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Comparison of Renal Function Changes in Chronic Hepatitis B Patients Treated with Tenofovir Disoproxil Fumarate and Entecavir

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Objective: The main aim of this study was to investigate the effects of prolonged TDF and Entecavir (ETV) treatment on renal function among patients with chronic hepatitis B.

Materials and Methods: In this retrospective observational study, a total of 150 patients with chronic hepatitis B who received TDF or ETV treatment at our hospital between January 2018 and December 2025 were evaluated. Demographic, clinical, and laboratory data were obtained from hospital records, and eGFR, creatinine, and urea levels were recorded at baseline and at the final follow-up. Changes in renal function were calculated as the difference between baseline and final follow-up values and compared between treatment groups.

Results: One-hundred-fifty patients were included in this study (TDF, *n*= 100; ETV, *n*= 50). Patients in the ETV group were older and had a higher body mass index (p=0.013 and p=0.006, respectively). Baseline renal function was significantly better in the TDF group, with higher eGFR and lower serum creatinine levels. At follow-up, changes in renal parameters differed significantly between groups. The decline in eGFR and increases in serum urea and creatinine were greater in patients treated with TDF (all p<0.05). Fasting glucose and gamma-glutamyl transferase levels were higher, while magnesium levels were lower, in the ETV group. Sex distribution, bone mineral density status, and cirrhosis prevalence were comparable between groups.

Conclusion: TDF treatment was found to be associated with a more pronounced deterioration in renal function during follow-up compared with ETV, highlighting the need for close monitoring of kidney function.

Key Words: *Chronic hepatitis B, entecavir, tenofovir disoproxil fumarate, glomerular filtration rate*

Tenofovir Disoproksil Fumarat ve Entekavir ile Tedavi Edilen Kronik Hepatit B Hastalarında Böbrek Fonksiyonlarındaki Değişimlerin Karşılaştırılması

Amaç: Bu çalışmanın temel amacı, kronik hepatit B hastalarında uzun süreli Tenofovir Disoproxil Fumarate (TDF) ve Entekavir tedavisinin böbrek fonksiyonları üzerindeki etkilerini araştırmaktır.

Gereç ve Yöntem: Bu retrospektif gözlemsel çalışmada, Ocak 2018–Aralık 2025 arasında hastanemizde TDF veya entekavir tedavisi alan kronik hepatit B'li 150 hasta değerlendirildi. Demografik, klinik ve laboratuvar veriler hastane kayıtlarından elde edildi; eGFR, kreatinin ve üre başlangıç ve son izlemde kaydedildi. Böbrek fonksiyonlarındaki değişim, son izlem ile başlangıç değerleri arasındaki fark olarak hesaplandı ve tedavi grupları arasında karşılaştırıldı.

Bulgular: Çalışmaya 150 hasta dâhil edildi (TDF, n=100; entekavir, n=50). Entekavir grubundaki hastalar daha yaşlıydı ve vücut kitle indeksi daha yüksekti (sırasıyla p=0.013 ve p=0.006). Başlangıç böbrek fonksiyonları TDF grubunda anlamlı olarak daha iyiydi; eGFR daha yüksek, serum kreatinin düzeyleri daha düşüktü. İzlem sonunda böbrek parametrelerindeki değişimler gruplar arasında anlamlı farklılık gösterdi. eGFR'deki azalma ile serum üre ve kreatinin artışları tenofovir disoproxil fumarate ile tedavi edilen hastalarda daha belirgindi (tüm p<0.05). Açlık glukozu ve gama-glutamil transferaz düzeyleri entekavir grubunda daha yüksekken, magnezyum düzeyleri daha düşüktü. Cinsiyet dağılımı, kemik mineral yoğunluğu durumu ve siroz prevalansı gruplar arasında benzerdi.

Sonuç: TDF tedavisi, entekavire kıyasla izlem süresince böbrek fonksiyonlarında daha belirgin bozulma ile ilişkili bulunmuş olup, bu durum yakın böbrek fonksiyon takibini gerekli kılmaktadır.

Anahtar Kelimeler: *Kronik hepatit B, entekavir, tenofovir disoproxil fumarate, glomerüler filtrasyon hızı*

Introduction

Chronic hepatitis B represents a major global health burden, affecting hundreds of millions of individuals worldwide (1). It remains a challenging public health problem owing to its association with progressive liver disease, including cirrhosis and hepatocellular carcinoma (HCC) (2). Chronic hepatitis B infection is recognized as one of the primary etiological factors for HCC worldwide, accounting for a substantial proportion of liver-related morbidity and mortality (3).

Over the past decades, several antiviral agents have been developed for the treatment of chronic hepatitis B, significantly improving long-term disease control and patient outcomes (4). Currently, nucleos(t)ide analogues such as TDFand ETV are

widely used as first-line agents because of their potent antiviral activity and high resistance barrier. (5). These agents effectively inhibit hepatitis B virus replication, thereby reducing the risk of disease progression, cirrhosis, and hepatocellular carcinoma (6).

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Long-term antiviral therapy, particularly with nucleos(t)ide analogues such as TDF and ETV, has been related to the emergence of treatment-related adverse effects (7, 8). Among these, renal toxicity has been a particular concern, especially in patients receiving Tenofovir disoproxil fumarate-based regimens. Several studies have reported declines in renal function, proximal tubular dysfunction, and alterations in bone–mineral metabolism during prolonged TDF use. In contrast, ETV is generally considered to have a more favorable renal safety profile (9, 10).

Consequently, in this study we aimed to evaluate and compare the adverse effect profiles, with a primary focus on renal function deterioration, in chronic hepatitis B patients treated with TDF or ETV.

Materials and Methods

All study procedures were performed in compliance with internationally accepted ethical standards. Approval was granted by the Ethics Committee of Firat University prior to study started on 18 August 2025 (approval number: 12-19).

This study included a total of 150 patients with chronic hepatitis B who were followed at our hospital and treated with TDF or ETV between January 2018 and December 2025. The study followed a retrospective observational design.

Patient demographics, clinical characteristics, and laboratory findings were obtained retrospectively through a review of hospital medical records. The collected variables comprised age (years), body mass index (BMI, kg/m²), duration of antiviral therapy (months), hemoglobin (g/dL), platelet count (×10³/μL), white blood cell count (×10³/μL), fasting glucose (mg/dL), and baseline renal function parameters, including estimated glomerular filtration rate (eGFR, mL/min/1.73 m²), serum creatinine (mg/dL), and urea (mg/dL).

Renal function parameters at the last follow-up visit, including eGFR, serum creatinine, and serum urea levels, were recorded to assess longitudinal changes in kidney function. These parameters were collected to enable comparison of baseline renal characteristics and to evaluate changes in renal function between patients receiving TDF and ETV during follow-up.

Renal function changes were assessed by calculating the difference between baseline and final follow-up values of renal function parameters. Specifically, delta values (Δ) for eGFR, serum urea, and serum creatinine were derived (Δ = last visit − baseline). These change scores were subsequently compared between the TDF and ETV treatment groups to evaluate differences in renal function over time.

The presence of cirrhosis was evaluated in all patients and recorded for each treatment group. Comparisons of cirrhosis prevalence between the TDF and ETV groups were performed as part of the baseline clinical assessment.

Distributional assumptions were evaluated using the Kolmogorov–Smirnov test. Continuous variables demonstrating a normal distribution are reported as mean±standard deviation, while variables not conforming to normality are summarized as median with minimum and maximum values. For between-group comparisons, parametric continuous data were analyzed with the independent samples t test, while non-parametric data were evaluated using the Mann–Whitney U test. Categorical variables were compared using the chi-square test. Levene's test indicated heterogeneity of variances for last-visit eGFR; therefore, nonparametric analyses of change scores were used as the primary method for between-group comparisons. A p value of less than 0.05 was accepted as indicating statistical significance. Statistical analyses were conducted using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 150 patients were analyzed, including 100 receiving TDF and 50 treated with ETV. The ETV group was characterized by a higher mean age (53.3±9.6 vs. 50.5±12.0 years, p=0.013) and greater body mass index (p=0.006). Treatment duration also differed significantly between groups (p=0.037). At baseline, renal function parameters favored the TDF group, with significantly higher estimated glomerular filtration rate values (109.0±13.9 vs. 105.6 [55.9–121.3] mL/min/1.73 m², p=0.003) and lower serum creatinine concentrations (p=0.016). Although eGFR remained significantly different at the final follow-up (p=0.023), serum creatinine and urea levels were comparable between groups. Patients receiving ETV exhibited higher fasting glucose and gamma-glutamyl transferase levels (p=0.026 and p=0.015, respectively), whereas lower magnesium levels were observed in this group (p=0.006). In contrast, parathyroid hormone concentrations were elevated among TDF-treated patients (p=0.033). No significant intergroup differences were found in other hematologic, hepatic, skeletal, or thyroid-related parameters (Table 1).

Table 1. Comparison of clinical and laboratory characteristics between TDF and ETV groups

Variable	TDF (n:100)	Entecavir (n:50)	*p* values
Age (years)	50.5±12.0	53.3±9.6	0.013
BMI (kg/m²)	26.3±3.9	28.1 (19.4–40.0)	0.006*
Drug duration (months)	96 (60–180)	96 (60–180)	0.037*
Hemoglobin g/dL	14.2±1.8	14.6±1.9	0.257
Platelet ×10³/µL	239340±73095	225400±78693	0.285
WBC ×10³/µL	6453±1930	7055±1979	0.077
Glucose mg/dL	93 (74–208)	98 (74–319)	0.026*
eGFR (baseline) mL/min/1.73 m²	109.0±13.9	105.6 (55.9–121.3)	0.003*
Creatinine (baseline) mg/dL	0.70±0.18	0.70 (0.50–1.48)	0.016*
Urea (baseline) mg/dL	29.9±7.4	31.8±9.1	0.168
eGFR (Last visit)	90 (31-90)	90 (75-90)	0.023*
Creatinine (Last visit)	0.70 (0.4-1.7)	0.70 (0.4-1.3)	0.708*
Urea (Last visit)	33.6±10.9	32.0±7.7	0.359
AST	24 (13–73)	23.5 (12–88)	0.517*
ALT	22.5 (2–116)	26.5 (8–140)	0.412*
GGT	17 (4–113)	23.5 (8–246)	0.015*
ALP	84 (13–209)	79 (14–188)	0.272*
Albumin	4.52±0.30	4.48±0.36	0.533
INR	1.0 (0.8–12.0)	0.9 (0.8–1.8)	0.418*
DEXA T-score	-1.39±1.16	-1.25±1.35	0.525
Calcium	9.32±0.47	9.42±0.48	0.222
Phosphorus	3.3 (2.0–14.6)	3.32±0.69	0.703*
PTH	60 (19.5–268)	55.5±20.3	0.033*
Magnesium	2.09 (1.6–3.2)	1.9 (1.4–4.6)	0.006*
Vitamin D	16.6 (4.2–64)	17.0 (5.3–50)	0.538*
TSH	1.39 (0.1–6.4)	1.4 (0.1–3.8)	0.721*

BMI indicates body mass index; WBC, white blood cell count; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; INR, international normalized ratio; PTH, parathyroid hormone; and TSH, thyroid-stimulating hormone. *Statistical comparisons were performed using the Mann–Whitney U test where appropriate*

Table 2. Categorical baseline characteristics of patients according to antiviral treatment

Variable	TDF (n=100)	Entecavir (n=50)	Total (n=150)	*p* values
Gender				
Male	52 (52.0%)	33 (66.0%)	85 (56.7%)	0.118
Female	48 (48.0%)	17 (34.0%)	65 (43.3%)	
Bone mineral density status				
Normal	44 (44.0%)	20 (40.0%)	64 (42.7%)	
Osteopenia	36 (36.0%)	21 (42.0%)	57 (38.0%)	0.775
Osteoporosis	20 (20.0%)	9 (18.0%)	29 (19.3%)	
Cirrhosis				
No	92 (92.0%)	41 (82.0%)	133 (88.7%)	0.099
Yes	8 (8.0%)	9 (18.0%)	17 (11.3%)	

TDF, tenofovir disoproxil fumarate; ETV, entecavir

Table 3. Changes in renal function parameters according to antiviral treatment

Variable	TDF	Entecavir	*p* values
ΔeGFR	−24.2 (−60.8 to 12.2)	−15.6 (−41.9 to 25.1)	0.001
ΔUrea	3.0 (−26 to 52)	0.5 (−15 to 14)	0.037
ΔCreatinine	0.00 (−0.20 to 0.70)	0.00 (−0.40 to 0.30)	0.023

TDF, tenofovir disoproxil fumarate; ETV, entecavir; eGFR, estimated glomerular filtration rate; Δ, change between baseline and last follow-up

Sex distribution was similar between the TDF and ETV groups, with no significant difference detected (p=0.118). Likewise, bone mineral density categories—normal bone density, osteopenia, and osteoporosis—were comparably distributed across both treatment groups (p=0.775). Although cirrhosis was more frequently observed among patients receiving ETV (18.0%) than those treated with TDF (8.0%), this difference did not achieve statistical significance (p=0.099). Overall, treatment groups did not differ significantly in terms of sex, bone mineral density status, or cirrhosis prevalence (Table 2).

Changes in renal function parameters differed significantly between treatment groups. The decline in eGFR was significantly greater in the TDF group compared with the ETV group (median −24.2 mL/min/1.73 m² [−60.8 to 12.2] vs. −15.6 mL/min/1.73 m² [−41.9 to 25.1], p=0.001). Similarly, the increase in serum urea levels was significantly higher in patients receiving TDF (median 3.0 mg/dL [−26 to 52]) than in those receiving ETV (median 0.5 mg/dL [−15 to 14], p=0.037). Although the median variation in serum creatinine was comparable between the two groups, the difference was statistically significant, with patients receiving TDF demonstrating a larger increase than those treated with ETV (0.00 mg/dL [−0.20 to 0.70] vs. 0.00 mg/dL [−0.40 to 0.30], p=0.023) (Table 3).

Discussion

In the treatment of CHB, nucleos(t)ide analogues are generally administered long term, often lifelong, due to their ability to suppress viral replication. This prolonged use necessitates careful monitoring, particularly with regard to potential renal toxicity. In this retrospective study, changes in renal function were compared between patients with CHB receiving long-term TDF or ETV therapy. During follow-up, a greater decline in eGFR and more pronounced increases in urea and creatinine levels were observed in the TDF group. Previous studies have reported a gradual reduction in eGFR, proximal tubular dysfunction, and the development of chronic kidney disease during TDF therapy (10). These results align with previous reports describing unfavorable renal outcomes associated with prolonged TDF exposure (11).

ETV has been reported to have a more favorable renal safety profile and to be associated with a more stable course of kidney function (12). In our study, patients treated with ETV had a higher mean age and BMI compared with those in the TDF group, theoretically representing a population at higher risk for renal function decline. Despite this, renal impairment was more pronounced in the TDF group, suggesting that the observed effect cannot be explained solely by patient-related factors and supporting the likelihood of a TDF-specific nephrotoxic effect. Similarly, in the study by Trinh et al. (13), a greater decline in eGFR was reported among patients receiving TDF compared with those treated with ETV, even when baseline clinical characteristics differed between groups.

The better baseline renal function observed in the TDF group is an important factor that should be considered when interpreting the change scores. However, in the present study, renal function changes were assessed using the difference (Δ) between baseline and last follow-up values, which partially reduces bias related to baseline measurements. Despite this, the significantly greater decline in eGFR and the more pronounced increases in urea and creatinine levels in the TDF group represent clinically meaningful findings.

In this study, differences were also detected among the treatment groups in several parameters related to electrolyte balance and bone–mineral metabolism. Magnesium levels were lower in the ETV group, whereas parathyroid hormone levels were higher in the TDF group, suggesting potential indirect effects of nucleos(t)ide analogues on renal tubular function and mineral metabolism. Previous studies have reported phosphate wasting, secondary hyperparathyroidism, and reductions in bone mineral density associated with TDF use (10). However, as these parameters are influenced by multiple factors, further prospective studies incorporating detailed biochemical assessments are required to clarify the causal relationship underlying these findings.

Contemporary international guidelines for chronic hepatitis B management emphasize periodic assessment of kidney function in patients treated with nucleos(t)ide analogues (5). This recommendation is particularly relevant for individuals receiving TDF disoproxil fumarate, in whom close surveillance of eGFR, serum creatinine, and coexisting renal risk factors is advised. Within this framework, our results offer real-world data that reinforce these guideline-based recommendations.

Several limitations of this study should be acknowledged. First, the retrospective and single-center design may have introduced selection bias and limits how confidently the results can be generalized to broader patient populations. The relatively small number of patients is another important constraint and may have

reduced the ability to detect more subtle associations. In addition, renal tubular function could not be evaluated in detail, as parameters such as phosphaturia, urinary glucose excretion, and β2-microglobulin were not assessed. The absence of these markers limits a more comprehensive interpretation of tubular dysfunction and its potential role in the study outcomes. Another limitation is the lack of clearly defined criteria for treatment selection. Physician preference, patient comorbidities, and baseline renal risk factors that may have influenced the choice between TDF and ETV were not systematically evaluated, raising the possibility of indication bias. Future prospective, multicenter studies with larger cohorts and a more detailed assessment of tubular function and treatment preference would help to address these limitations and strengthen the evidence base.

In conclusion, close and periodic assessment of kidney function is clinically essential in patients receiving long-term TDF therapy. Renal risks should be carefully considered, particularly in patients of advanced age, those with comorbid conditions, and individuals with a history of long-term antiviral therapy. To better elucidate causal relationships, further prospective, multicenter studies incorporating markers of renal tubular injury are warranted.

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