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HEPATITIS B (JK LIM, SECTION EDITOR)

Epidemiology, Diagnosis, and Management of Bone Disease in Patients with Chronic HBV Infection

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Abstract

Purpose of Review Chronic hepatitis B (CHB) and treatment may be associated with increased risk of osteopenia/osteoporosis. Here, we review the prevalence of osteopenia/osteoporosis among patients with CHB and the effect of antiviral therapy on bone density. We also highlight screening and management strategies for bone disease among patients with CHB.

Recent Findings While there are concerns with first-line antiviral therapy such as tenofovir disoproxil fumarate in the development of osteopenia/osteoporosis, the available data remain rather unclear. However, with the development of tenofovir alafenamide, these concerns may be mitigated. At present, EASL recommends dual-energy X-ray absorption (DEXA) scans for patients with osteoporotic risk factors, with a repeat DEXA scan based upon baseline findings.

Summary Patients with CHB have higher incidence and prevalence of osteopenia/osteoporosis compared with patients without CHB. Further studies are needed to understand the impact of antiviral therapy on bone therapy, and more CHB specific recommendations are needed for bone health management.

Keywords Hepatitis B · Tenofovir disoproxil fumarate · Entecavir · Osteoporosis · Tenofovir alafenamide

Introduction

Chronic hepatitis B (CHB), listed as one of the top 20 causes of mortality globally, has been estimated to have caused 884,000 deaths in 2015 [1, 2]. As of 2010, 248 million individuals were estimated to have chronic hepatitis B, with significant regional variation in disease burden [3]. Up to 40% of untreated individuals can develop cirrhosis, incurring the risk of cirrhotic complications as well as hepatocellular carcinoma (HCC) [4].

Osteoporosis is defined as a "disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased risk of fractures of the hip, spine, and wrist" [5•]. Osteoporosis is usually diagnosed by dual-energy X-ray absorption (DEXA) to assess bone mineral density (BMD) [6]. Specifically, osteoporosis is defined by the World Health Organization as BMD that lies 2.5 standard deviations below that of young healthy women (T-score < -2.5 SD) [7]. As of 2010, an estimated 10.3% of adults 50 years or older had osteoporosis, and 43.9% had low bone mass [8, 9].

Patients with the chronic liver disease tend to have a higher risk of bone fracture, reduced bone formation, decreased bone turnover, and decreased osteoblast function, especially in patients with cholestatic liver diseases [10–12]. This phenomenon of bone disease among patients with chronic liver diseases has been termed hepatic osteodystrophy [13]. Complications in the analysis of patients with chronic liver disease are that many of them have other known risk factors of osteopenia and osteoporosis, such as increased age, low sun exposure, low body mass index, smoking, alcohol use disorder, and nutritional deficiencies (e.g., vitamin D) [10, 14].

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Association Between CHB and Risk of Osteopenia/Osteoporosis

Several population studies have suggested that CHB leads to a higher risk of osteopenia/osteoporosis. In an insurance claims-based study in Taiwan using ICD-9 codes, on multivariate analysis, Chen et al. found HBV to be a risk factor for osteoporosis (aHR 1.13, 95% CI, 1.03–1.25) and osteoporotic fractures (aHR 1.20, 95% CI, 0.77–1.86) [15]. In a cross-sectional study of Korean adult males utilizing the 2008–2010 Korean National Health and Nutrition Examination Survey (KNHANES), HBsAg(+) males had significantly lower femoral neck BMD compared with HBsAg(−) males (0.810 vs 0.827 g/cm^2, $p = 0.035$). However, no statistically significant difference was identified for pre- and postmenopausal women [13].

Prevalence of Bone Disease in Patients with CHB (Table 1)

Among patients with chronic viral hepatitis, several small-scale studies have estimated between 14 and 53% of patients to have osteoporosis, though some of these studies have focused on patients with cirrhosis [10, 11, 14, 16]. The wide range is likely due to selection bias such as sex, age, percentage of a patient with cirrhosis included and how the diagnosis of hepatitis and osteoporosis were made. In any case, among larger studies, such as an insurance claims–based study by Nguyen et al., patients with CHB had a prevalence of osteoporosis between 1.9 and 2.2% [18•]. Interestingly, Nguyen found that among patients with commercial or Medicare insurance, patients with CHB had a higher prevalence of osteoporosis (2.2%) compared with patients without CHB (0.9%) [$p < 0.001$]. This difference was not statistically significant among patients with Medicaid (1.9 vs 1.6%, $p = 0.325$) [18•]. The overall low prevalence of osteoporosis identified in the study may be due to the data being based on insurance databases (Truven, Medicare, Medicaid) and as such osteoporosis may not have been fully captured in the ICD-9 coding. In a separate study evaluating a university medical center and several community primary care clinics, the prevalence of osteoporosis increased from 2000–2005 (2.9%) to 2011–2015 (8.7%) ($p < 0.001$), attributable at least in part to an aging population (mean age 43.3 [2000–2005] vs 49.1 [2011–2015]) [19]. To date, while there is a significant proportion of foreign-born persons in the USA with CHB, no studies focused on ethnic differences in osteopenia/osteoporosis.

Effects of HBV Therapy on Bone Disease

Currently, first-line therapies for the management of CHB include tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), entecavir (ETV), and pegylated interferon alfa (PegIFNα) [21•, 22•, 23]. There has been a concern whether these first-line nucleos(t)ide analogs may increase the risk of osteopenia or osteoporosis, borne primarily out of the HIV literature [24–27]. In CHB, abnormalities in renal tubular function and disequilibrium in renal phosphate handling have been cited as some of the mechanisms by which antiviral therapy may lead to osteomalacia [28, 29]. However, overall the data on nucelos(t)ide analogs and impact on osteopenia/osteoporosis among patients with CHB have been conflicting (Table 2) [17, 24, 28, 30–32, 34–36]. In particular, in our own work, looking at the 8-year incidence of osteopenia/osteoporosis among patients taking TDF, ETV, or remaining untreated, we did not identify any statistically significant difference among the three groups [20]. With regard to bone fracture, some studies found an increased risk among patients with HBV [15, 18•]. However, in a large study by Wong et al., no increased risk of bone fracture (all, hip, or vertebral) between nucleos(t)ide analog-treated and untreated CHB patients was identified. Nevertheless, in this study, nucleotide but not nucleoside analogs (e.g., ETV) may increase the risk of hip fracture compared with untreated patients, but the incidence was very low [33].

Tenofovir Alafenamide: the Solution?

The introduction of tenofovir alafenamide (TAF) in 2016 has provided a possible alternative to tenofovir disoproxil fumarate (TDF), for which there has been a concern for worsened bone mineral density [18•]. At the approved dose of 25 mg daily, plasma levels of tenofovir are about 90% lower for TAF compared with TDF at 300 mg daily, with similar efficacy [37, 38]. In two landmark trials, Buti et al. and Chan et al. found similar antiviral efficacy between TDF and TAF while TAF at a 48-week follow-up appeared to have a lesser decrease in BMD compared with TDF [28, 39, 40••, 41••]. In a 96-week follow-up study of the two landmark trials, CHB patients receiving TAF had significantly smaller decreases in hip BMD (0.33 vs 2.51%, $p < 0.001$) and spine BMD (0.75 vs 2.57%, $p < 0.001$) compared with patients receiving TDF. Notably, at 96-week follow-up, the frequency of fractures was similar between TAF and TDF (1 vs 2%, $p = 0.43$) (Table 3) [42].

At this point, the AASLD feels that there is no preference between ETV and TDF in terms of long-term risk of bone disease, but the quality of evidence was rated very low [22•]. In addition, they feel there is insufficient evidence for or against monitoring of BMD in patients on TDF in the absence of risk factors for osteoporosis. While AASLD and EASL practice guidelines remain uncertain on the risk of osteopenia/osteoporosis, in the event of the development of bone disease felt to be related to TDF or at risk for bone disease, the patient should be switched over to TAF or ETV. In particular, in the EASL guidelines, among patients aged

Table 1 Summary of studies on the prevalence of osteopenia/osteoporosis among patients with chronic hepatitis B

Author/publication year/country	Study design	Patients	Study goal	Main findings
Gallego-Rojo/1997/Spain [16]	Case-controlled cross-sectional	32 male patients with viral cirrhosis (8 CHB), 24 male controls	Evaluate the prevalence of osteopenia/osteoporosis among patients with cirrhosis by DEXA.	53% of patients with cirrhosis had osteoporosis; higher prevalence of osteoporosis with higher Child-Pugh class (A 37.5%, B 60%, C 66%).
Wariaghli/2010/Morocco [11]	Matched case-control	64 chronic liver disease patients (33 primary biliary cirrhosis, 31 chronic viral hepatitis), 97 controls	Assess the prevalence and risk factors of osteoporosis among patients with the chronic liver disease using DEXA.	45.3% of patients with chronic liver disease had osteoporosis, compared with 19.6% of controls. 38.7% of patients with chronic viral hepatitis had osteoporosis, compared with 16.1% of controls.
Tien/2014/USA [17]	Cross-sectional	42 TDF, 44 ETV, 60 untreated	Evaluate changes in BMD and renal phosphate wasting among CHB patients receiving tenofovir, entecavir, or untreated.	Prevalence of osteoporosis by DEXA was 14%.
Chen/2015/Taiwan [15]	Retrospective observational	36,146 CHB, 144,584 controls	Assess association between HBV and risk of osteoporosis using ICD-9.	In multivariate analysis, CHB patients had a higher risk for osteoporosis (aHR 1.13, 95% CI 1.03–1.25) and osteoporotic fractures (aHR 1.20, 95% CI 0.77–1.86).
Nguyen/2018/USA [18•]	Retrospective observational	44,026 CHB, 121,568 controls	Determine the prevalence and incidence of non-liver comorbidities among CHB patients using ICD-9.	Prevalence of osteoporosis was higher for CHB patients than non-CHB patients (2.2 vs 0.9%, $p < 0.001$) for patients with commercial insurance; no statistical significance for Medicaid (1.9 vs 1.6%, $p = 0.325$). When looking at osteoporosis and/or pathologic bone fracture in 2015, the prevalence of CHB patients was higher compared with non-CHB patients regardless of whether the patients had commercial/Medicare (142.1 vs 127.9 per 1000 persons, $p < 0.05$) or Medicaid (314.3 vs 204.4 per 1000 persons, $p < 0.05$).
Liu/2018/USA [19]	Retrospective observational	2734 CHB	Study prevalence of non-liver comorbidities among CHB patients over 15 years, defined by ICD-9 codes.	Between 2000–2005 and 2011–2015, the prevalence of osteoporosis increased from 2.9 to 8.7% ($p < 0.001$), while osteopenia increased from 5.4 to 13.4%.
Wei/2019/USA [20]	Retrospective cohort	1224 CHB patients (276 TDF, 335 ETV, 613 untreated)	Evaluate the incidence of osteopenia or osteoporosis among CHB patients receiving tenofovir, entecavir, or untreated, using ICD-9.	8-Year cumulative incidence rate of osteopenia/osteoporosis was 13.17% for TDF, 15.09% for ETV and 10.17% for untreated patients, with no statistically significant difference among the three groups ($p = 0.218$).

BMD, bone mineral density; *CHB*, chronic hepatitis B; *ETV*, entecavir; *ICD-9*, international classification of diseases, ninth revision; *TDF*, tenofovir disoproxil fumarate

Table 2 Summary of studies evaluating the impact of antiviral therapy on the development of osteopenia/osteoporosis

Author/publication year/country	Study design	Patients	Study goal	Main findings
Buti/2014/multinational [30]	Randomized controlled with open-label phase	585 TDF	7-Year efficacy of treating HBeAg-positive and negative CHB patients with TDF with the first year randomized to ADV or TDF.	No significant change in BMD noted between years 4 to 7 in either hip or spine.
Fung/2014/multinational [31]	Double-blind randomized controlled trial	141 TDF, 139 FTC/TDF	Clinical efficacy of using TDF or FTC/TDF to treat CHB patients with lamivudine-resistant mutations.	Baseline spine/hip DEXA demonstrated 34%/22% of patients had osteopenia, 7%/1% had osteoporosis. At week 96, mean change of − 1.4%/− 1.8% in spine/hip BMD.
Gill/2014/England [24]	Cross-sectional	122 TDF, 48 untreated	Studying BMD change among patients with chronic hepatitis B ± TDF.	Compared with no treatment, TDF was associated with increased odds of hip T-score < − 1 (OR 2.95, 95% CI 1.14–7.45).
Maggi/2014/Italy [32]	Cross-sectional	60 LAM + ADV switched to TDF	Evaluate the impact of switching LAM + ADV to TDF on bone and renal toxicity.	52.7% and 28.6% of patients had femoral and spinal osteopenia/osteoporosis at baseline, respectively. At 12 months, this percentage was 60.6 ($p = 0.123$) and 37.5% ($p = 0.221$), respectively.
Tien/2014/USA [17]	Cross-sectional	42 TDF, 44 ETV, 60 untreated	Evaluate changes in BMD and renal phosphate wasting among CHB patients receiving TDF, ETV, or untreated.	No statistically significant difference in prevalence of osteoporosis among TDF (14%), ETV (16%) and untreated (12%) [$p = 0.82$].
Wong/2015/Hong Kong [33]	Cross-sectional	7046 treated, 46,454 untreated	Compare fractures (hip, vertebral, all) for CHB patients with or without nucelos(t)ide analog therapy as defined by ICD-9.	With propensity score weighting, nucleos(t)ide analog therapy did not increase the risk of fracture compared with untreated.
Bunchorntavakul/2016/Thailand [34]*	Cross-sectional	7 TDF, 3 ADV, 8 LAM, 2 ETV	Assess prevalence of bone disease among CHB patients and impact of nucleos(t)ide analogs on BMD and renal function.	Overall prevalence of osteopenia was 45%. No significant difference in the lumbar spine and femoral neck BMD among different antivirals.
Saeedi/2016/Canada [35]	Cross-sectional	36 TDF, 17 ETV, 36 LAM, 36 untreated	Evaluate BMD and biochemical abnormalities among CHB patients receiving antiviral therapy.	Among patients with biochemical abnormalities, there was no statistically significant difference in BMD in the spine for TDF (0.920 ± 0.162) compared with controls (0.896 ± 0.150).
Tonon/2017/Italy [36]	Observational cohort	49 TDF, 22 ETV	Compare the effects of TDF and ETV on BMD among patients with CHB-related cirrhosis.	No statistically significant difference in total lumbar or femoral neck T-score was noted between ETV and TDF.
Wei/2019/USA [20]	Retrospective cohort	276 TDF, 335 ETV, 613 untreated	Evaluate the incidence of osteopenia/osteoporosis among CHB patients receiving tenofovir, entecavir, or untreated.	On multivariate Cox regression, neither TDF (adjusted HR 0.74, 95% CI 0.34–1.59) nor ETV (adjusted HR 0.98, 95% CI 0.51–1.90) was associated with increased osteopenia/osteoporosis risk compared with untreated patients.

*Only abstract available

ADV, adefovir; *BMD*, bone mineral density; *CHB*, chronic hepatitis B; *DEXA*, dual-energy x-ray absorptiometry; *ETV*, entecavir; *FTC*, emtricitabine; *LAM*, lamivudine; *TDF*, tenofovir disoproxil fumarate

Table 3 Summary of studies evaluating the impact of tenofovir alafenamide on bone mineral density

Author/publication year/country	Study design	Patients	Study goal	Main findings
Chan/2016/multinational [41••]	Double-blind randomized controlled trial	581 TAF, 292 TDF	Determine the efficacy and safety of TAF against TDF in the treatment of HBeAg-positive CHB patients.	TAF had less BMD loss in the hip (− 0.10%, 95% CI − 0.29 to 0.09 vs − 1.72%, 95% CI − 2.02 to − 1.41) as well as the spine (− 0.42%, 95% CI − 0.66 to − 0.17 vs − 2.29%, 95% CI − 2.67 to − 1.92) compared with TDF
Buti/2016/multinational [40••]	Double-blind randomized controlled trial	285 TAF, 141 TDF	Determine the efficacy and safety of TAF against TDF in the treatment of HBeAg-negative CHB patients	TAF had less BMD loss in the hip (− 0.29%, 95% CI − 0.55 to − 0.03 vs − 2.16%, 95% CI − 2.53 to − 1.79) as well as the spine (− 0.88%, 95% CI − 1.22 to − 0.54 vs − 2.51%, 95% CI − 3.09 to − 1.94) compared with TDF
Seto/2018/multinational [42]	Double-blind randomized controlled trial	866 TAF, 432 TDF	Evaluate BMD of TAF compared with TDF following 2 years of treatment for CHB patients	At week 96, patients receiving TAF had smaller decreases in the hip (mean reduction of 0.33 vs 2.51%, $p < 0.001$) and spine (reduction in 0.75 vs 2.57%, $p < 0.001$) BMD compared with TDF.

BMD, bone mineral density; *CHB*, chronic hepatitis B; *CI*, confidence interval; *HBeAg*, hepatitis B e antigen; *TAF*, tenofovir alafenamide; *TDF*, tenofovir disoproxil fumarate

> 60, with renal disease, with osteoporosis or risk factors for renal dysfunction or low bone mineral density (history of fragility fracture, history of chronic steroid use, or other bone-affecting medications), TAF or ETV is recommended over TDF [21•, 22•]. However, at this time, TAF is not recommended for pregnant patients as well as patients on dialysis or with creatinine clearance < 15 ml/min [21•, 22•, 43].

Prevention and Management

As mentioned previously, some studies have found that there is an increased risk of bone disease among patient with HBV. It is logical to treat chronic hepatitis B with currently approved regimen if patients meet current treatment recommendations [21•, 22•]. However, a few randomized controlled trials exist evaluating management strategies for osteoporosis among patients with chronic liver disease, and among those, they primarily focus on patients with primary biliary cirrhosis [44]. To date, there are no randomized controlled trials looking specifically at patients with CHB. As such, many of the recommendations for prevention and management of chronic hepatitis B are extrapolations of existing general guidelines for osteoporosis and guidelines written for chronic liver disease [45••].

In general, patients need to maintain adequate calcium (1000 mg/day for men aged 50–70; 1200 mg/day for men age > 70, or women age > 50) and vitamin D (800–1000 IU/day for age > 50), but it is unclear these supplements prevent bone loss among patients with liver disease [8, 45••]. Importantly, given risk factors such as smoking and alcohol use, stopping these habits are paramount in the management of patients with CHB in preventing further bone loss. Other risk factor management includes physical exercise and weight control [6, 10, 24]. Given concurrence of osteopenia/osteoporosis and vitamin D, it may be worthwhile to check 25(OH)D levels in patients with chronic hepatitis B, as vitamin D deficiency may prevent optimized management of low BMD [6]. This is especially important as low vitamin D is very common among patients with chronic liver disease, with estimates of 91% of patients awaiting liver transplantation [46].

Bone Mineral Density Monitoring

In general, all women aged 65 or older should receive hip and lumbar spine BMD screening via DEXA [47, 48•]. For patients younger than age of 65 years, clinical risk assessment tools have often been recommended for decisions regarding DEXA scans, such as the Simple Calculated Osteoporosis Risk Estimation (SCORE), Osteoporosis Risk Assessment Instrument (ORAI), Osteoporosis Self-Assessment Tool (OST), and Osteoporosis Index of Risk (OSIRIS) and Fracture Risk Assessment Tool (FRAX®) [48•]. However, with the exception of FRAX®, none of these tools take into account the presence of liver disease [6, 48•]. While the USPSTF and American Association of Clinical Endocrinologists (AACE)/American College of

Endocrinology feel that clinical risk factors for osteoporosis (including chronic liver disease) may argue for BMD assessment among younger postmenopausal women, DEXA is not generally recommended for premenopausal women and healthy young men [6]. Without more concrete guidelines, for patients who have had fragility fractures, are on long-term corticosteroid therapy (> 3 months), or are postmenopausal, a DEXA scan is advised to determine bone mineral density [12].

At present, EASL recommends obtaining DEXA scans for patients with prior pathologic fractures, on prolonged corticosteroids or prior to liver transplantation. Patients with baseline normal DEXA scan should receive repeat DEXA in 2–3 years. For patients with osteopenia, repeat DEXA in 1–2 years is recommended, as well as consideration for bisphosphonates. For patients with osteoporosis, a repeat in 1 year is recommended (Fig. 1) [45••].

Pharmacologic Therapies

Pharmacologic therapies approved by the US Food and Drug Administration (FDA) include estrogen, raloxifene, parathyroid hormone, and bisphosphonates [48•]. Most of these management strategies are based on outcomes of postmenopausal women. As per the AACE, pharmacologic therapies should be considered for patients with osteoporosis, patients with osteopenia/low bone mass but with history of a fragility fracture of the hip or spine, and patients with osteopenia but FRAX® 10-year probability of major osteoporotic fracture ≥ 20% or a 10-year probability of hip fracture ≥ 3% [6].

Role of Bisphosphonates

Beyond vitamin D and calcium supplementation, additional therapies for osteoporosis include raloxifene, estrogen replacement therapy, calcitonin, and bisphosphonates [12]. At present, medications recommended for management of osteopenia/osteoporosis include bisphosphonates (e.g., alendronate, risedronate, zoledronic acid) and denosumab [6]. In studies for primary biliary cirrhosis, bisphosphonates have been found to improve bone mineral density among patients with osteopenia/osteoporosis [10, 49, 50].

In a small prospective study performed in Turkey, Yurci et al. treated patients with chronic liver disease with different combinations of bisphosphonate, calcium, vitamin D, and calcitonin. The patients, who had chronic hepatitis B or C, were found to have statistically significant improvement in bone mineral density when receiving bisphosphonates (alendronate or risedronate). Notably, calcitonin was found to improve T-score for the lumbar spine but not for femoral neck or distal radius [51]. Separately, in another small-scale study, Bansal et al. found that osteoporotic patients with non-cholestatic liver cirrhosis had statistically significant improvement in bone mineral density with ibandronic acid following 6 months of treatment [52].

At this point, EASL currently recommends bisphosphonates among cirrhotic patients with osteoporosis and those on the liver transplant list [45••]. For patients unable to tolerate oral medications, the next line of osteoporosis management may involve teriparatide, denosumab, or zoledronic acid [6].

Conclusions

Optimal management of CHB includes not only achieving viral suppression, monitoring for cirrhosis, and managing complications of cirrhosis but also managing comorbidities associated with CHB. Patients with CHB have higher incidence and prevalence of osteopenia/osteoporosis compared

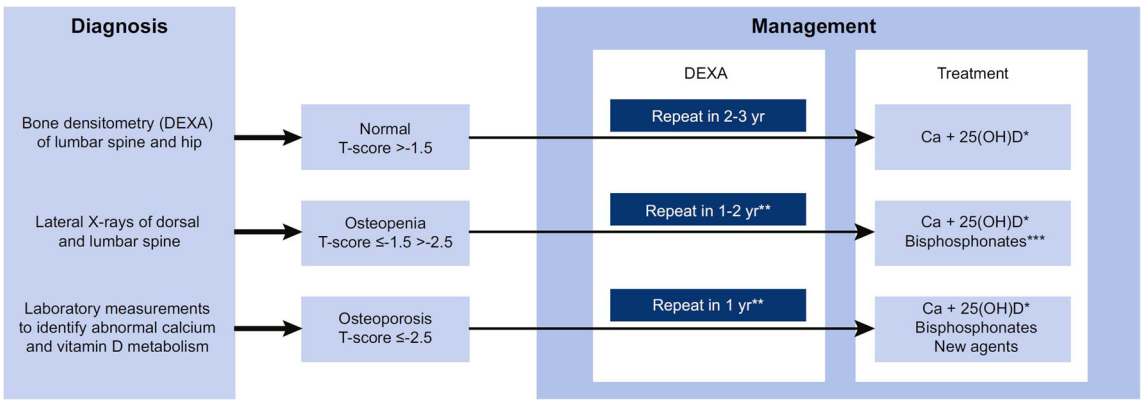

Fig. 1 Diagnosis and management of bone disease in patients with chronic liver disease. *Calcium (1,000–1,500 mg/d) and 25(OH)D (400–800 IU/d or 260 μg every two weeks) to preserve normal levels. **According to the severity of liver disease and cholestasis, and in patients taking corticosteroids. ***Depending on additional risk factors. 25(OH)D, 25-hydroxyvitamin D. DEXA; dual-energy X-ray absorptiometry. EASL diagnosis and management of bone disease among patients with chronic liver disease (Reprinted from Journal of Hepatology, Volume 70 (1), Merli, Manuela et al., EASL Clinical Practice Guidelines on nutrition in chronic liver disease; 172-193; 2019, with permission from Elsevier [45••]

with patients without CHB. While there are some concerns that certain current first-line nucleos(t)ide analogs such as TDF may increase the risk of osteopenia/osteoporosis; these data remain unclear. Further, with the introduction of TAF, this concern may be mitigated but long-term data is still pending. In the management and prevention of bone disease, beyond adequate intake of calcium and vitamin D and exercise and the elimination of risk factors such as smoking and alcohol usage, DEXA scans are recommended for patients with osteoporotic risk factors. At this point, multiple medications, in particular bisphosphonates, are available for the management of osteoporosis. With increasing awareness of comorbidities of CHB, more research into individualized assessment and particularly the effectiveness of osteopenia/osteoporosis treatment among patients with CHB is required.

Compliance with Ethical Standards

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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