Bone Mineral Density and Renal Function in Chronic Hepatitis B Patients Receiving Nucleotide versus Nucleoside Analogs: A Pilot Prospective Study

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Background: *The use of nucleotide analogs (NTAs) can be associated with negative effects on renal function and bone mineral density (BMD) due to proximal tubular dysfunction and hypophosphatemia; however, prospective data assessing the bone and renal safety of these agents are limited.*
Objective: *This study aimed to evaluate the prevalence of bone diseases among chronic hepatitis B (CHB) patients without cirrhosis and the changes in BMD and glomerular filtration rate (GFR) between patients receiving NTAs versus nucleoside analogs (NSAs).*
Material and Method: *We prospectively collected data from non-cirrhotic CHB patients who had been treated for <1 year in Rajavithi Hospital (Bangkok, Thailand) between 2012 and 2014. Patients with significant comorbidities or those being treated for bone diseases were excluded. BMD assessment was performed at the lumbar spine (LS) and femoral neck (FN). BMD T-scores were used to define osteopenia (-2.5 to -1) and osteoporosis (<-2.5), and the GFR was estimated using the Cockcroft-Gault method.*
Results: *Twenty patients were included: 65% were men; 40% were HBeAg positive; and the median age was 42.7 (25.6-64.2) years. Ten patients had been treated with NTAs (7 with tenofovir, 3 with adefovir) and 10 patients had been treated with NSAs (8 with lamivudine, 2 with entecavir), with a median follow-up period of 1.5 years (1.2-1.6). At baseline, the overall prevalence of osteopenia was 45% and the median GFR was 94 (51-144) mL/min. BMD in CHB patients was slightly lower than in an age-matched population based on Z-scores. Changes in LS-BMD and FN-BMD were not significantly different between groups. The annual reduction in GFR was more pronounced in the NTA group (-7.4% vs. -1.39%, p = 0.018).*
Conclusion: *Osteopenia is common in CHB patients without cirrhosis. Changes in BMD were not significantly different between groups. The annual reduction in GFR was more pronounced in the NTA group.*

Keywords: *Bone mineral density, Renal function, Chronic hepatitis B, Nucleotide analog, Nucleoside analog, Osteopenia*

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Chronic hepatitis B (CHB) is a leading cause of cirrhosis and hepatocellular carcinoma worldwide. Treatment of CHB with pegylated interferon or oral antivirals is recommended in patients with high hepatitis B virus (HBV)-DNA levels and active liver disease[1]. Pegylated interferon treatment for 48 weeks' duration was effective in a small subgroup of patients, but mainly in those who were younger and had high serum alanine aminotransferase and HBV-DNA levels ($<10^8$ log)[1]. Oral antiviral agents are effective and are the treatment of choice for most CHB patients; however, the majority of patients with oral therapy require long-term or indefinite treatment. Several oral antiviral agents have been approved and have been increasingly used for CHB treatment in the past decade, including lamivudine, adefovir, clevudine, telbivudine, entecavir, and tenofovir. These agents are generally safe and well tolerated, although their long-term side effects are largely unknown, and the safety data beyond 8 years are very limited[1].

The overall safety profile of nucleoside analogs (NSAs), including lamivudine, clevudine, telbivudine and entecavir, is excellent, although there have been rare reports of myopathy, neuropathy, and pancreatitis, as well as lactic acidosis, in patients with

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decompensated liver disease (MELD >20)[2,3]. In contrast, the safety profile of nucleotide analogs (NTAs), including tenofovir and adefovir, has been increasingly questioned in the past few years, particularly with regard to their long-term use[2]. Approximately 20-30% of NTA is excreted unchanged in the urine through active secretion by transporters (OAT, MRP-2, and MRP-4) within proximal tubular cells[4,5]. Disturbances in the secretory pathway of NTAs by various mechanisms may lead to increased NTA concentrations within the cell, which can cause mitochondrial DNA depletion and dysfunction in proximal tubular cells[4,5]. Several animal and human studies have shown that NTAs are associated with dose-dependent renal toxicity[4,5]. Risk factors for NTA-associated nephrotoxicity include a high dose and/or long duration of administration, increased age, low body weight, pre-existing chronic kidney disease (estimated glomerular infiltration rate [eGFR] <60-90 mL/min), co-morbidities (e.g. diabetes and hypertension), concomitant use of antiretroviral and nephrotoxic drugs (such as nonsteroidal anti-inflammatory drugs [NSAIDs], decompensated cirrhosis, solid organ transplantation, human immunodeficiency virus (HIV) infection with low CD4 count, and genetic polymorphisms of MRP-2 or MRP-4 genes[4-8]. Proximal tubular dysfunction "Fanconi-like renal tubular acidosis", characterized by hypophosphatemia, hypokalemia, acidosis, phosphaturia, glucosuria, and proteinuria, occurs in 17-22% of patients with long-term NTA use[4,5]. Renal impairment (increased serum creatinine and decreased GFR) develops in approximately 1-2% of patients. The onset of nephrotoxicity typically occurs after 6-12 months of therapy, but it can occur at any time during treatment[4,5]. The cumulative incidence of NTA-associated nephrotoxicity in CHB mono-infected patients is approximately 15% after 5-10 years of exposure[9,10].

In addition, the use of nucleotide analogs (NTAs) can be associated with negative effects on renal function and bone mineral density (BMD) owing to proximal tubular dysfunction and hypophosphatemia[2]. In HIV patients, several prospective, randomized studies (48-96 weeks of follow-up) have demonstrated that tenofovir-containing antiretroviral regimens are associated with increases in bone turnover markers and decreases in BMD (both spine and hip) compared with other regimens[11-13]. Cumulative tenofovir exposure was associated with an increased risk of osteoporotic fracture (yearly hazard ratio (HR) 1.13; 95% confidence interval (CI): 1.05-1.21, $p = 0.001$) in a large case-control study of 32,439 HIV patients[14]. Prospective data on bone disease in CHB monoinfected patients treated with NTAs are very limited[15-17]. In a long-term open-label study of 585 CHB patients treated with tenofovir (following 1 year of randomized study), no significant change in BMD was observed from year 4 to year 7 of treatment[15]. Nevertheless, several anecdotal cases of severe hypophosphatemic osteomalacia have been reported in CHB patients receiving NTAs[18-21]. Typical presentations were bone pain with or without multiple fractures (ribs, spine, and lower extremities). The onset of symptoms ranged from two to several years of treatment, and reversibility of bone scintigraphy findings was observed after cessation of therapy[18-21].

This pilot prospective study aimed to evaluate the prevalence of bone disease among patients with non-cirrhotic CHB receiving antiviral therapy and the changes in BMD and eGFR between CHB patients receiving NTAs versus NSAs.

Material and Method

Patients

This pilot prospective study was conducted in a single tertiary center (Rajavithi Hospital, Bangkok, Thailand) between 2012 and 2014. Non-cirrhotic CHB patients, aged 18-65 years, who were indicated for treatment and had been receiving oral antiviral therapy for <1 year were included in the study. Selection of antiviral agent was based on the Thailand Practice Guidelines, individual reimbursement scheme and patient-physician preference. CHB infection was defined as HBsAg detected two or more times at least 6 months apart. Indications for treatment were based on the Asian-Pacific Guidelines (HBV-DNA >20,000 IU/mL for HBeAg-positive patients or HBV DNA >2,000 IU/mL for HBeAg-negative patients with elevated ALT levels >2 times upper limit of normal on at least 2 occasions at least 3 months apart). The diagnosis of cirrhosis was based on clinical and laboratory findings, such as signs of chronic liver disease (spider angioma, palmar erythema, parotid gland enlargement, gynecomastia, and testicular atrophy) or portal hypertension (ascites, splenomegaly, superficial vein dilatation, and esophageal varices). The laboratory results suggestive of cirrhosis were thrombocytopenia (platelets <150,000/mm^3), a reversed albumin-to-globulin ratio, and prolonged prothrombin time (>13 seconds or INR >1.2). Abdominal ultrasonography or computed tomography revealed morphological changes in cirrhosis and portal hypertension. Exclusion criteria

were patients who: had osteoporosis; had received previous treatment with interferon within the last 6 months; had chronic kidney disease with eGFR <50 mL/min; had severe co-morbidities; or were receiving medications that could affect BMD (including corticosteroids, estrogen, vitamin D >400 IU/day, calcium >1.2 g/day, and bisphosphonates). Additionally, pregnant or lactating women and patients with HIV or hepatitis C coinfection were not included. This study protocol was reviewed and approved by the Medical Ethics Committee of Rajavithi Hospital (No. 048/2555). All participants provided informed consent before enrollment.

Methods

Personal history data (e.g. present and past illness, use of medications and supplements, cigarette smoking, and alcohol consumption), physical examination findings (including weight and height), laboratory test results (e.g. liver function and blood urea nitrogen, serum creatinine, calcium, and phosphate levels), and virologic parameters (e.g. HBeAg status, HBV-DNA viral loads) were collected at baseline and during the follow-up period of at least one year. Significant alcohol consumption was defined as ongoing or recent alcohol consumption >21 drinks on average per week in men and >14 drinks on average per week in women (approximately 10 g alcohol per drink unit).

BMD assessment was performed using dual x-ray absorptiometry at the lumbar spine (LS) and the femoral neck (FN) at baseline and after one year of follow-up. The BMD results were compared with the mean BMD of age- and sex- matched controls from an Asian population database and expressed as SD of the mean (Z-score). Osteopenia and osteoporosis were defined as BMD between 1 and 2.5 (T-score -1 to -2.5) and >2.5 (T-score <-2.5), and SD below the mean BMD for young adults, consistent with World Health Organization criteria. The GFR was estimated using the Cockcroft-Gault method.

Statistical analysis

Because the study made no assumptions about the probability distribution, all data are presented as number (%) or median (min-max). Chi-square and Fisher exact tests, which are nonparametric, were used to compare data between patients who received NTAs versus those who received NSAs. The significance level was set at $p<0.05$ using 2-sided tests. All statistical analyses were conducted with STATA version 13 (Stata Corp, Texas, USA).

Results

Twenty patients were included: 65% (13/20) were men, 40% (8/20) were HBeAg positive, and the median age was 42.7 (25.6-64.2) years. Ten patients had been treated with NTAs (7 with tenofovir 300 mg/day and 3 with adefovir 10 mg/day), and the other 10 had received NSAs (8 with lamivudine 100-150 mg/day and 2 with entecavir 0.5 mg/day). All patients had normalized serum ALT with HBV DNA <2,000 IU/mL at study enrollment. At baseline, the overall prevalence of osteopenia was 45% (9/20). BMD in CHB patients was slightly lower than that of the age-matched population, with median Z-scores of 0.0 (-2.6 to 2.0) at the LS and -0.2 (-1.6 to 2.1) at the FN region. The median eGFR was 94 (51-144) mL/min. Baseline demographic, laboratory, and BMD data are summarized in Tables 1 and 2. There was no significant difference in baseline characteristics between the two groups (patients receiving NTAs versus those receiving NSAs). The median follow-up period was 1.5 years (1.2-1.6).

After at least 1 year of follow-up, BMD and renal function evaluations were repeated in all patients (Table 3). The annual changes in LS and FN BMD and FN-BMD were not significantly different between the two groups (Fig. 1). The eGFR decreased significantly more in patients who received NTAs than in those who received NSAs (Fig. 2). There was no incidence of severe or symptomatic hypophosphatemia during the study period.

Discussion

Although our sample size was small, our study is one of the few to have both documented the prevalence of bone disease in noncirrhotic CHB patients and prospectively evaluated changes in BMD and eGFR in CHB patients receiving NTAs versus NSAs. Several differences between Asian and Western CHB patients could affect bone metabolism, including ethnicity, diet, exercise, levels of sun exposure, HBV genotype, and other environmental factors. This study may provide important data regarding bone disease in non-cirrhotic CHB among Asians about which the available data are scant.

At baseline, BMD in CHB patients receiving antiviral therapy was slightly lower than that of the age-matched population. Thus, osteopenia appeared to be quite common, being found in up to 45% of patients. Increased prevalence of osteopenia in patients with CHB may be largely attributable to a chronic

Table 1. Baseline characteristics of the 20 study patients

Parameter	NTAs (n = 10)	NSAs (n = 10)	*p*-value
Age, years	39.05 (25.6-64.2)	48.25 (25.6-55.0)	0.627
Sex (male)	7 (70%)	6 (60.0%)	>0.999
BMI, kg/m^2	22.80 (18.1-28.3)	25.65 (20.4-33.8)	0.136
Significant alcohol consumption	1 (10%)	0 (0%)	>0.999
Currently smoking	0 (0%)	0 (0%)	NA
Serum ALT, IU/L	24.50 (15.0-61.0)	37.50 (15.0-141.0)	0.191
Serum AST, IU/L	25.50 (20.0-72.0)	31.00 (19.0-76.0)	0.304
Serum albumin, g/dL	4.70 (4.1-4.9)	4.40 (4.1-4.8)	0.075
HBeAg positive	4 (40%)	4 (40%)	>0.999

Data are presented as number (%) or median (min-max).
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; NA = not applicable; NTAs = nucleotide analogs; NSAs = nucleoside analogs

Table 2. Baseline renal functions and bone mineral density in the 20 study patients

Parameter	NTAs (n = 10)	NSAs (n = 10)	*p*-value
LS BMD, g/cm^2	1.09 (0.88-1.35)	1.08 (0.96-1.15)	0.346
T-score	-0.40 (-2.50-1.40)	-0.40 (-1.80-1.10)	0.890
Z-score	0.10 (-2.60-2.00)	-0.10 (-2.40-1.20)	0.663
FN BMD, g/cm^2	0.87 (0.70-1.07)	0.90 (0.82-1.17)	0.244
T-score	-0.65 (-1.90-1.60)	-0.40 (-0.80-1.70)	0.697
Z-score	0.05 (-1.60-2.10)	-0.35 (-1.50-2.10)	0.721
Osteopenia (t-score -1 to -2.5)	5 (50%)	4 (40%)	>0.999
Serum creatinine, mg/dL	0.95 (0.70-1.10)	0.80 (0.80-1.00)	0.411
eGFR*, mL/min	88.50 (51.00-137.00)	98.00 (65.00-144.00)	0.394
Serum calcium, mg/dL	9.40 (9.00-9.80)	9.40 (8.80-10.60)	0.554
Serum phosphate, mg/dL	3.45 (1.70-4.20)	3.45 (2.90-4.60)	0.292

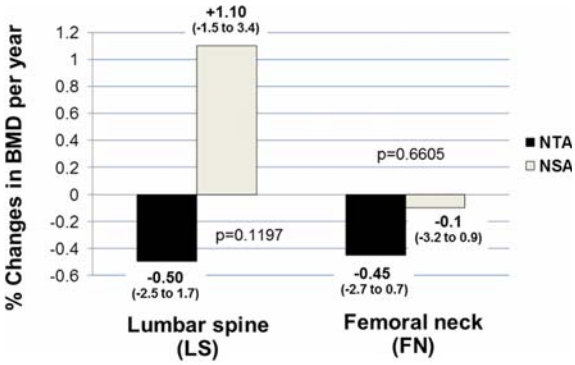
Data are presented as number (%) or median (min-max).
* The GFR was estimated using the Cockcroft-Gault method.
BMD = bone mineral density; FN = femoral neck; eGFR = estimated glomerular filtration rate; LS = lumbar spine; NTAs = nucleotide analogs; NSAs = nucleoside analogs

Table 3. Changes in bone mineral density and estimated glomerular filtration rate

Parameter	NTAs (n = 10)	NSAs (n = 10)	*p*-value
Change in LS BMD per year, %	-0.50 (-2.50 to 1.70)	1.10 (-1.50 to 3.40)	0.120
Change in FN BMD per year, %	-0.45 (-2.70 to 0.70)	-0.10 (-3.20 to 0.90)	0.661
Change in GFR per year, %	-7.40 (-41.39 to -0.82)	-1.39 (-7.91 to 21.24)	0.018

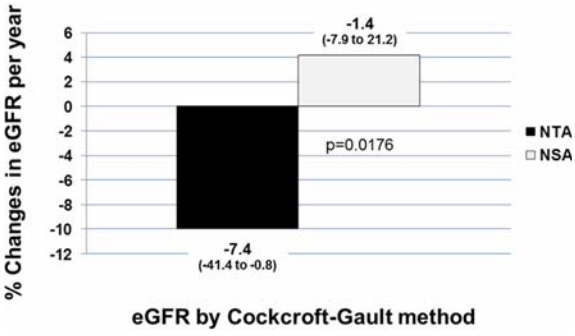
Data are presented in number (%) or median (min-max).
BMD = bone mineral density; eGFR = estimated glomerular filtration rate; NTAs = nucleotide analogs; NSAs = nucleoside analogs

inflammatory state, which adversely affects bone metabolism (i.e., reduced bone formation and low bone turnover)[22,23]. Bone diseases are well-known complications of chronic liver disease, particularly in



BMD = bone mineral density; NTA = nucleotide analog; NSA = nucleoside analog

Fig. 1 Changes in bone mineral density.



eGFR = estimated glomerular filtration rate; NTA = nucleotide analog; NSA = nucleoside analog

Fig. 2 Changes in estimated glomerular infiltration rate assessed using the Cockcroft-Gault method.

patients with cirrhosis or chronic cholestasis[22,23]; however, some studies have investigated the prevalence of osteoporosis/osteopenia in patients with chronic viral hepatitis but without overt cirrhosis. A small German study revealed that the prevalence of osteoporosis in patients with non-cirrhotic CHB (n = 13) and chronic hepatitis C (n = 30) was 15% and 20%, respectively[24]. A study from Thailand reported that BMD was lower in non-cirrhotic CHB patients (n = 54) than in the general population, and the overall prevalence of osteoporosis and osteopenia was 7.4% and 38.9%, respectively[25]. Another Thai study of non-cirrhotic chronic hepatitis C patients (n = 57) reported a prevalence of osteoporosis and osteopenia of 3.5% (95% CI: 0.97-11.92) and 22.8% (95% CI: 13.8-38.98), respectively[26].

After a median follow-up period of 1.5 years, changes in BMD per year in both trabecular (represented by the LS region) and cortical bone (represented by the FN region) were not significantly different between patients receiving NTAs compared to those taking NSAs. This is similar to results from a previous longitudinal cohort of CHB patients receiving NTAs[15-17], thus supporting the view that treatment with NTAs does not affect bone metabolism in CHB monoinfected patients. Careful monitoring of bone disease is recommended in CHB patients receiving NTAs who have risk factors for osteoporosis (e.g., low body weight, postmenopausal status, chronic cholestasis, corticosteroid use, physical inactivity, smoking, alcohol abuse, malnutrition, and vitamin D deficiency) or signs of proximal tubular dysfunction, especially hypophosphatemia. Thus, the safety of NTAs on bone metabolism is still a concern in HIV patients receiving tenofovir-containing antiretroviral regimens[11-14]. Interestingly, BMD at the LS region appeared to be increasing slightly (approximately +1% per year) among patients receiving NSAs. This observation may be anecdotal or may be due in part to a reduction in liver inflammation after sustained HBV-DNA suppression induced by antiviral therapy. An improvement in BMD after antiviral therapy has been observed in patients with chronic hepatitis C[26].

In a large, double-blind, phase 3, randomized study (n = 641) comparing tenofovir and adefovir in the treatment of CHB, the incidence of a confirmed serum creatinine increase of $\geq$0.5 mg/dL above the baseline value at 48 weeks of treatment was <1% in both groups[27]. Subsequently, 585 patients entered the open-label phase of tenofovir monotherapy, and 437 out of 585 patients (74.7%) remained on study after 7 years[15]. At year 7, the incidence of serum creatinine $\geq$0.5 mg/dL above baseline was 1.7%, serum phosphate <2 mg/dL was 1.5%, and eGFR <50 mL/min was 1.0%[15]. It should be noted that patients with the above-mentioned risk factors for NTA-associated nephrotoxicity are generally excluded from randomized trials. In the present study, a reduction in eGFR following 1.5 years of antiviral treatment appeared to be more pronounced in patients who had taken NTAs than in those who had taken NSAs. This finding supports an observation from previous longitudinal cohorts of CHB patients receiving NTAs[9,10,16,17]. In real-life practice, there is a substantial heterogeneity of CHB patients, and it is very common to see elderly patients with co-morbidities and concomitant medications that may predispose them to NTA-associated nephrotoxicity. We believe that longitudinal cohorts with less stringent inclusion criteria than that

of randomized studies may better reflect the incidence of NTA-associated nephrotoxicity in real-life situations. Accordingly, proper timely monitoring of serum phosphate levels and eGFR is recommended in all CHB patients receiving NTAs, with increasing frequency in those at higher risk[1,4,10,28]. The NTA dose should be adjusted according to the eGFR, and the concomitant use of other nephrotoxic drugs, particularly NSAIDs, should be avoided[1,4,10,28]. Treatment discontinuation (and the switch to another agent) or dosage modification is recommended in patients with confirmed proximal tubular dysfunction or renal impairment[4,10]. NTA-associated nephrotoxicity is often reversible if therapy is discontinued[4,5]; however, when renal impairment develops, the eGFR may not fully return to the baseline value[29,30].

Limitations of the present study include its small sample size and relatively short follow-up period. It is likely that changes in BMD and eGFR due to external factors are often gradual, in which case the follow-up period of 1.5 years may not be sufficient to demonstrate significant variations. Therefore, larger studies with longer follow-up periods (preferably ≥4 years) are needed to confirm the results of the present pilot study.

In conclusion, osteopenia is relatively common in CHB patients without cirrhosis who are receiving oral antiviral therapy. Changes in BMD were not significantly different between patients who received NTAs versus NSAs. The annual reduction in GFR was slightly, but significantly, more pronounced in patients who received NTAs.

What is already known on this topic ?

Treatment of chronic hepatitis B with nucleotide analogs may be associated with proximal tubular dysfunction with or without renal impairment.

Treatment of chronic hepatitis B with nucleotide analogs may be associated with negative effects on bone mineral density.

There have been conflicting data regarding the incidence of bone disease and renal dysfunction in chronic hepatitis B patients receiving long-term nucleotide analogs.

What this study adds ?

This study was one of the few studies that prospectively evaluated bone mineral density and renal function in chronic hepatitis B patients receiving long-term nucleotide analogs with a comparative group.

Osteopenia is common in chronic hepatitis B patients without cirrhosis.

Changes in bone mineral density over 1.5 years were not significantly different between patients receiving nucleotide versus nucleoside analogs.

Reduction in glomerular infiltration rates over 1.5 years was significantly more pronounce in patients receiving nucleotide analogs.

Potential conflicts of interest

None.

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การศึกษาความหนาแน่นมวลกระดูกและการทำงานของไตในผู้ป่วยโรคตับอักเสบ บี เรื้อรัง ที่ได้รับยาในกลุ่มนิวคลีโอไทด์อะนาล็อกเทียบกับยาในกลุ่มนิวคลีโอไซด์อะนาล็อก: การศึกษานำร่องชนิดไปข้างหน้า

เฉลิมรัฐ บัญชรเทวกุล, วิฑูรย์ ทวีวัฒนะกิจบวร, อัมพร อัศวรุ่งเรืองกิจ

ภูมิหลัง: *ยาในกลุ่มนิวคลีโอไทด์อะนาล็อกอาจมีผลลบต่อการทำงานของไตและความหนาแน่นมวลกระดูก ซึ่งสามารถอธิบายโดยความผิดปกติของการทำงานบริเวณท่อหน่วยไตส่วนต้นและภาวะฟอสเฟสในกระแสเลือดต่ำ อย่างไรก็ตามยังพบว่าข้อมูลจากการศึกษาแบบไปข้างหน้าในการประเมินผลความปลอดภัยต่อกระดูกและไตสำหรับยาในกลุ่มนี้ยังคงมีจำกัด*

วัตถุประสงค์: *ประเมินความชุกของโรคกระดูกในผู้ป่วยไวรัสตับอักเสบบีเรื้อรังที่ไม่มีภาวะตับแข็งและการเปลี่ยนแปลงของมวลกระดูกและการทำงานของของไต (glomerular filtration rate) ระหว่างผู้ป่วยที่ได้รับยากลุ่มนิวคลีโอไทด์อะนาล็อก เปรียบเทียบกับยากลุ่มนิวคลีโอไซด์อะนาล็อก*

วัสดุและวิธีการ: *ผู้นิพนธ์ทำการเก็บข้อมูลแบบไปข้างหน้าจากกลุ่มผู้ป่วยไวรัสตับอักเสบบีเรื้อรังที่ไม่มีภาวะตับแข็ง ซึ่งได้รับการรักษาเป็นระยะเวลาด้วยยาต้านไวรัสแบบรับประทานน้อยกว่า 1 ปี ในโรงพยาบาลราชวิถี (กรุงเทพมหานคร, ประเทศไทย) ระหว่างปีพ.ศ. 2555 ถึง 2557 โดยผู้ป่วยที่มีภาวะโรคร่วมที่ส่งต่อมวลกระดูก รวมถึงการทำงานของไตและผู้ป่วยที่กำลังได้รับการรักษาโรคกระดูกจะถูกคัดออก การประเมินความหนาแน่นมวลกระดูกจะถูกประเมินที่ระดับกระดูกสันหลังส่วนเอวและคอกระดูกสะโพก โดยค่าความหนาแน่นมวลกระดูกจะรายงานเป็นค่า T-score ซึ่งสำหรับภาวะกระดูกบางจะมีค่าระหว่าง -2.5 ถึง -1 และภาวะกระดูกพรุนค่าจะน้อยกว่า -2.5 และประเมินการทำงานของไตโดยวิธีของ Cockcroft-Gault*

ผลการศึกษา: *ผู้ป่วยจำนวนในการทดลองมีทั้งหมด 20 คน เป็นเพศชายร้อยละ 65 HBeAg เป็นบวกร้อยละ 40 และค่ามัธยฐานของอายุเท่ากับ 42.7 (25.6-64.2) ปี ผู้ป่วย 10 คน ได้รับการรักษาด้วยยากลุ่มนิวคลีโอไทด์อะนาล็อก (tenofovir 7 คน และ adefovir 3 คน) ผู้ป่วย 10 คน ได้รับการรักษาด้วยยากลุ่มนิวคลีโอไซด์อะนาล็อก (lamivudine 8 คน และ entecavir 2 คน) โดยค่าระยะการติดตามการรักษามีค่าเฉลี่ยอยู่ที่ 1.5 ปี (1.2-1.6) ภาพรวมความชุกของภาวะกระดูกบางเท่ากับร้อยละ 45 และค่ามัธยฐานการทำงานของไตเท่ากับ 94 (51-144) มิลลิลิตรต่อนาที ค่าความหนาแน่นมวลกระดูกในผู้ป่วยไวรัสตับอักเสบบีเรื้อรังมีค่าน้อยกว่าเล็กน้อย เมื่อเทียบกับค่ามาตรฐานของประชากรที่มีอายุเท่ากัน (Z-score) และไม่พบการเปลี่ยนแปลงอย่างมีนัยสำคัญของมวลกระดูกที่กระดูกสันหลังส่วนเอวและคอกระดูกสะโพก ในผู้ป่วยสองกลุ่มการทดลองพบว่าการทำงานของไตมีค่าลดลงมากกว่าอย่างมีนัยสำคัญในผู้ป่วยกลุ่มที่ได้รับยานิวคลีโอไทด์ (ร้อยละ -7.4 ต่อปี เทียบกับร้อยละ -1.39 ต่อปี, p = 0.018)*

สรุป: *ภาวะกระดูกบางพบได้บ่อยในผู้ป่วยไวรัสตับอักเสบบีเรื้อรังที่ไม่มีภาวะตับแข็ง ค่าการเปลี่ยนแปลงของความหนาแน่นมวลกระดูกไม่แตกต่างอย่างมีนัยสำคัญระหว่างผู้ป่วยในสองกลุ่มการทดลอง การทำงานของไตมีค่าลดลงมากกว่าอย่างมีนัยสำคัญในผู้ป่วยกลุ่มที่ได้รับยานิวคลีโอไทด์*