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The Effect of Entecavir and Tenofovir Disoproxil on Bone Mineral Density in Chronic Hepatitis B Treatment

Kronik Hepatit B Tedavisinde Entekavir ve Tenofovir Disoproksilin Kemik Mineral Yoğunluğuna Etkisi

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Abstract

Aim: Evaluation of the relationship between drugs and osteoporosis in patients receiving entecavir (ETV) or tenofovir disoproxil fumarate (TDF) treatment for chronic hepatitis B infection (CHB).

Material and Method: The study included patients who received ETV or TDF treatment for at least 12 months between 2016 and 2021 and underwent bone mineral densitometry (BMD) measurement at different times during the treatment period. Demographic characteristics of the patients and the association of antiviral drug use with osteopenia/osteoporosis were evaluated. retrospectively.

Results: The study included 170 patients, 92 (54.1%) of whom were male, with a mean age at diagnosis of 36.57±14.88 years. Of the patients, 24 (14.1%) were on ETV and 146 (85.9%) were on TDF. The mean age at BMD measurement was 48.62±13.4 years. The median time from diagnosis to BMD was 138.5 (15-373) months. Osteopenia/osteoporosis was found in 14 (15.2%) of male patients and 25 (32.1%) of female patients. The frequency of osteopenia/osteoporosis was significantly higher in women (p=0.011). There was no significant difference in the frequency of osteopenia/osteoporosis between ETV and TDF (p=0.112). Lumbar spine (LS) BMD was significantly higher in TDF users (p=0.043). While no patient had a BMD within 12 months of treatment initiation, 6 (3.5%) of the patients had a BMD within 24 months, 8 (4.7%) within 36 months and 25 (14.7%) within 60 months of treatment initiation.

Conclusion: There was no significant difference in the development of osteopenia/osteoporosis in patients using TDF and ETV. It was found that bone mineral measurements of patients with CHB were not performed regularly and appropriately.

Keywords: Chronic hepatitis B, osteoporosis, tenofovir disoproxil fumarate, entecavir.

Öz

Amaç: Kronik hepatit B enfeksiyonu (KHB) nedeniyle entekavir(ETV) veya tenofovir disoproksil fumarat (TDF) tedavisi alan hastalarda ilaçların osteoporoz ile ilişkisinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: 2016-2021 yılları arasında en az 12 ay boyunca ETV veya TDF tedavisi başlanan ve sonraki takiplerinde kemik mineral dansitometri (KMD) ölçümü yapılan hastaların demografik özellikleri ile antiviral ilaç kullanımının osteopeni/ osteoporoz ile ilişkisi retrospektif olarak değerlendirildi.

Bulgular: Çalışmaya 92'si (%54,1) erkek, ortalama tanı yaşı 36,57±14,88 yıl olan 170 hasta dâhil edildi. Hastaların 24'ü (%14,1) ETV, 146'sı (%85,9) ise TDF kullanıyordu. Ortalama KMD ölçüm yaşı 48,62±13,4 yıl idi. Tanıdan itibaren KMD'ye kadar geçen süre ortanca 138,5 (15-373) ay idi. Erkek hastaların 14'ünde (%15,2), kadın hastaların ise 25'inde (%32,1) osteopeni/osteoporoz saptanırken, kadınlarda osteopeni/osteoporoz sıklığı anlamlı olarak daha yüksek idi (p=0,011). ETV ve TDF arasında osteopeni/osteoporoz sıklığı açısından anlamlı farklılık izlenmedi (p=0,112). KMD parametrelerinde Lomber spine(LS) KMD TDF kullananlarda anlamlı olarak daha yüksek idi (p=0,043). Tedavi başlandıktan sonra 12 ay içinde hiçbir hastaya KMD istenmezken, hastaların 6 'sına (%3,5) tedavi başlandıktan sonraki 24 ay içinde, 8'ine (%4,7) 36 ay içinde, 25'ine de (%14,7) 60 ay içinde KMD istenmişti.

Sonuç: TDF ve ETV kullanan hastalarda osteopeni/osteoporoz gelişimi açısından anlamlı farklılık saptanmadı. KHB'si olan hastaların kemik mineral ölçümlerinin düzenli ve uygun bir şekilde yapılmadığı saptandı.

Anahtar Kelimeler: Kronik hepatit B, osteoporoz, tenofovir disoproksil fumarat, entekavir.

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INTRODUCTION

Despite an effective vaccination program, CHB infection continues to be a major global health problem, affecting nearly 300 million people and causing approximately 900,000 deaths annually due to cirrhosis and hepatocellular carcinoma (HCC), according to data released by the World Health Organization.[1]

Although hepatitis B surface antigen (HBsAg) seroconversion is expected in the treatment of CHB, treatment continues throughout the patient's life since seroconversion occurs at low rates. The aim of treatment is to prevent disease progression and the development of cirrhosis and hepatocellular carcinoma.[2-5]

Nucleos(t)it analogs such as ETV, TDF and tenofovir alafenamide fumarate (TAF) are used in treatment due to their high antiviral efficacy and favorable long-term safety profile.[2-5]

Hepatic osteodystrophy is a general term used to describe metabolic bone diseases that develop in patients with chronic liver disease. The definition of hepatic osteodystrophy includes both osteopenia and osteoporosis.[6] There are many factors that cause osteoporosis in liver diseases. Malnutrition due to impaired liver function, malabsorption and impaired vitamin D synthesis are the main factors. In addition, deficiency of albumin and binding globulins involved in vitamin D transport also contributes to the mechanism. Diuretics, steroids and antiviral drugs used in treatment are also suspected. Studies in animal models have shown that tenofovir, one of the antiviral drugs, decreases bone mineral density.[7,8]

In our study, we aimed to evaluate the relationship between antiviral drugs and osteopenia/osteoporosis and the status of screening examinations in patients receiving ETV or TDF treatment for CHB infection with real-life data.

MATERIAL AND METHOD

The study included patients aged 18 years and older who received ETV or TDF treatment for at least 12 months between 2016 and 2021 and had bone mineral densitometry (BMD) measurements during the treatment period.Patients using specific drug groups [such as glucocorticosteroids (5 mg prednisone or equivalent for at least 3 months), anticonvulsants, anticoagulants, long-term proton pump inhibitors], have hyperthyroidism, hyperparathyroidism, cirrhosis, and alcohol-dependent patients were excluded. (**Figure 1**). Patients' age at diagnosis, gender, menopausal state, chronic HBV medications, follow-up period and BMD results were evaluated retrospectively by scanning from the hospital electronic information system. HBV DNA was found to be <20 IU/ml in patients receiving antiviral treatment and the disease was considered inactive. Vitamin D levels were not included because of the long follow-up period.

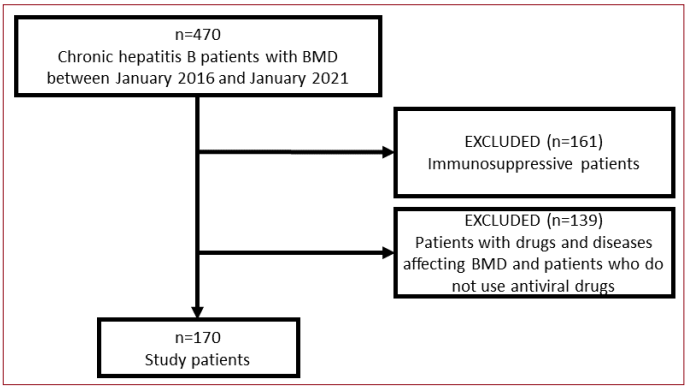

Figure 1. Flow chart of patients included in the study

BMD was measured by dual-energy X-ray absptiometry (DEXA). All DEXA measurements were made using the Hologic Discovery scanner and evaluated by the same person. T-score was used in postmenopausal women and men over 50 years of age, Z-score was used in premenopausal women and men under 50 years of age.T-score less than -2.5 standard deviation (SD) was defined as osteoporosis, between -1 and -2.5 SD as osteopenia and SD greater than -1 as normal. A Z score of -2 SD and below was considered as "lower than expected bone mass for chronological age/osteoporosis" and above -2 as "normal bone mass for chronological age/normal".[9]

Ethical Consideration

The study was carried out with the permission of Karadeniz Technical University Faculty of Medicine Ethics Committee (Date:13.01.2022 Decision no:315). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Statistical Analysis

SPSS Windows version 22 program was used for statistical tests. Continuous variables were evaluated in terms of normal distribution by histogram, Q-Q graph and Shaphiro-Wilk or Kolmogorov-Smirnov tests according to the number of variables. The normally distributed continuous variables were presented as mean±standard deviation throughout the study and independent-variables t-test was used to compare the two groups.

Other continuous variables were presented with median (minimum-maximum) values and the nonparametric Mann-Whitney U test was used to compare the groups.

Categorical variables were presented as frequencies and percentages, and Pearson Chi-square test or Fischer's exact probability test was used to compare the groups. Tests with a p value of 0.05 or less at the 95 percent confidence interval were considered statistically significant.

RESULTS

The study included 170 patients. 92 (54.1%) of the patients were male and 78 (45.9%) were female. The mean age at diagnosis was 36.57±14.88 years and the mean age at

BMD measurement was 48.62±13.4 years. The mean age at diagnosis and age at BMD assessment were lower in women than in men (p=0.014, p=0.004, respectively. Twelve (7.1%) of the patients at the time of diagnosis and 18 (10.6%) at the time of drug initiation were aged 60 and over. The median time from diagnosis to BMD was 138.5 (15-373) months. Of the patients, 24 (14.1%) were on ETV and 146 (85.9%) were on TDF. The median duration of TDF use was longer than ETV (p=0.001). Osteopenia/osteoporosis was found in 14 (15.2%) of male patients and 25 (32.1%) of female patients, and the frequency of osteopenia/osteoporosis was significantly higher in women (p=0.011) (**Table 1**).

Table 1. Demographic characteristics of the patients

Value		p
Male/Female, n (%)	92 (54.1) / 78 (45.9)	
Antiviral drug, n (%)		
ETVa	24 (14.1)	
TDFb	146 (85.9)	
≥ 60 years, n (%)		
Diagnosis	12 (7.1)	
Medication initiation	18 (10.6)	
Age (Diagnosis), mean± SD	36.57±14.88	
Male	39.14±14.75	0.014*
Female	33.54±14.55	
Age** (BMDc), mean±SD	48.62±13.4	
Male	51.35±13.36	0.004*
Female	45.41±12.81	
Osteopenia/osteoporosis, n (%)		
Male	14 (15.2)	0.011†
Female	25 (32.1)	

*:t Test, †: Chi-square test SD: Standard derivation,
**at diagnosis time, a :Entecavir , b :Tenofovir disoproxil fumarate, c :Bone mineral density

During the period from diagnosis to BMD, osteopenia or osteoporosis was detected in 9 (37.5%) patients on ETV and 30 (20.5%) patients on TDF, but there was no significant difference in the frequency of osteopenia/osteoporosis between drugs (p=0.11).

When BMD was analyzed, LS BMD was significantly higher in TDF users (p=0.043), while no significant difference was found in LS T/Z-score, Femoral Neck (FN) BMD, FN T/Z-score, Total Femur (TF) BMD and TF T/Z-score (p>0.05) (**Table 2**).

None of the patients had a BMD within 12 months of treatment initiation. 6 (3.5%), 8 (4.7%) and 25 (14.7%) patients had a BMD within 24, 36 and 60 months, respectively (**Table 2**).

DISCUSSION

TDF and ETV are antiviral drugs that have a high genetic barrier in CHB, reduce liver-related mortality and are recommended in first-line treatment.[2,10,11] In our study, we investigated the effect of antiviral drugs on BMD in patients receiving TDF or ETV treatment.

TDF use may cause osteoporosis through various pathways including the development of Fanconi syndrome and hypophosphatemic osteomalacia by accumulating in the proximal tubule and decreasing bone formation by decreasing osteoblast gene expression.[12-14] The decreasing effect of TDF on BMD has been demonstrated primarily in HIV patients and then in monoinfected CHB patients in various studies.[15-17]

In the study conducted by Wei et al.[18] in the USA examining the effect of ETV and TDF on BMD in patients using ETV or TDF, no increase in the risk of osteopenia/osteoporosis was found in the short and medium term. In our study, osteopenia/osteoporosis was found in 30 (20.5%) patients on TDF, while osteopenia/osteoporotikse was found in 9 (37.5%) patients on ETV, and no significant difference was found in the frequency of osteopenia/osteoporosis between the two drugs (p=0.112).

Table 2. Association of antiviral drugs with BMD

Value	ETVa	TDFb	p
BMD*, n (%)			
Normal	15 (62.5)	116 (79.5)	0.112†
Osteopenia/osteoporosis	9 (37.5)	30 (20.5)	
Gender, n (%)			
Male	13 (54.2)	79 (54.1)	1†
Female	11 (45.8)	67 (45.9)	
Duration of drug use, months mean±SD	37.42±28.65	57.97±28.02	0.001*
Age(Diagnosis), year	40.38±16.21	35.95±14.62	0.177*
BMD, diagnosis(month)	124.83±88.13	154.68±82.34	0.105*
LSc BMD,mean±SD	1.07±0.213	1.15±0.181	0.043*
LS T/Z-score, mean±SD	-0.5042±1.8066	0.0784±1.4071	0.073*
FNd BMD, mean± SD	0.9199±0.1869	0.9588±0.1513	0.262*
FN T/Z-score, mean±SD	-0.3833±1.4621	-0.1959±1.2227	0.500*
TFe BMD, median (iqr)	0.931 (0.16)	1.007 (0.22)	0.071 ‡
TF T/Z-score, mean± SD	-0.4042±1.519	-0.0055±1.197	0.148*
Time to BMD month			
12	0	0	
24	2 (8.3)	4 (2.7)	0.201†
36	4 (16.7)	4 (2.7)	0.015†
60	4 (16.7)	21 (14.4)	0.758†

*: t Test, †: Chi-square test , ‡: Mann-Whitney u test SD: Standard derivation, iqr: Interquertile range, * :Bone mineral density, a :Entecavir, b : Tenofovir disoproxil fumarate, c:Lomber spine, d :Femoral neck, e :Total femur

In the meta-analysis including 16 studies conducted by Yang et al. no significant difference was found in the incidence of osteoporosis/osteopenia between patients using TDF and ETV (p=0.13).[19] In our study, despite the longer duration of TDF use, LS BMD was higher than ETV (p=0.043), while no significant difference was found in L1-L4 T-score, FN BMD, FN T-score, TF BMD and TF T-score (p>0.05).

Tenofovir alafenamide (TAF) molecule, the new formulation of tenofovir, is thought to have less negative effects on bone health. In a double-blind randomized study by Seto et al.[20] it was found that patients who received TDF for 2 years had a greater decrease in hip and spine bone mineral density than patients who received TAF. Due to the long-term use of TDF, which is associated with a decrease in BMD, studies examining its effect on the development of osteopenia/osteoporosis are of special importance.

The EASL 2017 guideline recommends switching TDF to TAF or ETV in patients aged 60 years and older and in patients with existing bone disease (stress fractures, long-term use of corticosteroid drugs, osteoporosis) because of the high risk of side effects.[2] In our study, 18 (10.6%) of the patients were 60 years of age or older at the time of drug initiation, and 13 (72.2%) of these patients were started on TDF.

According to the Turkish Society of Endocrinology and Metabolism (TEMD) guideline, BMD measurement is recommended for every patient with a diagnosis of chronic liver disease. An evaluation should also be performed due to the additional risks that may occur on bone metabolism after the initiation of antiviral agents.[21] In our study, only 6 patients (3.5%) had BMD measurement within 24 months after initiation of treatment.

The most important limitations of our study are that it was retrospective and single centered. In addition, the number of patients on ETV and TDF is not evenly distributed.

The age at diagnosis is probably earlier, but the accepted date of diagnosis of the disease was taken as the date of first detection.

CONCLUSION

In conclusion, in our study, although the duration of TDF use was longer in patients receiving ETV or TDF treatment, no statistically significant difference was found in osteoporosis/osteopenia rates. More long-term and prospective studies are needed to examine the effects of antiviral treatments on the development of osteopenia/osteoporosis.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Karadeniz Technical University Faculty of Medicine Ethics Committee (Date: 13.01.2022, Decision no: 315).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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