Effects of Long-Term Tenofovir and Entecavir Treatment on Bone Mineral Density in Patients with Chronic Hepatitis B

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ABSTRACT

Background: *We aimed to investigate the long-term effects of tenofovir disoproxil fumarate and entecavir treatment on bone mineral density and evaluated the fracture risk assessment tool score in patients with chronic hepatitis B.*

Methods: *A total of 58 chronic hepatitis B patients treated with tenofovir disoproxil fumarate (n = 40) and entecavir (n = 18) were included in this prospective study from 2012 to 2016. To evaluate bone mineral density, dual-X-ray absorptiometry, fracture risk assessment tool, and laboratory examinations were performed in all patients first at baseline and second at the end of the study.*

Results: *Age, sex, body mass index, fibrosis score, and viral load were similar in both groups. The mean follow-up was 33 months in the tenofovir disoproxil fumarate group and 31 months in the entecavir group. In patients treated with entecavir, there was no statistically significant difference between baseline and second bone mineral density including lumbar spine (L) and total hip T score. In patients treated with tenofovir disoproxil fumarate, there was a significant difference in the second bone mineral density compared with baseline bone mineral density for L3 (P = .033) and the major fracture risk assessment tool score (P = .03). When patients were divided into 3 groups (normal bone mineral density, osteopenic, and osteoporotic), there was a significant increase in the number of osteopenic patients in the total hip T score after tenofovir disoproxil fumarate treatment (P = .034).*

Conclusion: *Our results suggest a decrease in the bone mineral density for lumbar spine (L3), an increase in the number of patients with hip osteopenia, and major fracture risk assessment tool score after long-term tenofovir disoproxil fumarate treatment in patients with rechronic hepatitis B.*

Keywords: *Bone mineral density, chronic hepatitis B, entecavir, osteopenia, tenofovir*

INTRODUCTION

Tenofovir disoproxil fumarate (TDF) and entecavir (ETV) are the first-line antiviral drugs used to treat chronic hepatitis B (CHB) patients.[1,2] Tenofovir disoproxil fumarate is a nucleotide analog reverse transcriptase inhibitor that is also a component of human immunodeficiency virus (HIV) treatment. Entecavir is a cyclopentyl guanine nucleoside analog reverse transcriptase inhibitor.

Studies have shown that the use of tenofovir in animal models reduces bone mineral density (BMD).[3,4] Tenofovir disoproxil fumarate causes osteoporosis via various mechanisms. Intracellular accumulation of TDF leads to proximal tubular dysfunction and Fanconi syndrome, resulting in hypophosphatemic osteomalacia.[5-7] Another mechanism is that TDF causes a reduction in osteoblast gene expression which causes defective osteoblast function leading to decreased bone formation.[8] Clinical trials have found that TDF treatment in HIV-infected patients leads to bone disorders such as osteopenia, osteoporosis, and bone fractures.[9-11] Bone mineral density measurements have been shown to improve in HIV patients in whom TDF therapy is changed to other antiviral therapies.[12,13] The risk of hip fracture increases in HIV patients who are co-infected with hepatitis B.[14] A retrospective cohort study of CHB patients in which long-term safety of oral nucleos(t)ide analogs was assessed revealed that the use of nucleotide analogs increased the risk of hip fracture.[15] However, another study demonstrated that the risk of osteoporosis was not increased in patients with CHB who were treated with TDF for more than 18 months.[16] Studies evaluating the effects of TDF on BMD in patients with hepatitis B are limited.

In this study, we aimed to investigate the long-term effects of TDF and ETV on BMD and fracture risk in CHB patients.

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MATERIALS AND METHODS

Fifty-eight CHB patients who were started on TDF (n = 40 patients, 25 males/15 females) or ETV (n = 18 patients, 11 males/7 females) treatments between January 2012 and December 2014 in gastroenterology and hepatology clinic were included. The mean follow-up was 31 months in the TNF group and 33 months in the ETV group. The median follow-up durations of TDF and ETV groups were 33 (12-57) months and 34 (12-60) months, respectively. Patients' demographic data, laboratory results including serum alkaline phosphatase, calcium, phosphorus, 25-hydroxy vitamin D, parathyroid hormone, thyroid hormone, albumin, and urinary calcium levels were noted. Histologic activity index in liver biopsies, fibrosis stages according to the Ishak-modified Knodell liver fibrosis scoring system, duration of treatment, and hepatitis B virus loads were recorded.[17] Individuals with chronic conditions that may affect BMD, such as renal disorders, thyroid dysfunction, and diabetes; patients with metabolic bone disease and postmenopausal women; or patients treated with growth hormone, anabolic steroids, or glucocorticoid drugs were excluded. The study protocol was approved by the local ethics committee. Written informed consent was obtained from all patients.

Bone Mineral Density Measurement

Bone mineral density measurements were performed using dual-energy X-ray absorptiometry (DEXA) at the beginning of the treatment (baseline BMD) and at the end of the study (second BMD) in 2016 examinations. All DEXA measurements were made using the Hologic Discovery scanner (Hologic Inc., Waltham, Mass, USA) and evaluated by the same person. The patient's first lumbar spine (L1), second lumbar spine (L2), third lumbar spine (L3), fourth lumbar spine (L4), and total lumbar spine (L1-4) T scores, and the total hip T score were recorded according to age, sex, and body mass index. T values between 1 and −1 were considered to be normal, while T values between −1 and −2.5 were considered to be osteopenic, and values of −2.5 and lower indicated osteoporosis as defined in World Health Organization guidelines for bone health.[18] Baseline and second BMD measurements were compared between TDF and ETV groups. Moreover, the change in each BMD score over time was also assessed for TDF- and ETV-treated patients, separately.

Estimated Fracture Risk Calculation

An estimated 10-year major osteoporotic and hip fracture probability was calculated using an automatic data entry program from the FRAX web calculator.[19]

Statistical Analysis

Data were analyzed using the Social Sciences 24 (SPSS 24.0, IBM Statistics for Windows Version 24, SPSS Inc.; Chicago, IL, USA) and PAST 3 (Hammer, Ø., Harper, D.A.T., Ryan, P.D. 2001. Paleontological Statistics) software packages. While the normal distribution of univariate data was assessed using the Shapiro–Wilk test, the variability coefficient and the multivariate normality were tested through the Mardia, Doornik, & Omnibus test. Variance homogeneity was assessed by the Levene test. In the comparison of 2 independent groups, the independent *t*-test was applied together with the bootstrap test results, while the Mann–Whitney *U*-test was used with the Monte Carlo simulation technique. The interaction of repeated measures of dependent variables was observed with general linear model repeated analysis of variance (ANOVA) test. Categorical variables were compared using Pearson's chi-square test and Fisher–Freeman–Holton tests with the Monte Carlo simulation technique. Quantitative variables were expressed as mean ± standard deviation (SD) and the median range (maximum-minimum) values. Categorical data were expressed as n (number) and percentage (%). The variable data were evaluated with a 95% CI, and statistical significance was based on a value of $P < .05$.

RESULTS

Fifty-eight CHB patients were evaluated. Demographic characteristics, serum biochemical parameters, and thyroid hormone and parathyroid hormone levels, hepatitis B virus DNA level, histologic activity index, and follow-up time were not statistically significant between TDF and ETV groups (Table 1).

Tenofovir Disoproxil Fumarate Treatment Group

There was a significant difference in the L3 spine second BMD results compared with baseline BMD results in patients treated with TDF (−1.06 ± 1.17 vs −0.90 ± 1.06, $P = .033$, Table 2, Figure 2). There was no statistically significant difference between second BMD and baseline BMD for the L1 spine ($P = .44$), L2 spine ($P = .083$), L3 spine ($P = .477$), L4 spine ($P = .386$), total lumbar spine ($P = .821$), and total hip ($P = .615$) in patients treated with TDF (Table 2, Figure 2).

The baseline BMD and second BMD measurements were compared after dividing the patients into 3 groups as follows: normal BMD, osteopenic, and osteoporotic (Table 3). There was a significant increase in the number of osteopenic patients according to total hip score after

Table 1. Demographic Data of Patients With Chronic Hepatitis B Treated With Entecavir and Tenofovir Disoproxil Fumarate

	Tenofovir*	Entecavir*	*P*
Age	40.08 ± 10.76	40.11 ± 11.32	.791
BMI	26.13 ± 3.39	27.17 ± 2.86	.259
Sex, n (%)			
Female	15 (37.5%)	7 (38.9%)	1.000
Male	25 (62.5%)	11 (61.1%)	
Follow-up time (months)	31.75 ± 13.14	33.89 ± 14.47	.590
Serum calcium (mg/dL)	9.5 ± 0.22 (9.5)	9.48 ± 0.18 (9.5)	.447
Serum phosphorus (mg/dL)	3.3 ± 0.41	3.2 ± 0.35	.365
ALP (U/L)	77.57 ± 17.47	72.17 ± 18.54	.285
25 OH vitamin D (ng/mL)	18.26 ± 11.8	12.6 ± 10.3	.513
Serum PTH (ng/L)	33.2 ± 0.41	32.4 ± 0.35	.365
Urine calcium (mg/day)	193.22 ± 97.44	153.17 ± 77.42	.400
Total cholesterol (mg/dL)	153.73 ± 33.11	164.47 ± 26.13	.263
LDL (mg/dL)	91.73 ± 28.6	98.75 ± 25.79	.396
Triglyceride (mg/dL)	59.28 ± 25.46	60.75 ± 26.62	.847
Glucose (mg/dL)	95.86 ± 21.51	94.76 ± 19.87	.857
ALT (U/L)	31.26 ± 24.52	37.94 ± 17.02	.245
AST (U/L)	27.95 ± 21.79	31.06 ± 19.75	.326
Albumin (mg/dL)	4.26 ± 0.44	4.22 ± 0.32	.802
INR	1 ± 0.11	0.94 ± 0.11	.124
TSH (mU/L)	1.4 ± 1.25	1.45 ± 0.48	.134
AFP (mg/L)	3.49 ± 2.86	2.64 ± 1.23	.134
Anti-Hbe, n (%)			
Positive	10 (25%)	4 (22.2%)	1.000
Negative	30 (75%)	14 (77.8%)	
HBV DNA, n (%)			
<1 000 000 IU/mL	12 (30%)	6 (33.3%)	.447
≥1 000 000 IU/mL	28 (70%)	12 (66.6%)	
HAI	6.25 ± 2.58	6 ± 2.41	.777
Liver biopsy, n (%)			
Fibrosis score 1–2	13 (32.5%)	8 (44.4%)	.612
Fibrosis score 3–4	19 (47.5%)	6 (33.3%)	
Fibrosis score 5–6	8 (20%)	4 (22.3%)	

TSH, thyroid-stimulating hormone; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AFP, alpha-fetoprotein; INR, international normalized rate; HBV DNA, hepatitis B virus deoxyribonucleotide; HAI, histologic activity index fibrosis score; according to the Ishak-modified Knodell liver fibrosis scoring system; Anti-Hbe, Hepatitis b e antibody; LDL, low-density lipoprotein.
*Mean ± standard deviation.

TDF treatment (15% (6/43) vs 30% (12/43), *P* = .034). No significant difference was found in the number of normal, osteopenic, and osteoporotic individuals in the second BMD measurement according to baseline BMD L1, L2, L3, L4, and total L1–4 spine.

There was a significant difference in second major FRAX score results compared with baseline major FRAX score results in patients treated with TDF (3.8 vs 3.6, *P* = .03, Table 2). During follow-up, a calcaneus bone fracture in 1 patient was observed.

Table 2. Comparison of Baseline and Second BMD Measurement, FRAX Risk Scores, and Serum Bone Biochemistry

	Entecavir (ENT)			Tenofovir Disoproxil Fumarate (TDF)			*P*				
	Baseline (A)	Second (B)	Difference (B – A)	Baseline (A)	Second (B)	Difference (B – A)	P^1	P^2	P^3	P^4	P^5
L1 spine T score*	−0.87 ± 1.02	−0.76 ± 1.03	0.11 ± 0.57	−0.91 ± 1.04	−1.04 ± 1.03	−0.13 ± 0.50	.121	.900	.335	.440	.115
L2 spine T score**	−0.8 (−2.3/1.5)	−0.8 (−3.3/0.9)	−0.1 (−1.2/0.6)	−1.3 (−2.8/2.2)	−1.1 (−3.2/2.6)	0 (−1.5/4.5)	.314	.243	.452	.083	.651
L3 spine T score*	−0.62 ± 1.34	−0.67 ± 1.29	−0.05 ± 0.29	−0.90 ± 1.06	−1.06 ± 1.17	−0.17 ± 0.48	.341	.436	.262	.477	**.033**
L4 spine T score**	−0.8 (−2.9/3.2)	−1.2 (−2.4/2.5)	0 (−0.9/0.6)	−1.4 (−3.1/2.4)	−1.6 (−4/2)	0 (−2.4/0.8)	.891	.345	.240	.386	.138
Total L spine T score**	−0.8 (−2.4/2.1)	−0.8 (−2.7/1.6)	0 (−0.5/0.4)	−1.2 (−2.7/2.4)	−1.3 (−3/2.3)	−0.1 (−2.1/0.5)	.418	.488	.230	.821	.053
Hip T score*	−0.32 ± 0.92	−0.37 ± 0.78	−0.06 ± 0.46	−0.42 ± 0.64	−0.52 ± 0.81	−0.09 ± 0.59	.814	.658	.522	.615	.324
Major FRAX score**	3.9 (2.4/8.2)	3.8 (2.4/7.3)	0 (−0.9/1.3)	3.6 (2.7/6.5)	3.8 (2.7/6.2)	0 (−0.8/1.1)	.153	.330	.703	.704	**.030**
Hip FRAX score**	0.5 (0/2.2)	0.4 (0/1.6)	0 (−0.6/0.9)	0.3 (0/2)	0.4 (0/1.9)	0 (−1.8/1.2)	.249	.518	.541	.951	.130
Serum calcium**	9.5 (9.2/9.9)	9.5 (9.3/9.8)	0 (−0.3/0.4)	9.5 (9/9.9)	9.5 (9/10)	0.1 (−0.3/0.9)	.603	.426	.425	.226	.051
PTH**	49.1 (28.6/56)	53 (26.3/62.8)	2.8 (−4.2/7.6)	54.5 (32/68)	54.8 (34/68)	4 (2/8.6)	.332	.725	.517	.160	.060
25-OH D3**	9.6 (6.1/24.9)	9.7 (7.3/19)	1.3 (−6.3/2.1)	11.2 (5.1/39)	12.9 (5.4/29)	1.4 (−17/14.3)	.427	.490	.274	.766	.087
Serum phosphorus**	3.2 (2.7/4)	3.3 (2.6/3.9)	0 (−0.2/0.4)	3.3 (2/4)	3.4 (2.1/4)	0 (−0.8/1.3)	.849	39	.35	.220	.291

General linear model repeated analysis of variance, independent samples *t*-test (bootstrap), Mann–Whitney *U*-test (Monte Carlo), Wilcoxon signed-rank test (Monte Carlo); P^1, between-group for difference; P^2, between-group for baseline; P^3, between-group for second; P^4, for (baseline − second) entecavir; P^5, for (baseline − second) tenofovir disoproxil fumarate. Bolded text indicate significantly different values.

*Mean ± standard deviation; **median (minimum/maximum); BMD, bone mineral density; L1 spine, lumbar first spine; FRAX, fracture risk assessment tool score; PTH, parathyroid hormone; 25-OH D3, 25-hydroxy vitamin D3; SD, standard deviation.

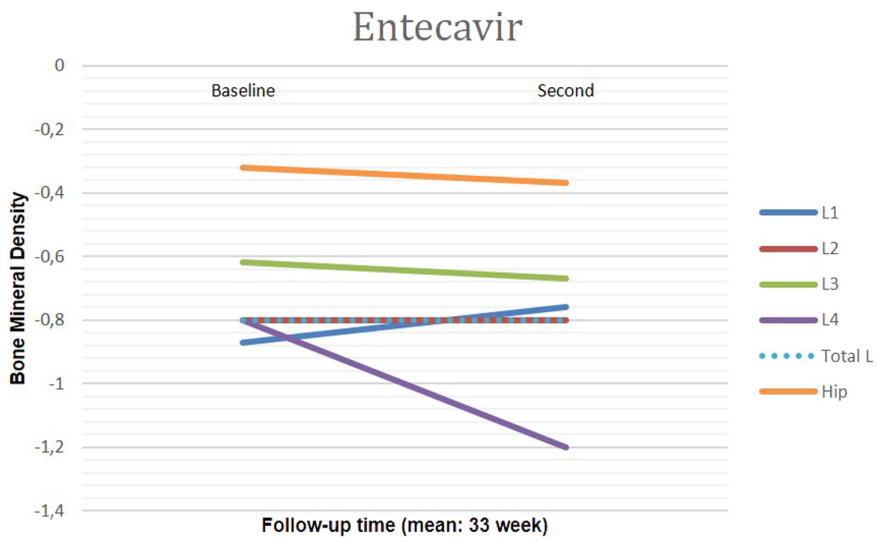

Figure 1. Baseline and second BMD changes in entecavir group. BMD, bone mineral density.

Entecavir Treatment Group

There was no statistically significant difference between baseline BMD and second BMD for the L1 spine (P = .44), L2 spine (P = .083), L3 spine (P = .477), L4 spine (P = .386), total lumbar spine (P = .821), and total hip (P = .615) in patients treated with ETV (Table 2, Figure 1).

The baseline BMD and second BMD measurements were compared after dividing the patients into 3 groups as follows: normal BMD, osteopenic, and osteoporotic (Table 3). No significant difference was found in the number of normal, osteopenic, and osteoporotic individuals in the second BMD measurement according to baseline BMD L1, L2, L3, L4 spine, total L1–4 spine, and total hip (Table 3).

There was no statistically significant difference between baseline major FRAX score and second major FRAX scores in patients treated with ETV (3.9 vs 3.8, P = .704, Table 2). During follow-up, a fibula fracture in 1 patient was observed.

DISCUSSION

In this study, we investigated the long-term effect of TDF and ETV treatments on BMD and fracture risk in patients

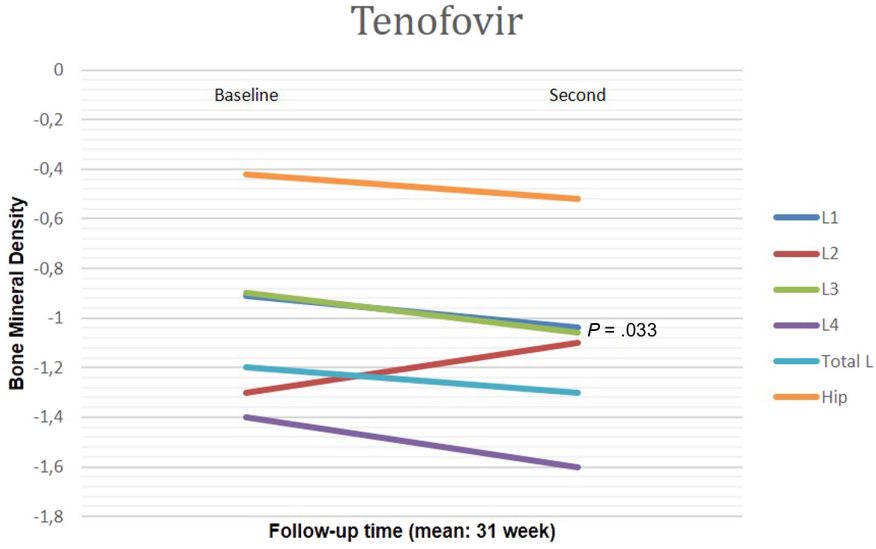

Figure 2. Baseline and second BMD changes in tenofovir group. BMD, bone mineral density.

Table 3. Comparison of the Normal, Osteopenia, and Osteoporosis Classification According to Baseline and Second BMD Scores

	Entecavir (ENT)			Tenofovir Disoproxil Fumarate (TDF)			
BMD	Normal, n (%)	Osteopenia, n (%)	Osteoporosis, n (%)	Normal, n (%)	Osteopenia, n (%)	Osteoporosis, n (%)	P^1
L1 spine T score							
Baseline	11 (61.1)	6 (33.3)	1 (5.6)	21 (52.5)	17 (42.5)	2 (5.0)	.802
Second	11 (61.1)	5 (27.8)	2 (11.1)	17 (42.5)	21 (52.5)	2 (5.0)	.190
P^2		**1**			.334		
L2 spine T score							
Baseline	11 (61.1)	7 (38.9)	0 (0)	17 (42.5)	20 (50.0)	3 (7.5)	.412
Second	10 (55.6)	6 (33.3)	2 (11.1)	17 (42.5)	17 (42.5)	6 (15.0)	.680
P^2		**.244**			.581		
L3 spine T score							
Baseline	9 (50.0)	8 (44.4)	1 (5.6)	18 (45.0)	21 (52.5)	1 (2.5)	.702
Second	10 (55.6)	7 (38.9)	1 (5.6)	17 (42.5)	18 (45.0)	5 (12.5)	.656
P^2		**1**			.232		
L4 spine T score							
Baseline	9 (50.0)	6 (33.3)	3 (16.7)	15 (37.5)	19 (47.5)	6 (15.0)	.595
Second	7 (38.9)	11 (61.1)	0 (0)	13 (32.5)	18 (45.0)	9 (22.5)	.083
P^2		**1**			.297		
Total L Spine T score							
Baseline	9 (50.0)	9 (50.0)	0 (0)	17 (42.5)	22 (55.0)	1 (2.5)	.846
Second	10 (55.6)	7 (38.9)	1 (5.6)	14 (35.0)	22 (55.0)	4 (10.0)	.476
P^2		**1**			.108		
Hip T score							
Baseline	14 (77.8)	4 (22.2)	0 (0)	34 (85.0)	6 (15.0)	0 (0)	.483
Second	15 (83.3)	3 (16.7)	0 (0)	28 (70.0)	12 (30.0)	0 (0)	.348
P^2		**.317**			**.034**		

Pearson's-chi-square test (Monte Carlo), Fisher–Freeman–Halton test (Monte Carlo), marginal homogeneity test (Monte Carlo); P^1, for between-group; P^2, for within-group; L1 spine, lumbar first spine; BMD, bone mineral density. Bold text indicates statistically significant values.

with CHB. This study showed an increase in the number of patients with hip osteopenia and major fracture risk score after long-term TDF treatment in CHB patients.

Initial studies of adverse effects of TDF on bone metabolism have been observed during treatment with TDF in patients with HIV disease. In 2007, Brim and colleagues[20] presented an HIV-positive patient who developed Fanconi syndrome resulting from TDF use, and this patient later developed pathological bone fractures. In 2007, Cassetti et al[21] investigated the safety and efficacy of TDF in combination with lamivudine and efavirenz in a 6-year study enrolling antiretroviral-naive HIV-1-infected patients. There were minor osteopenic changes in the lumbar spine and hips during the first 48 weeks, but osteopenia did not progress. In 2010, Stellbrink and colleagues[22] conducted a study comparing bone density and bone turnover changes with tenofovir–emtricitabine and abacavir–lamivudine in HIV-infected adults. Patients treated with tenofovir–emtricitabine showed a marked decrease in BMD compared to patients treated with abacavir–lamivudine.[22] In a randomized controlled trial conducted by Bernardino et al[23] the raltegravir-based treatment regimen and the TDF-based treatment regimen administered to HIV patients were compared for the development of osteoporosis in these patients. There was a significant decrease in BMD and an increase in bone fractures in the TDF group. Due to the results of these

studies, it has been started to investigate whether TDF treatment causes risk of osteoporosis in CHB patients. In a cohort study by Wong et al[15] long-term safety of oral nucleos(t)ide analogs was assessed in a total of 53 500 CHB patients (46 454 untreated and 7046 treated patients). In this study, patients were followed up for 3 years, and exposure to nucleotide analogs was found to increase the risk of hip fracture compared to nucleoside analogs (hazard ratio = 5.69, 95% CI: 1.98-16.39, $P = .001$).[15] In the study of Gill et al[24] bone mineral density and fracture risk score were compared with healthy controls in patients with CHB treated with TDF. There was a decrease in hip BMD score and an increase in fracture risk score in patients with CHB treated with TDF. Similar to the results of these studies, in our study, in the TDF group, there was an increase in the number of osteopenic patients according to hip BMD and an increase in major FRAX score. However, no significant change was found in BMD and major FRAX score in our patients with ETV treatment. There are limited data on the development of bone loss associated with TDF treatment in patients with HBV infection. Various mechanisms of TDF causing osteoporosis have been reported. Tenofovir disoproxil fumarate contains phosphanate in its formulation and therefore binds to osteoclasts in the bone, similar to bisphosphonates. Tenofovir disoproxil fumarate may cause osteoporosis by inhibiting DNA synthesis in osteoclasts in the bone and by proximal renal tubule dysfunction (Fanconi syndrome) in the kidney.[8] Adverse effects on bone metabolism associated with TDF treatment may be present in the first year of treatment similar to steroid-induced osteoporosis.[25] There is evidence to support this idea in the study of Cassetti et al[21] who showed that osteopenic changes in the lumbar spine and hip BMD measurements were observed during the first 48 weeks, but it did not progress thereafter the follow-up. In a recent study by Seto et al[26] the bone resorption marker was shown to be significantly higher in TDF patients than in the tenofovir alafenamide group in 96-week follow-up. This information supports the effect of TDF on bone turnover in early period. In our study, we found a significant decrease in L3 lumbar spine BMD in the second BMD measurements when comparing the baseline in the TDF group. However, at the end of follow-up, there was an increase in the osteopenic patient numbers in the hip BMD in TDF group. There are no data on when these changes in BMD began because we measured BMD only at the beginning and at the end of the study.

On the contrary, in a study conducted by Tien et al[16] there was no increase in the risk of osteoporosis with TDF treatment. In this study, BMD measurements were assessed only once after 18 months or longer TDF therapy. Similarly, in a study conducted by Buti and colleagues,[27] the annual BMD measurements of CHB patients treated with TDF were investigated between the fourth and the seventh years of treatment. In this study, there was no statistically significant osteopenia and osteoporosis.[27] In both trials, BMD measurements were not performed at baseline. Therefore, if measurements were made after 1 year in TDF exposure, there may not be a significant difference in BMD. Thus, in latest guideline, follow-up of BMD measurement at baseline and during treatment is recommended in patients at risk of fracture or osteopenia.[28]

There are some studies with different results on this subject. In a study by Tonon et al[29] no significant difference was found between BMD measurements and fracture risks in patients with HBV-associated cirrhosis treated with TDF and ETV. In a similar manner, Bunchorntavakul et al[30] compared BMD and kidney functions in CHB patients taking nucleotide and nucleoside analogs. They enrolled 10 patients who were treated with nucleotide analogs (7 with TDF and 3 with adefovir) and 10 patients treated with nucleoside analogs (8 patients treated with lamivudine and 2 patients treated with ETV), and median follow-up was 1.5 years (range, 1.2-1.6 years). The BMD measurements were not significantly different between the groups.[30] On the other hand, in our study, there was no difference between baseline results and second BMD measurements in only ETV group. In studies related to entecavir, it is generally seen that there is no negative effect on BMD. Current guidelines also recommend that entecavir be preferred in patients with bone disease. However, in cases of suspected TDF-associated bone disease, discontinuation of TDF treatment and substitution with Tenofovir alafenamide or entecavir is recommended.[28]

The limitation of this study is the small number of patients and not analyzing the serum bone turnover markers of patients. However, the positive aspect of this study was that the study compared baseline BMD and FRAX score with a second BMD and FRAX score measurements prospectively in long-term follow-up time.

In conclusion, this study suggests that there was an increase in the number of patients with hip osteopenia and major fracture risk score and significant decrease in L3 lumbar spine BMD after long-term TDF treatment in CHB patients. It is suggested that CHB patients treated with TDF should be followed and treated for osteoporosis

if there is a risk factor for osteoporosis. In this regard, further studies are needed.

Ethics Committee Approval: This study was approved by the medical ethics committe of Ümraniye Training and Research Hospital (No: 2012-4873).

Informed Consent: Written informed consent was obtained from all patients.

Peer Review: Externally peer-reviewed.

Author Contributions: Consept – R.K., A.S.; Design – R.K., A.S.; Supervision – K.O., O.O.; Resources – E.K., RK.; Materials – T.C., R.K.; Data Collection and/or Processing – E.K., T.C.; Analysis and/or Interpretation – O.Ö., L.D.; Literature Search – R.K., A.S.; Writing Manuscript – R.K., O.Ö.; Critical Review – K.Ö., S.S.

Conflict of Interest: The authors have no conflict of interest to declare.

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