones, meglitinides, bile acid sequestrants, alpha-glucosidase inhibitors, dopamine receptor agonists, sodium-glucose transporter protein 2 (SGLT2) inhibitors, dipeptidyl peptidase IV (DPP-4) inhibitors and oral glucagon-like peptide 1 (GLP-1) receptor agonists (3, 4). Managing T2DM requires both lifestyle adjustments and medication, with metformin being the first-line therapy due to its proven efficacy, safety profile, and potential benefits in weight management (5). Metformin effects on mineral and electrolyte balance should also be considered. It is a member of the biguanide drug class and functions by reducing glucose production in the liver, increasing insulin sensitivity, and promoting the uptake of glucose in peripheral tissues (6). DPP-4 inhibitors, including vildagliptin and linagliptin, also have a crucial impact in T2DM management; they enhance insulin secretion depending on blood glucose concentrations and inhibit the release of glucagon, thereby contributing to improved glycemic regulation without notable weight gain (7). Additionally, while DPP-4 inhibitors are typically considered safe, some studies have indicated that they may influence electrolyte levels, particularly sodium and potassium (8, 9).

While minerals are important for glucose metabolism and contribute to antidiabetic activity, studies also indicate that diabetes may disrupt the homeostasis of trace elements (4,5,7). Initial disturbances in certain elements may have a significant impact on insulin metabolism. Macro elements primarily include chloride (Cl), calcium (Ca), phosphorus (P), magnesium (Mg), sodium (Na), potassium (K) and Fe, while some trace elements such as chromium (Cr), copper (Cu), sulfur (S), iodine (I) and Zn activate insulin receptor sites and increase insulin action (10). The role of these trace elements is critical in the onset and advancement of T2DM, and the physiological effects of various macro- and trace elements exhibit variability within the context of this disease (10,11). Metformin, along with Ca, Cu, Cr, Fe, Mg, Mn, K, Se, Zn, and vitamin D, is closely associated with the physiology of pancreatic β-cells. These elements significantly contribute to hormone synthesis, secretion, and signaling, particularly insulin, thereby contributing to the adjunctive enhancement of glycemic control (12-17).

Additionally, chronic use of metformin has been linked to vitamin B12 deficiency in certain individuals (18). This may be due to alterations in the gut microbiota or changes in the absorption of vitamin B12 in the intestines (5). Similarly, reduced serum vitamin B12 concentrations have been reported in patients treated with DPP-4 inhibitors (19). Depending on the population studied, between 5% and 40% of metformin users may experience B12 vitamin deficiency. Findings from the National Health and Nutrition Examination Survey (NHANES) indicates that 5.8% of diabetic patients taking metformin display signs of vitamin B12 insufficiency, compared to only 2.4% in those who are not on the medication (19). Although the literature reveals an association between vitamin B12 levels and administration of metformin and DPP-4 inhibitors, the exact mechanisms by which these medications affect vitamin B12 levels remain unclear, emphasizing the importance of regularly assessing vitamin B12 status in patients with T2DM.

Therefore, the present research aims to evaluate serum Na^+, K^+, Ca^{2+}, Cl^-, Mg^{2+} concentrations along with vitamin B12 status in individuals diagnosed with T2DM who are receiving antidiabetic treatments (metformin, DPP-4 inhibitors, or their combination) as well as in a control group.

MATERIALS and METHODS

Study Design and Population

We identified four research groups of 91 patients with T2DM and 33 healthy control who started metformin and DPP-4 inhibitors, and combination of metformin+DPP-4 inhibitors, including available data between 2022 and 2024 (Republic of Turkey Ministry of Health, Sinan Sipahi Family Health Center). In the current retrospective research, we observed the medical records of T2DM patients who attended a family health center for routine follow-up. Inclusion criteria included patients aged between 40 and 75 years who were on a stable regimen of metformin or DPP-4 inhibitor or metformin+ DPP-4 inhibitor combination for at least six months (metformin, 1000 mg; vildagliptin, 50 mg; linagliptin, 5 mg; metformin+vildagliptin, 50 mg/1000 mg). The control group, consisting of healthy people, was selected as people of similar age and gender to the patient groups without any chronic disease, especially diabetes mel-

Table 1: Characteristics of the patients and control subjects.

Characteristics	Control (n=33)	T2DM (n=91)	Total (n)	*p* value
Gender, n (%)				0,146
Male	15 (45.45)	46 (49.45)	61 (49.19)	
Female	18 (54.55)	45 (50.55)	63 (50.81)	
Age, mean ± SD, years	55.24±1.98	58.01±1.91		0.246
Fasting serum glucose (mg/dL ± SD)	88.81±9.20			<0.001
Metformin		121.57±5.69		
DPP-4 inhibitor		165.26±12.11		
Metformin+DPP-4 inhibitor		165.82±10.84		
HbA1c (% ± SD)	5.93±0.18			<0.001
Metformin		6.17±0.11		
DPP-4 inhibitor		7.51±0.25		
Metformin+DPP-4 inhibitor		7.65±0.29		

SD: Standard deviation. **Gender:** Chi-square test. Age, fasting serum glucose, and HbA1c; one way ANOVA test.

Participant demographic and clinical profiles in the study, including control and treatment groups, are summarized in the table. Data are presented as mean ± standard deviation (SD) for continuous variables and percentages for categorical variables. Age and gender distribution are detailed for each group.

Table 2: The study design and sample distribution.

Parameters *	Control (n=33)	T2DM (n=91)	Metformin (n=48)	DPP-4 inhibitor (n=22)	Metformin + DPP-4 inhibitor (n=21)
Na^{+}	32 (97.0)	-	45 (93.8)	18 (81.8)	19 (86.4)
Ca^{+2}	31 (93.9)	-	42 (87.5)	18 (81.8)	17 (77.3)
K^{+}	31 (93.9)	-	44 (91.7)	17 (77.3)	19 (86.4)
Mg^{+2}	29 (87.9)	-	36 (75.0)	16 (72.7)	16 (72.7)
Cl^{-}	26 (78.8)	-	23 (47.9)	10 (45.5)	12 (54.5)
B12	29 (87.9)	-	23 (47.9)	12 (54.5)	10 (45.5)

*Data shown as number and percent (n(%)). T2DM: Type 2 diabetes mellitus

The sample size (n, %) and the number of measurements available for each biochemical parameter across study groups have been outlined. The groups include healthy participants, patients with T2DM, and subgroups of T2DM patients using metformin, DPP-4 inhibitor, or metformin+DPP-4 inhibitor combination therapy.

litus (Table 1). Blood samples were collected during routine clinical visits, and information such as patients' age, gender, and clinical background was retrieved from their electronic medical records.

Electrolyte, Mineral and Vitamin B12 Analysis

Electrolyte and mineral levels (including sodium, potassium, calcium, magnesium, and chloride), along with vitamin B12 concentrations, measured through standard laboratory methods in blood samples from T2DM patients receiving metformin and DPP-4 inhibitors, as well as healthy controls, were retrospectively obtained from medical records. The results were analyzed by comparing the control group with the treatment groups and the treatment groups with each other. Additionally, fasting blood glucose and glycated hemoglobin (HbA1c) levels were documented for each participant to provide a comprehensive metabolic profile (Table 2).

Statistical Analysis

Sample size and effect size calculations were completed via G*Power 3.1 software, employing a one-way ANOVA framework with four research groups. With an alpha of 0.05, a power of 0.95, and an effect size of 0.45, the required sample size was calculated as 100. However, 91 participants with T2DM were included in the study. According to Cohen's conventional criteria, large effect sizes were observed for sodium (f = 0.78) and chloride (f = 0.50), suggesting substantial group differences in these electrolytes. In contrast, potassium (f = 0.12), magnesium (f = 0.05), vitamin B12 (f = 0.07), and calcium (f = 0.04) exhibited small effect sizes, indicating more modest variations among the groups.

All statistical analyses were conducted using GraphPad Prism software version 10.5.0. The Shapiro–Wilk test was applied to assess the normality of the data, confirming that all variables followed a normal distribution. Comparisons of serum levels of Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, and vitamin B12 across four groups (metformin, DPP-4 inhibitors, combination therapy, and healthy controls) were performed using one-way ANOVA, followed by pairwise comparisons through Tukey's post-hoc test. The outcomes are expressed as mean ± standard error of the mean (SEM) or standard deviation (SD). A *p*-value below 0.05 was considered indicative of statistical significance.

RESULTS

Glycemic Parameters

In the control group, fasting serum glucose was 88.81 ± 9.20 mg/dL, and HbA1c was 5.93 ± 0.18%, representing the mean ± SD values. In the metformin group, fasting serum glucose was 121.57 ± 5.69 mg/dL and HbA1c was 6.17 ± 0.11%. In the DPP-4 inhibitor group, glucose was 165.26 ± 12.11 mg/dL and HbA1c was 7.51 ± 0.25%. In the metformin + DPP-4 inhibitor group, glucose was 165.82 ± 10.84 mg/dL and HbA1c was 7.65 ± 0.29%, representing the mean ± SD values. (HbA1c, $p<0.001$; fasting serum glucose, $p<0.001$). All data are shown in Table 1.

Serum Mineral-Trace Element

Comparisons between groups were made among patients using different antidiabetic drugs, including metformin, DPP-4 inhibitors, and the metformin+DPP-4 inhibitor. Additionally, these diabetic patient groups were compared with the control group. Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, and vitamin B12 values between groups are shown in Figure 1.

The Na^+ levels were 140.29 ± 2.42 in the control group, 140.44 ± 2.30 in the metformin group, 139.29 ± 2.71 in the DPP-4 inhibitor group, and 138.47 ± 3.42 in the metformin + DPP-4 inhibitor group, representing the mean ± SD values. Analysis of serum Na^+ levels showed a significant distinction between the metformin group and the metformin + DPP-4 inhibitor group. Specifically, the metformin group showed higher serum Na^+ concentrations compared to the combination treatment group (*p=0.034, Figure 1A). Serum Na^+ concentrations showed no meaningful differences among the control and other groups (p> 0.05).

The K^+ levels were 4.38 ± 0.21 in the control group, 4.66 ± 0.44 in the metformin group, 4.71 ± 0.43 in the DPP-4 inhibitor group, and 4.64 ± 0.26 in the metformin + DPP-4 inhibitor group, representing the mean ± SD values. K^+ concentrations were considerably elevated in all treatment groups (metformin, DPP-4 inhibitor, and metformin+DPP-4 inhibitor groups compared to the control group. However, only the metformin group and the DPP-4 inhibitor group showed significant differences relative to the control group (respectively, *p=0.010, **p=0.006 Figure 1B).

The Ca^{2+} levels were 9.50 ± 0.36 in the control group, 9.40 ± 0.91 in the metformin group, 9.49 ± 0.46 in the DPP-4 inhibitor group, and 9.46 ± 0.38 in the metformin + DPP-4 inhibitor group, representing the mean ± SD values. No significant differences were observed in serum Ca^{2+}levels between the groups (p> 0.05, Figures 1C). The Mg^{2+}levels were 2.03 ± 0.16 in the control group, 1.97 ± 0.21 in the metformin group, 1.87 ± 0.36 in the DPP-4 inhibitor group, and 1.90 ± 0.23 in the metformin + DPP-4 inhibitor group, representing the mean ± SD values. No significant differences were observed in serum Mg^{2+}levels between the groups (p> 0.05, Figures 1D). The Cl^- levels were 103.24 ± 1.89 in the control group, 103.46 ± 2.46 in the metformin group, 103.90 ± 2.64 in the DPP-4 inhibitor group, and 101.67 ± 3.87 in the metformin + DPP-4 inhibitor group, representing the mean ± SD values. No significant differences were observed in serum Mg^{2+}levels between the groups (p> 0.05, Figures 1E).

Serum Vitamin B12 Levels

The comparison of serum vitamin B12 levels between groups is presented in Figure 1. Vitamin B12 levels were significantly lower in the metformin and metformin+DPP-4 inhibitor groups compared to the control group. Vitamin B12 levels were 2.54 ± 0.20 in the control group, 2.44 ± 0.15 in the metformin group, 2.52 ± 0.14 in the DPP-4 inhibitor group, and 2.32 ± 0.20 in the metformin + DPP-4 inhibitor group, representing the mean ± standard deviation values. A statistically significant decrease was observed in the metformin+DPP-4 inhibitor group compared to the control group (**p=0.006, Figure 1F). However, no statistically significant difference was found between the metformin or DPP-4 inhibitor groups compared to control, and between the metformin+DPP-4 inhibitor groups compared to metformin (p>0.05).

DISCUSSION

The incidence of diabetes mellitus is rising worldwide, and a variety of drug classes are employed in the management of diabetes and its comorbidities (20). Although oral antidiabetic drugs have a safe profile, they have some metabolic and renal effects (21). Consequently, the findings of this research reveal the effects of metformin and DPP-4 inhibitors and their combinations on mineral, electrolyte, and vitamin B12 levels in individuals with T2DM.

T2DM itself is associated with hyponatremia and hypomagnesemia, regardless of antidiabetic drug use (22-24). Evi-

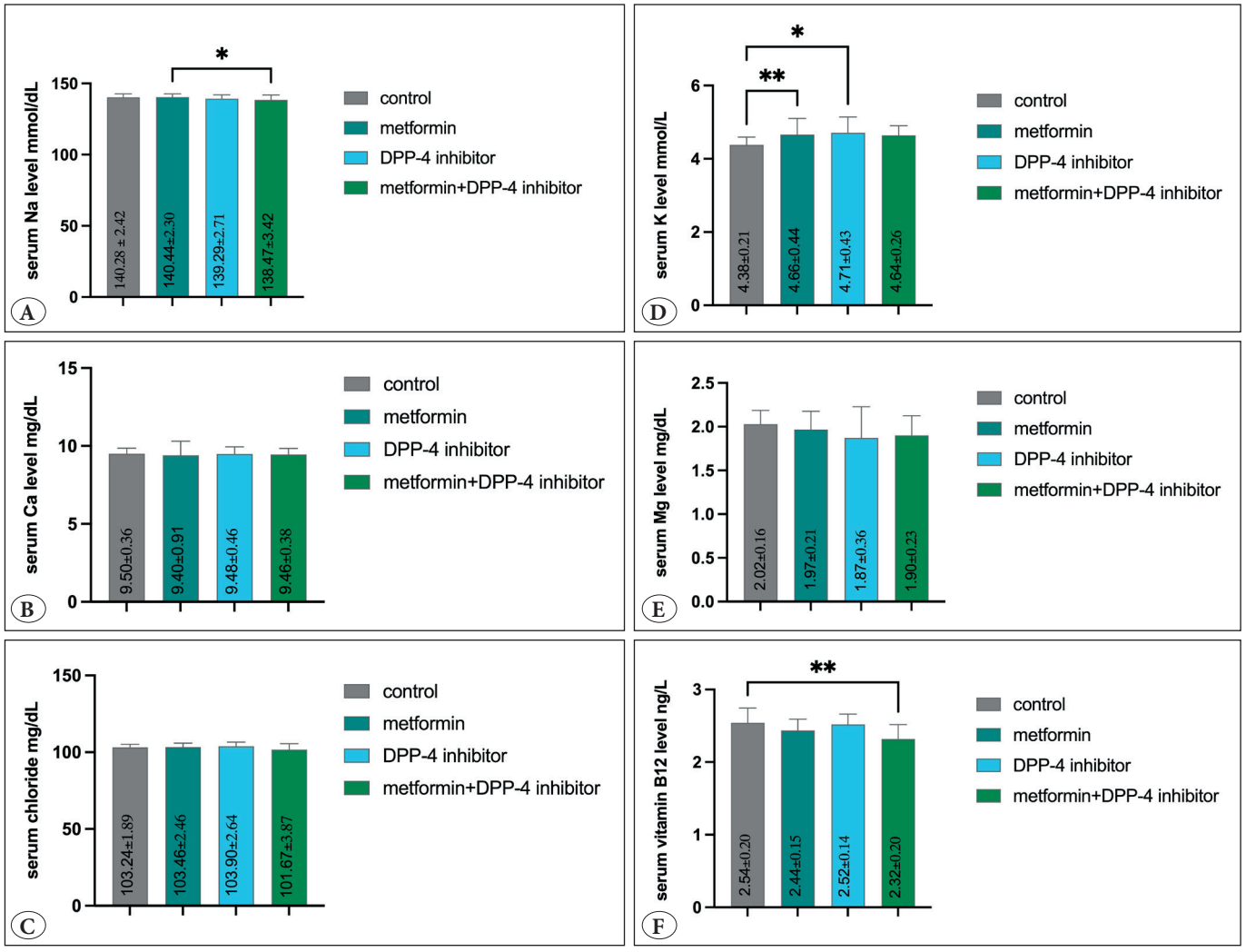


Figure 1: Serum Mineral-trace Element and Vitamin B12 Levels in Control and Treatment Groups. Comparison of serum biochemical parameters among control subjects, metformin users, linagliptin users, and vildagliptin/metformin users.
A) Serum sodium (Na) levels, showing statistically significant differences between (metformin vs metformin+DPP-4 inhibitor) groups, (*p=0.034). **B)** Serum calcium (Ca) levels, with no significant differences observed (p>0.05). **C)** Serum potassium (K) levels, indicating significant differences between (control vs metformin, control vs DPP-4 inhibitor), (*p=0.010, **p =0.006). **D)** Serum magnesium (Mg) levels, with no significant differences observed (p>0.05). **E)** Serum chloride (Cl) levels, with no significant differences detected (p>0.05). **F)** Serum vitamin B12 levels, highlighting significant differences between (control vs metformin + DPP-4 inhibitor) groups, (**p=0.006). Values are shown as mean ± SEM, with asterisks indicating statistically significant differences (*p < 0.05, **p < 0.01).

dence suggests that hypomagnesemia is present in approximately 20% of those with diabetes (24, 25). A case study describing metformin medication leading to clinically significant severe magnesium deficiency (0.33 mmol/L), which resolved after discontinuation of the drug, suggests that gastrointestinal Mg^{+2} loss associated with metformin may lead to the occurrence of hypomagnesemia (26). A study of 940 non-insulin-treated patients in the Fremantle Diabetes Study Phase I found that 19% had hypomagnesemia (<0.70 mmol/L). Individuals on metformin therapy, either alone or combined with a sulfonylurea, had reduced serum Mg^{+2} levels compared to those following a diet-only regimen (p<0.05) (24). A study involving 395 patients with T2DM found that those using metformin had lower plasma Mg^{+2} levels. Among all medications, metformin use showed the strongest correlation with plasma Mg^{+2} concentration, independent of estimated glomerular filtration rate or fasting glucose levels (27). On the other hand, another study involving 208 patients with T2DM found no impact of metformin treatment on serum magnesium levels (28). DPP-4 inhibitors, in addition to metformin, have been associated with reductions in serum M^{+2}. However, the mechanism of action of this condition is not fully known (29). Our findings suggest that metformin alone had no impact on serum Mg^{2+} concentrations.

The osmotic effect of excess glucose in the extracellular space causes water to shift from the intracellular to the extracellular compartment, resulting in a dilution of plasma Na^+ levels (30). This type of hyponatremia is hypertonic and reflects a disturbance in glucose regulation rather than an imbalance of water and Na^+. However, hypotonic hyponatremia, which indicates a primary disruption of water balance, has been associated with metformin (31). A recent study has shown that metformin increases urinary sodium excretion by decreasing phosphorylation of the thiazide-sensitive Na^+- Cl^- co-transporter during acute and chronic metformin use (32). Serum Na^+ levels were significantly reduced in the metformin+DPP-4 inhibitor group compared to the metformin-only group (*p=0.034, Figure 1A).

In patients with T2DM, the possibility of hyperkalemia is increased by many mechanisms, such as impaired K^+ excretion, impaired renal tubular function, and decreased ability of K^+ to pass into the cell (33). In a study by Fu et al., the use of SGLT-2 inhibitors was correlated with a lower rate of hyperkalemia compared with the use of DPP-4 inhibitors and a slightly reduced risk compared with GLP-1 receptor agonists (34). In this study, an increase in potassium levels across all the treatment groups suggests a possible drug-related shift in potassium homeostasis, which could be relevant for managing T2DM and avoiding complications related to hyperkalemia. Serum K^+ was considerably higher in patients receiving metformin and DPP-4 inhibitors compared to the control group (respectively, *p=0.01, **p=0.006, Figure 1B). The lack of significant changes in calcium and chloride levels may indicate that these electrolytes are less affected by the treatment regimens used in this study.

Although the exact mechanisms of metformin-induced vitamin B12 deficiency remain unclear, several possible explanations have been suggested. One theory suggests that metformin may impact small intestinal motility, leading to bacterial overgrowth, which in turn interferes with the absorption of the vitamin B12-intrinsic factor complex (18).

A recent study highlighted an important issue regarding the effects of certain diabetes medications on vitamin B12 levels. The research found that a daily dose of sulfonylureas in individuals with T2DM led to a considerable drop in mean blood vitamin B12 levels and an increase in the prevalence of vitamin B12 deficiency. Individuals with vitamin B12 deficiency were found to be older, consumed more sulfonylureas (often in combination with metformin), and had lower HbA1c levels compared to those without vitamin B12 deficiency. A separate study showed that the co-administration of metformin and DPP-4 inhibitors resulted in a severe reduction in vitamin B12 levels. However, the exact mechanism behind these findings remains unclear, and additional prospective researches are needed to better understand this observation (35). Our results show that serum vitamin B12 levels were significantly reduced in patients using metformin+DPP-4 inhibitors compared to the control group (**p=0.006, Figure 1F). As a result, the observed decrease in vitamin B12 levels in the metformin and metformin+DPP-4 inhibitor groups is consistent with previous research highlighting the potential for vitamin B12 depletion in patients treated with metformin over an extended period.

Impaired renal elimination due to diabetic nephropathy may predispose patients to hyperkalemia, as the kidney loses their ability to excrete potassium efficiently (19). Moreover, in patients with poorly controlled diabetes or those on antidiabetic medications, imbalances in sodium, potassium, magnesium, and phosphate are frequently observed, possibly due to mechanisms such as osmotic diuresis, secondary hyperaldosteronism, and insulin resistance (22). Prospective studies incorporating detailed diabetic nephropathy staging, dietary assessment, polypharmacy evaluation, and functional biomarkers (e.g., methylmalonic acid for B12 status) will be crucial for more accurately elucidating the observed biochemical changes and guiding clinical decision-making.

This study adds to the existing body of knowledge by investigating the effects of metformin and DPP-4 inhibitors on electrolyte and mineral balance in patients with T2DM. In particular, the significant effects of concomitant use of metformin and DPP-4 inhibitors on serum sodium and potassium levels have enabled further understanding of the effects of these drugs on electrolyte balance. Furthermore, despite conflicting results in the literature, the effect of metformin monotherapy on serum magnesium levels has not been shown to produce significant changes. In terms of vitamin B12 deficiency, the demonstration that concomitant use of metformin and DPP-4 inhibitors leads to a significant decrease in serum B12 levels supports the need for monitoring of vitamin B12 levels in patients receiving long-term treatment. This finding suggests that the risk of vitamin B12 deficiency may increase, particularly with combination therapy.

In conclusion, our study contributes to the literature on electrolyte balance and vitamin B12 deficiency. It provides insight into the metabolic effects that should be considered during long-term use of these medications. Additional large, prospective investigations are essential to corroborate these findings and deepen comprehension of their mechanisms.

Study Limitations

The major limitation identified in this study is that only patients registered in the Republic of Turkey Ministry of Health Sinan Sipahi Family Health Center were included. The retrospective design of the study resulted in certain limitations regarding the data. Additionally, the relatively small sample size affects the generalizability of the findings and may limit the ability to accurately represent the distribution of interactions between drugs, electrolytes, and vitamins in larger populations.

Conclusion

Metformin and DPP-4 inhibitors influence electrolyte and mineral balance in T2DM patients, with specific reductions in sodium and magnesium levels, as well as a significant decrease in vitamin B12. These findings highlight the importance of regular monitoring of these levels during treatment.

These findings highlight the potential impact of metformin and DPP-4 inhibitors on mineral and electrolyte homeostasis, emphasizing the need for careful monitoring of electrolyte levels and vitamin B12 status in patients undergoing these treatments. Further research is required to investigate the long-term effects of these medications on mineral balance and to assess the clinical significance of these changes, particularly in the context of combined therapy.

This study highlights the need for vigilant monitoring of electrolyte and mineral balance in patients with T2DM, particularly those treated with metformin and DPP-4 inhibitors. While both therapies effectively control blood glucose levels, they can lead to significant shifts in electrolyte levels, including reduced sodium and magnesium and increased potassium. Moreover, long-term metformin therapy may contribute to vitamin B12 deficiency, which necessitates regular assessment and supplementation when appropriate. These findings underscore the importance of individualized treatment plans and routine monitoring to ensure optimal metabolic health in T2DM patients.

Comprehensive studies with larger and prospective cohorts will be instrumental in clarifying the mechanisms and clinical effects of these electrolyte imbalances. This will help refine treatment protocols and improve patient outcomes in the management of T2DM.

Acknowledgment
We would like to express our gratitude to the patients and healthy control subjects who participated in this study.

Author Contributions
The study was designed by **Zeynep Gizem Todurga Seven**. Support in providing patient data was given by REA. **Zeynep Gizem Todurga Seven, Kubra Cigdem Pekkoc Uyanik,** and **Fatma Kubra Tombulturk** analyzed and interpreted the data. The original draft was written and the manuscript was edited by **Zeynep Gizem Todurga Seven** and **Kubra Cigdem Pekkoc Uyanik.** All contributing authors approved the final manuscript.

Conflict of Interest
The authors state that there are no potential conflicts of interest.

Financial Support
This study received no financial support.

Ethical Approval
This research adhered to the ethical guidelines outlined in the Declaration of Helsinki concerning medical studies involving human subjects. The study protocol was approved by the Ethics Committee of Haliç University (Approval Number: 2024/130). Written informed consent was obtained from all patients and healthy individuals. Written permission was secured from every patient and healthy volunteer before the study.

Peer Review Process
Extremely and externally peer-reviewed.

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