RESEARCH ARTICLE

Araştırma Makalesi

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Evaluation of Renal Toxicity in Chronic Hepatitis B Patients Treated with Tenofovir Disoproxil Fumarate

Tenofovir Disoproksil Fumarat Tedavisi Alan Kronik Hepatit B Hastalarında Renal Toksisitenin Değerlendirilmesi

ABSTRACT

Objective

Hepatitis B virus (HBV) infection remains a major global health concern. Tenofovir disoproxil fumarate (TDF), a widely used first line antiviral therapy, is associated with renal and mineral metabolism abnormalities. Although its nephrotoxic potential has been documented, real world data on long term outcomes remain limited in Turkey. This retrospective study aimed to evaluate renal function and mineral parameters in chronic HBV patients treated with TDF for at least 36 months and to provide evidence to optimize follow up strategies in clinical practice.

Material and Methods

We retrospectively analyzed 58 chronic HBV patients (mean age 50.7 ± 13.7 years, 60% male) treated with TDF for ≥36 months. Serial changes in serum creatinine, estimated glomerular filtration rate (eGFR, CKD-EPI), blood urea nitrogen (BUN), calcium, and phosphorus were assessed at baseline, month 1, month 6, year 1, and annually thereafter. Repeated measures ANOVA with Bonferroni correction was performed; statistical significance was defined as $p < 0.05$.

Results

No significant long term changes in serum creatinine or eGFR were observed over 36 months ($p = 0.20$ and $p = 0.07$, respectively). However, a transient decrease in eGFR was observed at month 1 compared with baseline ($p = 0.045$). BUN levels significantly increased over time ($p < 0.01$), with greater elevation in hypertensive patients ($p = 0.020$). Serum calcium remained stable ($p = 0.40$), whereas phosphorus levels showed a significant time dependent decline ($p < 0.01$), with hypophosphatemia detected in 11.7% of the patients.

Conclusion

TDF was generally well tolerated without significant deterioration in serum creatinine or eGFR during 36 months of follow up. However, a significant decline in serum phosphorus was observed in the overall cohort, while BUN levels increased more prominently among hypertensive patients, highlighting the importance of regular monitoring. Our study provides real world data from a Turkish cohort, emphasizing the need for close surveillance of renal and mineral parameters in high risk groups.

Key Words

Chronic hepatitis B, Tenofovir disoproxil fumarate, Renal toxicity, Glomerular filtration rate, Hypophosphatemia

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ÖZ

Amaç

Hepatit B virüsü (HBV) enfeksiyonu, önemli bir küresel sağlık sorunudur. İlk basamak antiviral tedavi olarak kullanılan tenofovir disoproksil fumarat (TDF), böbrek ve mineral metabolizması üzerinde olumsuz etkilerle ilişkilendirilmiştir. TDF'nin nefrotoksik potansiyeli literatürde tanımlanmış olsa da, Türkiye'den uzun dönemli gerçek yaşam verileri sınırlıdır. Bu çalışmada, TDF ile en az 36 ay süreyle tedavi edilen kronik HBV hastalarında böbrek fonksiyonlarını ve mineral parametrelerini değerlendirerek, klinik uygulamada takip stratejilerinin optimizasyonuna katkıda bulunmayı amaçladık.

Gereç ve Yöntemler

Toplam 58 kronik HBV hastası (ortalama yaş 50,7 ± 13,7 yıl, %60 erkek) retrospektif olarak incelendi. Serum kreatinin, tahmini glomerüler filtrasyon hızı (eGFR, CKD-EPI), kan üre azotu (BUN), kalsiyum ve fosfor düzeylerindeki seri değişiklikler; başlangıçta, 1. ay, 6. ay, 1. yıl ve sonrasında yıllık kontrollerde değerlendirildi. Tekrarlayan ölçümlerde ANOVA ve Bonferroni düzeltmesi kullanıldı; $p < 0,05$ istatistiksel anlamlılık sınırı olarak kabul edildi.

Bulgular

Otuz altı aylık takip süresince serum kreatinin ve eGFR düzeylerinde anlamlı bir uzun dönem değişiklik saptanmadı ($p = 0,20$ ve $p = 0,07$). Ancak, 1. ayda eGFR'de başlangıca kıyasla geçici bir düşüş eğilimi gözlendi ($p = 0,045$). BUN düzeyleri zaman içinde anlamlı olarak arttı ($p < 0,01$); bu artış hipertansif hastalarda daha belirgindi ($p = 0,020$). Serum kalsiyum düzeyleri değişmedi ($p = 0,40$), buna karşılık fosfor düzeylerinde zamanla anlamlı bir azalma görüldü ($p < 0,01$) ve hastaların %11,7'sinde hipofosfatemi saptandı.

Sonuç

TDF, 36 aylık takip süresince serum kreatinin veya eGFR düzeylerinde anlamlı bir bozulma olmaksızın genel olarak iyi tolere edildi. Bununla birlikte, tüm kohortta serum fosfor düzeylerinde anlamlı bir azalma gözlenirken, BUN düzeylerindeki artışın özellikle hipertansif hastalarda daha belirgin olduğu gözlendi. Çalışmamız, yüksek riskli gruplarda böbrek ve mineral parametrelerinin yakın takibinin gerekliliğini ortaya koyan, Türkiye kohortundan elde edilmiş gerçek yaşam verilerini sunmaktadır.

Anahtar Kelimeler

Kronik hepatit B, Tenofovir disoproksil fumarat, Renal toksisite, Glomerüler filtrasyon hızı, Hipofosfatemi

INTRODUCTION

Hepatitis B virus (HBV) infection remains a major global health problem, with over 250 million chronically infected individuals worldwide. Turkey is considered a moderately endemic country, with an HBsAg seroprevalence ranging from 2% to 7% (1). While most acute HBV infections require only supportive care, chronic HBV infection is defined by persistence of HBsAg for more than six months, and treatment decisions are guided by the presence of cirrhosis or hepatic inflammation and virological and host-related risk factors (2, 3).

The primary goal of antiviral therapy in chronic HBV is sustained suppression of HBV DNA to reduce disease progression and long term complications. Tenofovir has been widely used as a first line option in Turkey since 2008, making real world monitoring of its renal and mineral safety particularly relevant.

Tenofovir is available in two formulations; tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF). TDF has been shown to cause adverse effects on renal function and bone mineral density; however, the clinical relevance of this toxicity over the medium and long term remains a matter of debate. Current evidence suggests that TDF use may progressively increase urinary excretion of low molecular weight proteins, phosphate, uric acid, and glucose (4-7). With the rising number of patients on TDF and prolonged exposure, varying degrees of tubular abnormalities have been reported, including the development of Fanconi syndrome (8). Although progression to chronic kidney disease is relatively rare among TDF users, some large cohort studies have identified TDF use as a major risk factor for chronic kidney disease (6, 9). Additionally, secondary hyperphosphaturia due to tubular dysfunction may alter the interplay between bone, kidney, and regulatory hormones, potentially leading to bone loss and in rare cases, hypophosphatemic osteomalacia as seen in Fanconi syndrome (6).

Although TAF has demonstrated non-inferior antiviral efficacy and improved renal and bone safety compared with TDF, TDF remains widely used, and real-world long-term data on renal and mineral outcomes in Turkish cohorts are limited (10-12).

In this study, we retrospectively evaluated patients with chronic hepatitis B who had either previously received a different antiviral therapy or were treatment naive, had been started on TDF during follow up, and whose treatment was either ongoing or had been discontinued for any reason.
The renal side effects of TDF have been reported in many studies, but the results are not always consistent, and most of the available data come from trials or cohorts outside of Turkey. Real world long term data from Turkish patients are still limited, and such evidence could help clinicians decide how to monitor patients more effectively. We hypothesized that long term exposure to TDF may be associated

with time dependent changes in renal function and mineral metabolism; therefore, we evaluated longitudinal renal and mineral parameters in chronic HBV patients treated with TDF for at least 36 months in a Turkish real world cohort.

MATERIAL and METHODS

The medical records of patients evaluated at the Hepatology Outpatient Clinic of Akdeniz University Faculty of Medicine Hospital between May 1, 2014, and May 1, 2019, were reviewed. Patients over the age of 18 who had been followed for 36 months or more, who had either previously received a different antiviral treatment or had not received any treatment, who had been initiated on TDF during outpatient follow up and whose treatment was either ongoing or discontinued for any reason were included in the study. Patients were excluded if they had severe comorbidities that could cause renal damage or tubular dysfunction, were using medications associated with a high risk of renal damage or tubular dysfunction, had HDV co-infection or superinfection, had concurrent HCV or HIV infection, had not received TDF treatment regularly, had developed liver cirrhosis, were using immunosuppressive or immunomodulatory agents, or if sufficient data were unavailable.

Data collected for the 58 patients who met these criteria included age, sex, date of initiation of therapy, total follow up duration, history of prior antiviral treatment, presence of diabetes, presence of hypertension, antihypertensive medications used by hypertensive patients, and serum levels of creatinine, eGFR (estimated GFR (CKD-EPI)), BUN (Blood urea nitrogen), calcium, and phosphorus. These laboratory parameters were recorded at baseline, at the first and sixth months of treatment, at the end of the first year, and annually thereafter.

Patients with a systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg, and/or those who had previously been diagnosed with hypertension and had been prescribed antihypertensive medication during follow up, were classified as hypertensive. Patients with an HbA1c level ≥6.5% and/or fasting plasma glucose ≥126 mg/dL, and/or those who had been previously diagnosed with diabetes during follow up, were classified as diabetic.

Patients were categorized into subgroups according to age ranges (<30, 30–40, 40–50, 50–60, and >60 years), history of prior antiviral treatment before TDF initiation (yes or no), presence or absence of diabetes, presence or absence of hypertension, and presence or absence of both diabetes and hypertension.
The subgroup distribution of patients followed for more than 36 months is presented in Table II.

Table II. The subgroup distribution of patients

Group	Variable	Number of Patients (n=58)	Percentage (%)
Treatment Type	No prior treatment	25	43,1%
	Prior treatment	33	56,9%
Age group	<30 years	5	8,6%
	30-40 years	6	10,3%
	40-50 years	14	24,1%
	50-60 years	17	29,3%
	>60 years	16	27,6%
Gender	Male	35	60,3%
	Female	23	39,7%
Diabetes (DM)	No Diabetes	50	86,2%
	Diabetes	8	13,8%
Hypertension (HT)	No hypertension	43	74,1%
	Hypertension	15	25,9%
DM and HT	Neither present	42	72,4%
	Either present	10	17,2%
	Both present	6	10,3%

Statistical Analysis

Following data collection, statistical analysis support was obtained from the Statistical Consulting Unit of Akdeniz University. Descriptive statistics were presented as percentages, means, and standard deviations. The assumption of normality was assessed using the Shapiro-Wilk test, skewness and kurtosis values, and Q–Q plots.

Time dependent changes in creatinine, eGFR, BUN, calcium, and phosphorus levels across all patients were analyzed using one way repeated measures ANOVA. For subgroup comparisons, two way repeated measures ANOVA was used to evaluate between group differences in the time dependent changes of creatinine, eGFR, BUN, calcium, and phosphorus levels. In pairwise comparisons, the Bonferroni test was applied following repeated measures ANOVA.

P values less than 0.05 were considered statistically significant. Partial eta squared (η^2) values were used to assess the effect sizes of statistically significant differences. The interpretation of partial eta squared values was based on widely accepted guidelines $\eta^2 < 0.01$ was considered a small effect, $\eta^2 \sim 0.06$ a moderate effect, and $\eta^2 > 0.14$ a large effect (13, 14). All analyses were performed using SPSS version 23.0.

RESULTS

We included 58 patients with chronic HBV (mean age 50.7 ± 13.7 years; 60.3% male). At baseline, 43.1% were treatment naive and 56.9% had prior antiviral exposure; 13.8% had diabetes and 25.9% had hypertension. Mean values were creatinine 0.80 ± 0.16 mg/dL, eGFR 100.6 ± 17.7 mL/min/1.73 m², BUN 12.9 ± 3.2 mg/dL, calcium 9.39 ± 0.53 mg/dL, and phosphorus 3.63 ± 0.51 mg/dL. Detailed baseline characteristics are summarized in Table I.

Table I. Baseline demographic, clinical, and laboratory characteristics of the study population

Variable	Overall (n=58)
Age, years (mean ± SD)	50.7 ± 13.7
Male, n (%)	35 (60.3)
Female, n (%)	23 (39.7)
Prior antiviral therapy, n (%)	33 (56.9)
Diabetes, n (%)	8 (13.8)
Hypertension, n (%)	15 (25.9)
Both diabetes and hypertension, n (%)	6 (10.3)
Antihypertensive regimen including ACEi/ARB, n (% of HT)	10 (66)*
Creatinine, mg/dL	0.80 ± 0.16
eGFR (CKD-EPI), mL/min/1.73 m²	100.6 ± 17.7
BUN, mg/dL	12.9 ± 3.2
Calcium, mg/dL	9.39 ± 0.53
Phosphorus, mg/dL	3.63 ± 0.51
***Among hypertensive patients only.**	

All included patients had at least 36 months of follow-up after TDF initiation. At 36 months, all patients were still receiving TDF. No patients were lost to follow-up during the study period, and there were no deaths.

Serum creatinine, eGFR, BUN, serum calcium, and serum phosphorus levels were evaluated at baseline, at the first and sixth months, at the end of the first year, and annually thereafter (Table III).

Serum Creatinine Levels

No statistically significant time dependent change was observed in serum creatinine levels over the 36 month follow up period ($F = 1.476$, $\eta^2 = 0.026$, $p = 0.20$). However, the change in serum creatinine levels between baseline and month 1, although not statistically significant, approached the threshold for significance ($F = 3.939$, $\eta^2 = 0.06$, $p = 0.052$). The time dependent changes in serum creatinine levels are presented in Table III and Figure 1.

When subgroup comparisons were performed for serum creatinine levels measured over the 36 month period, no statistically significant time dependent differences were observed in any of the subgroups (Table IV).

Estimated GFR (CKD-EPI) Levels

No statistically significant time dependent change was observed in eGFR levels over the 36 month follow up period ($F = 2.084$, $\eta^2 = 0.037$, $p = 0.07$). However, the change between baseline and month 1 showed a downward trend bordering on statistical significance ($F = 4.196$, $\eta^2 = 0.072$, $p = 0.045$). The time dependent changes in eGFR levels are presented in Table III and Figure 2.

In the subgroup comparisons of eGFR levels over the 36 month period, no statistically significant time dependent differences were observed in any subgroup (Table IV).

Table III. Time-Dependent Changes in Serum Creatinine, Estimated GFR (CKD-EPI), BUN, Serum Calcium, and Serum Phosphorus Levels

Measurement Time	Creatinine	Estimated GFR (CKD-EPI)	BUN	Calcium	Phosphorus
Baseline	0,80±0,16 mg/dL	100,6±17,7 ml/min/1,73m²	12,9±3,2 mg/dL	9,39±0,53 mg/dL	3,63±0,51 mg/dL
1st month	0,83±0,17 mg/dL	97,8±16,7 ml/min/1,73m²	13,8±4,1 mg/dL	9,47±0,44 mg/dL	3,35±0,49 mg/dL
6th month	0,80±0,17 mg/dL	100,0±16,3 ml/min/1,73m²	13,8±3,8 mg/dL	9,41±0,45 mg/dL	3,31±0,46 mg/dL
12th month	0,79±0,18 mg/dL	100,1±16,2 ml/min/1,73m²	14,0±3,8 mg/dL	9,43±0,50 mg/dL	3,27±0,48 mg/dL
24th month	0,80±0,17 mg/dL	98,8±16,4 ml/min/1,73m²	13,6±3,7 mg/dL	9,40±0,41 mg/dL	3,11±0,45 mg/dL
36th month	0,81±0,18 mg/dL	97,3±17,8 ml/min/1,73m²	14,6±4,4 mg/dL	9,34±0,48 mg/dL	3,18±0,61 mg/dL

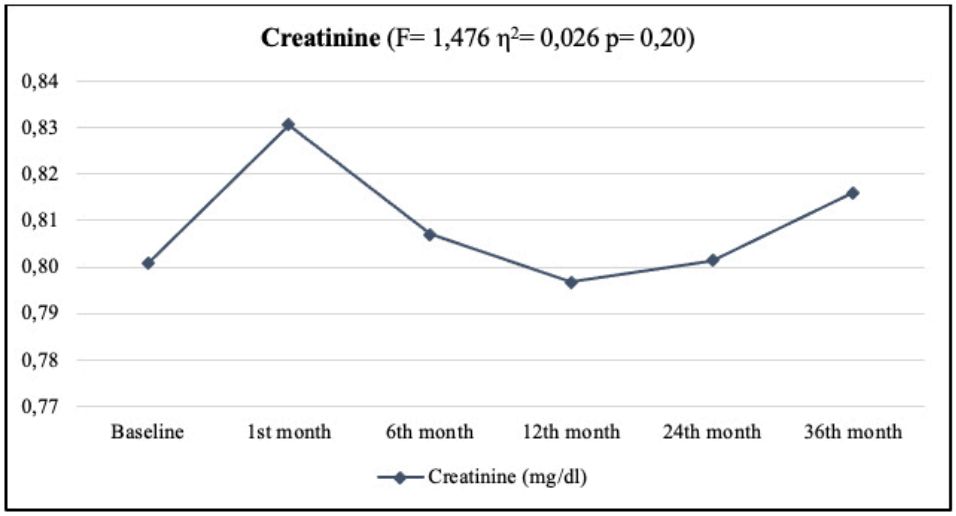

Figure 1. The time-dependent change of serum creatinine levels in all patients. Throughout the follow-up period F= 1,476 η2= 0,026 p= 0,20 Between baseline and the 1st month F= 3,939 η2= 0,060 p= 0,052

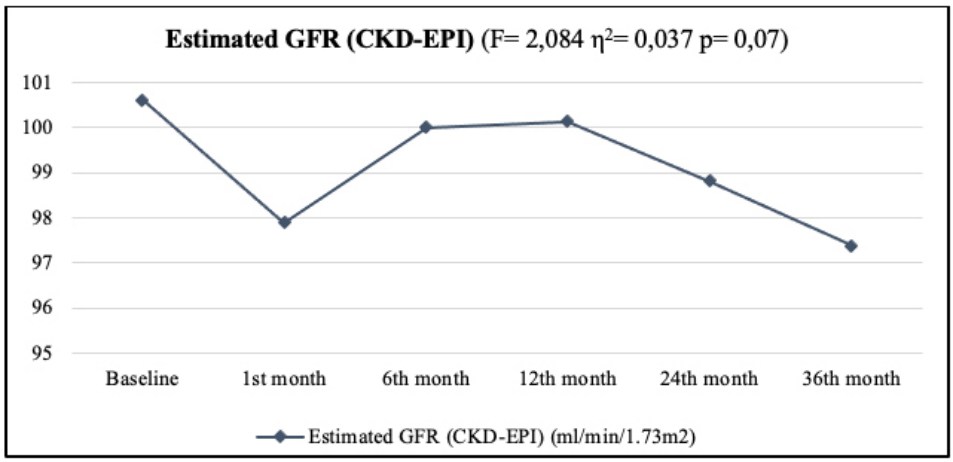

Figure 2. The time-dependent change of estimated GFR (CKD-EPI) levels in all patients
Throughout the follow-up period F= 2,084 η2= 0,037 p= 0,07
Between baseline and the 1st month F= 4,196 η2= 0,072 p= 0,045

Table IV. Differences in time-dependent changes of serum creatinine, estimated GFR (CKD-EPI), BUN, serum calcium, and serum phosphorus levels among subgroups.

Subgroups	Creatinine	Estimated GFR (CKD-EPI)	BUN	Calcium	Phosphorus
Treatment Group	F= 1,564 η2= 0,028 p= 0,17	F=0,814 η2=0,015 p= 0,81	F= 1,712 η2=0,031 p= 0,14	F= 0,252 η2= 0,043 p= 0,63	F= 1,676 η2=0,02 p=0,16
Age Group	F= 0,381 η²= 0,029 p=0,98	F= 0,534 η²= 0,041 p=0,92	F= 3,632 η²= 0,055 p=0,79	F= 1,287 η²= 0,089 p=0,19	F= 0,680 η²= 0,049 p=0,80
Gender	F= 1,640 η²= 0,029 p= 0,15	F= 0,895 η²= 0,017 p= 0,47	F= 1,297 η²= 0,024 p= 0,26	F= 1,510 η²= 0,026 p= 0,19	F= 1,272 η²= 0,022 p= 0,28
Diabetes (DM)	F= 1,242 η²= 0,022 p= 0,29	F= 1,553 η²= 0,028 p= 0,18	F= 6,260 η²= 0,005 p= 0,93	F= 0,834 η²= 0,015 p= 0,51	F= 1,007 η²= 0,018 p= 0,40
Hypertension (HT)	F= 1,257 η²= 0,023 p= 0,28	F= 0,909 η²= 0,017 p= 0,46	**F= 2,732 η²= 0,049 p=0,02**	F= 0,667 η²= 0,012 p= 0,62	F=2,284 η²= 0,039 p=0,06
DM and HT	F= 1,649 η²= 0,059 p= 0,11	F= 1,535 η²= 0,056 p= 0,12	F= 1,927 η²= 0,015 p= 0,95	F= 0,928 η²= 0,033 p= 0,50	F= 1,565 η²= 0,054 p= 0,14

BUN Levels

A statistically significant change was observed in BUN levels over the 36 month follow up period ($F = 3.325$, $\eta^2 = 0.058$, $p < 0.01$). Further analysis of the time points contributing to this change revealed that the differences between baseline and month 1, and between month 24 and month 36, were statistically significant ($F = 6.103$, $\eta^2 = 0.103$, $p = 0.016$ and $F = 4.389$, $\eta^2 = 0.075$, $p = 0.041$, respectively). The time dependent changes in BUN levels are presented in Table III and Figure 3. In subgroup comparisons over the 36 month period, a statistically significant difference in the time dependent change in BUN levels was found between patients with and without hypertension ($F = 2.732$, $\eta^2 = 0.049$, $p = 0.020$). In a post hoc analysis conducted to identify the specific time point of this difference, the change in BUN levels from baseline to month 36 was found to be statistically significant between hypertensive and non hypertensive patients ($F = 7.216$, $\eta^2 = 0.122$, $p = 0.01$). The time dependent changes in BUN levels in hypertensive and non hypertensive patients are shown in Figure 4. No statistically significant time dependent differences in BUN levels were observed among the other subgroups (Table IV).

Serum Calcium Levels

No statistically significant change was observed in serum calcium levels over the 36 month follow up period ($F = 1.018$, $\eta^2 = 0.02$, $p = 0.40$). The time dependent changes in serum calcium levels are presented in Table III and Figure 5. In subgroup comparisons, no statistically significant time dependent differences in serum calcium levels were observed in any subgroup (Table IV).

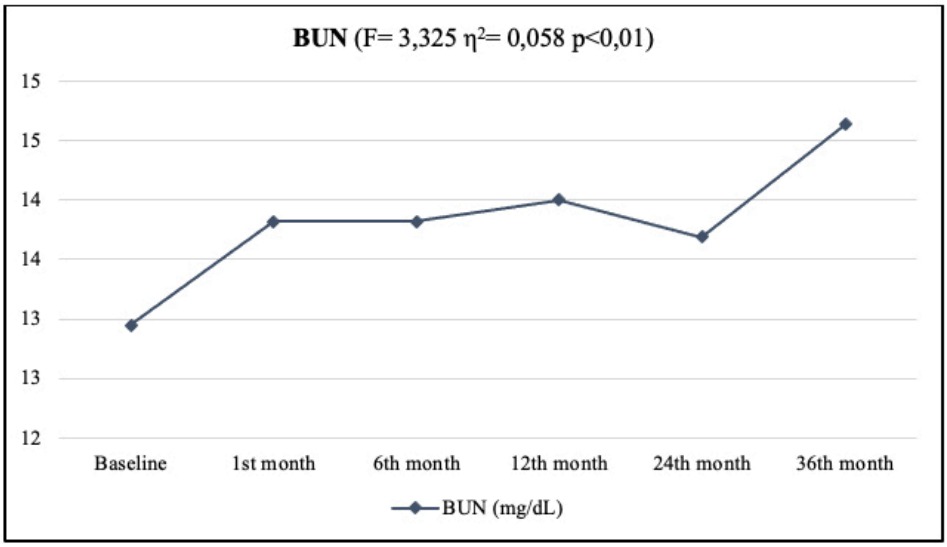

Figure 3. The time-dependent change of BUN levels in all patients
Throughout the follow-up period (F= 3.325, η^2= 0.058, p<0.01).
Between baseline and the 1st month (F= 6.103, η^2= 0.103, p=0.016).
Between the 24th and 36th months (F= 4.389, η^2= 0.075, p=0.041).

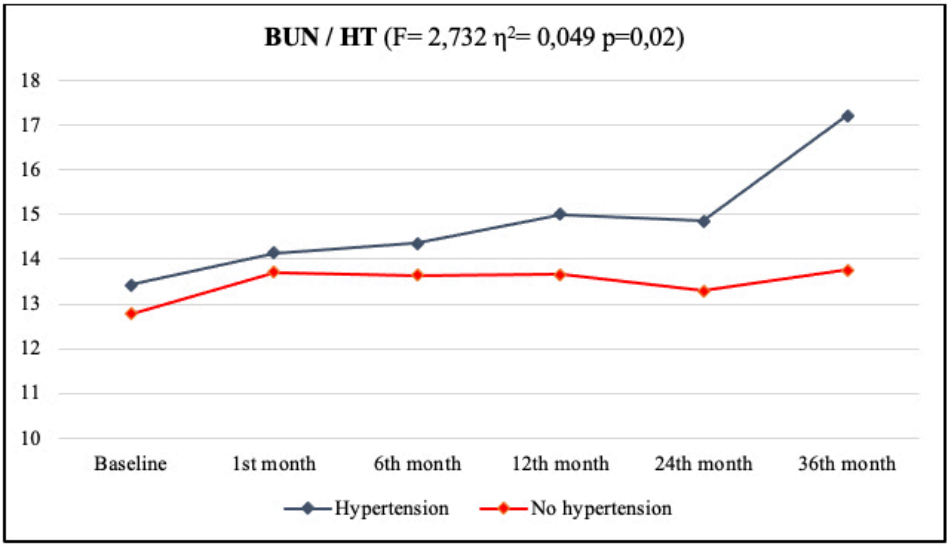

Figure 4. The time-dependent change of BUN levels in patients with and without hypertension
Throughout the follow-up period F= 2,732 η2= 0,049 p=0,02

Serum Phosphorus Levels

A statistically significant change was observed in serum phosphorus levels over the 36 month follow up period ($F = 15.980$, $\eta^2 = 0.219$, $p < 0.01$). Further analysis of the specific time points contributing to this change revealed that the differences between baseline and month 1, and between months 12 and 24, were statistically significant ($F = 37.596$, $\eta^2 = 0.406$, $p < 0.01$ and $F = 8.290$, $\eta^2 = 0.131$, $p < 0.01$, respectively). The time dependent changes in phosphorus levels for all patients are presented in Table III and Figure 6. In subgroup comparisons, no statistically significant time dependent differences in serum phosphorus levels were observed in any subgroup (Table IV).

DISCUSSION

Tenofovir is an acyclic nucleotide analog that can be used as a first line treatment option in treatment naive patients, and as a second line agent in those who have developed resistance to other nucleoside or nucleotide analogs, such as lamivudine.

Tenofovir is available in two formulations: TDF and TAF. TDF is the oral prodrug form, consisting of the fumarate salt of tenofovir disoproxil. After oral administration, it undergoes enzymatic conversion to its active metabolite, tenofovir diphosphate, which inhibits HBV polymerase activity. The use of TDF has been associated with adverse effects on renal function and bone mineral density; however, the clinical relevance of these toxicities in the medium or long

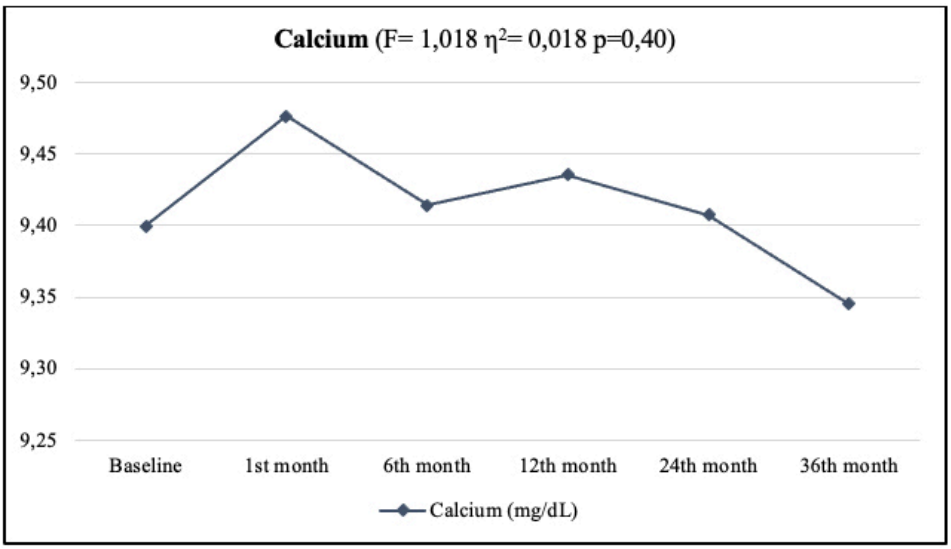

Figure 5. The time-dependent change of serum calcium levels in all patients
Throughout the follow-up period F= 1,018 η2= 0,018 p=0,40

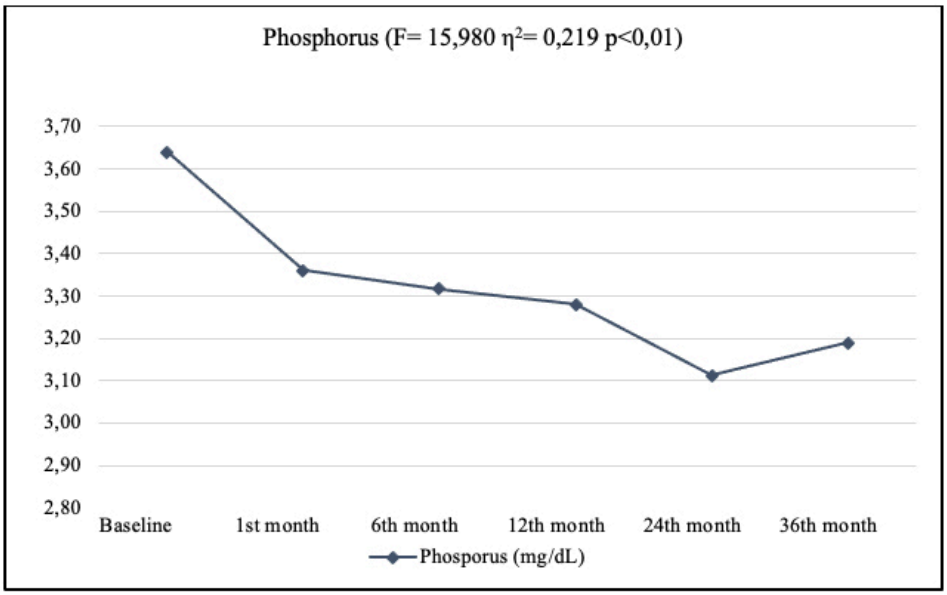

Figure 6. The time-dependent change of serum phosphorus levels in all patients.
Throughout the follow-up period F= 15.980, η^2= 0.219, p<0.01.
Between baseline and the 1st month: F= 37.596, η^2= 0.406, p<0.01.
Between the 12th and 24th months: F= 8.290, η^2= 0.131, p<0.01.

term remains a subject of ongoing debate.
In patients with renal impairment or decompensated cirrhosis, the selection of the appropriate tenofovir formulation is still subject to clinical discussion.

In this study, we retrospectively analyzed patients with chronic hepatitis B, including both treatment-naïve individuals and those with a history of antiviral therapy. All patients had been initiated on TDF in the outpatient setting, and their treatment was either ongoing or had been discontinued for various reasons.
This real world, retrospective analysis aimed to evaluate the renal toxicity profile of TDF and to inform the development of optimal follow up strategies for patients undergoing treatment with this agent.

In a study that followed 273 patients receiving TDF over a 24 month period, significant changes were reported in creatinine and GFR levels at all measured time points (15). Similarly, in another study involving 110 patients with chronic hepatitis B, a significant time dependent increase in serum creatinine levels was observed throughout the 24 month follow up, particularly between baseline and month 3, and between months 6 and 12 (16). Our findings were similar to these studies in terms of the increase observed between baseline and month 1; however, the overall trend across the 36 month period differed. An observational study involving 60 patients reported a statistically significant, though not clinically marked, decline in GFR during the first six months of TDF treatment. GFR levels approached baseline and stabilized after the 12th month, which is consistent with our findings (17).

In our study, a statistically significant change in BUN levels was observed. Further analysis of the time points contributing to this change revealed that the increases between baseline and month 1, as well as between months 24 and 36, were statistically significant. When subgroup comparisons were made, a statistically significant difference in the time dependent change in BUN levels was found between patients with and without hypertension. Post hoc analysis showed that the increase in BUN levels from baseline to month 36 was significantly greater in hypertensive patients compared to non hypertensive patients. In a study involving 51 patients, a strong association was reported between serum tenofovir concentrations and BUN levels (18). The more pronounced change in BUN levels observed among hypertensive patients may be related to the concomitant use of antihypertensive medications. It is well known that the use of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) can lead to reduced renal perfusion by causing vasodilation of afferent and efferent arterioles in the kidney (19). Among the hypertensive patients in our study, 10 (66%) were receiving an antihypertensive regimen that included either an ACE inhibitor or an ARB. Although the observed increase in BUN levels was mild, it was statistically significant and may be related to the use of these agents. Taken together, these observations suggest that the modest increase in BUN particularly among hypertensive patients may be influenced by hemodynamic factors (e.g., ACE inhibitor/ARB related changes in renal perfusion and/or diuretic use) rather than serving as a specific marker of intrinsic tubular injury (19). Because creatinine/eGFR remained largely stable and tubular markers (urinalysis indices and fractional excretion measurements) were not systematically available, we cannot distinguish prerenal azotemia from subclinical tubular dysfunction, and this finding should therefore be interpreted cautiously.
When serum calcium levels were evaluated, no statistically significant change was observed. Similarly, no significant differences were found in calcium level changes across subgroups.

Consistent with the findings of our study, a previous study involving 110 patients with chronic hepatitis B reported time dependent fluctuations in serum calcium levels among those receiving TDF; however, these changes were not statistically significant (16). Similarly, in a study that followed 273 patients with chronic hepatitis B over a 24 month period, no statistically significant difference was found when baseline and 24 month calcium levels were compared (15).
In another study involving 1,002 patients with HIV, calcium and parathyroid hormone (PTH) levels were compared between those receiving TDF and those who were not. The findings showed that patients on TDF had lower calcium levels and higher PTH levels, which contrasts with the results of our study (20).

When serum phosphorus levels were analyzed, a statistically significant change was observed. Further analysis of the contributing time points revealed that the decreases in serum phosphorus levels between baseline and month 1, and between months 12 and 24, were statistically significant. No statistically significant differences were observed between subgroups.

In a randomized, placebo controlled prospective study involving 101 participants, no statistically significant decrease in serum phosphorus levels was observed in patients receiving TDF compared to those in the placebo group (21). In another prospective study comparing patients treated with TDF or adefovir over a 7 year follow up, including 389 patients who had been on TDF for at least one year, a statistically significant difference was found in mean phosphorus levels between the two treatment groups. However, when patients with serum phosphorus levels falling below 2 mg/dL were compared, no statistically significant difference was observed between the TDF and adefovir groups (22). Similarly, in a study that followed 273 patients over 24 months, no significant changes in serum phosphorus levels were reported during follow up (15). Another study including 110 patients with chronic hepatitis B showed time dependent variations in serum phosphorus levels among those receiving TDF, although these changes did not reach statistical significance (16). In an observational study with 60 patients, a decrease in serum phosphorus levels was noted during the first six months of TDF therapy, although not statistically significant. After month 12, phosphorus levels approached baseline and remained stable (17). In a prospective study involving 515 HIV patients followed over four years, the

incidence of hypophosphatemia was significantly higher in those receiving TDF containing regimens compared to those who did not (23). In our cohort, serum phosphorus levels showed a significant time dependent decline. Hypophosphatemia was detected in 11.7% of patients (serum phosphate <2.5 mg/dL), which is consistent with previous reports of tubular effects associated with long term TDF use. According to current international guidelines, monitoring of phosphorus is mandatory during TDF therapy, and our findings support this recommendation by demonstrating that clinically relevant decreases can occur even in patients without baseline renal risk factors (24). This emphasizes the need for careful biochemical surveillance in all patients receiving TDF, regardless of their initial renal status.

From a mechanistic standpoint, the decline in serum phosphorus observed in our cohort likely stems from subclinical proximal tubular dysfunction associated with chronic TDF exposure. Previous research has established that TDF can lead to increased urinary losses of phosphate, glucose, uric acid, and low-molecular-weight proteins, a spectrum of injury ranging from mild tubular impairment to overt Fanconi syndrome (4-8). In such cases, secondary hyperphosphaturia arising from impaired proximal phosphate reabsorption can drive clinically significant reductions in serum phosphorus levels, even when eGFR remains relatively preserved (6). While fractional excretion indices are commonly used to characterize TDF-related hypophosphatemia in other populations the retrospective nature of our dataset meant these parameters were not systematically recorded (22). Consequently, we were unable to directly verify phosphate wasting or other specific markers of proximal tubulopathy in our patients.

Current international guidelines provide important context for our observations. They recommend regular monitoring of renal function and mineral parameters during TDF therapy, including serum creatinine/eGFR and phosphorus, and urinalysis particularly in individuals with increased renal risk (24). In patients with established renal impairment or additional risk factors, TAF is generally preferred over TDF due to its more favorable renal safety profile (24). In line with these recommendations, the significant decline in serum phosphorus in our cohort underscores the importance of periodic biochemical surveillance during long-term TDF treatment, even in patients without baseline renal dysfunction.

Limitations

There are several limitations to this study. The most important is that it was carried out in a single center with a relatively small sample size, which may restrict the broader applicability of the findings. The retrospective design restricted the scope of data collection and introduced potential bias. Although the mean follow up was 36 months, this period may still be considered short for fully assessing the long term renal effects of TDF. In addition, urinalysis data (e.g., proteinuria and glycosuria) and specific markers of proximal tubular dysfunction, such as the fractional excretion of phosphate, were not consistently available in this retrospective dataset; therefore, tubular injury could not be assessed comprehensively. Detailed information on the dose and duration of antihypertensive therapies was also unavailable, limiting our ability to account for the potential contribution of concomitant agents to changes in BUN and other renal indices. Bone mineral density measurements were not available, preventing further evaluation of mineral metabolism beyond serum calcium and phosphorus. These limitations should be considered when interpreting our findings.

Clinical implications

Despite these limitations, our study provides real life data from a Turkish cohort, highlighting that while TDF is generally well tolerated, early changes in renal and mineral parameters may occur. In particular, the significant decline in phosphorus levels and the increase in BUN among hypertensive patients underline the importance of close monitoring in specific subgroups. International guidelines advise using TAF rather than TDF in individuals considered at risk for kidney impairment (24). Taken together, our findings support the practice of periodic surveillance of creatinine, eGFR, phosphorus, and BUN in HBV patients maintained on TDF, and suggest that shorter follow up intervals may be advisable for those with additional risk factors such as hypertension.

CONCLUSION

In conclusion, this study provides real world evidence from a Turkish cohort showing that long term TDF therapy was generally well tolerated, with no significant deterioration in serum creatinine or eGFR during 36 months of follow up. Nevertheless, the decline in serum phosphorus and the increase in BUN, especially among hypertensive patients, indicate that early changes in renal and mineral parameters may occur. These findings emphasize the importance of regular monitoring in HBV patients receiving TDF, and suggest that shorter follow up intervals may be required for those with additional risk factors.

Ethics Committee Approval

This research complies with all the relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration and has been approved by the Akdeniz University Faculty of Medicine Ethics Committee (approval number: 531-12/06/2019).

Informed Consent

Owing to the retrospective design of the study, the requirement for informed consent was waived by the Ethics Committee.

Conflict of Interest

The authors have no conflict of interest to declare.

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