Observational Study

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Risk factors associated with hepatic osteopathy in HBV related cirrhosis measured by liver stiffness

An Observational study

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Abstract

Objective To investigate the differences in bone mineral density between patients with liver cirrhosis and healthy control, and to analyze the risk factors of hepatic osteoporosis in patients with HBV related liver cirrhosis.

Research design and methods A total of 189 patients with liver cirrhosis and 207 health controls were enrolled. The bone mineral density of lumbar spine and femoral neck was examined by dual energy X-ray absorptiometry. $-2.0 <$T value < -1.0 defined as osteopenia, T value ≤ -2.0 defined as osteoporosis.

Results Bone mineral density in the cirrhotic group was significantly lower than that in the control group (lumbar: 1.02 ± 0.16 vs 1.08 ± 0.13, $P < .001$; femoral neck: 0.86 ± 0.14 vs 0.91 ± 0.14, $P < .001$). Both 2 groups showed a tendency that decrease bone density correlated with age and decrease body mass index (BMI). Multivariate correlation analysis showed that women (OR = 6.931, $P = .002$), age (OR = 1.096, $P < .001$), low BMI (OR = 0.874, $P = .037$), and high liver stiffness value (OR = 1.125, $P = .046$) were independent risk factors for osteopenia and low body weight (OR = 0.934, $P = .006$) and high liver stiffness value (OR = 1.246, $P = .034$) were independent risk factors for osteoporosis.

Conclusions Our study shows that bone mineral density in patients with liver cirrhosis decreased significantly, especially in the elderly and low BMI patient. For HBV-related cirrhosis with risk factors, a regular bone density screening should be given, and timely intervention should be taken into consideration.

Abbreviations: BMD = bone mineral density, BMI = body mass index, DXA = dual-energy X-ray absorptiometry, HBV = hepatitis B virus, HCV = hepatitis C virus, SD = standard deviation.

Keywords: bone mineral density, chronic hepatitis B, cirrhosis, hepatic osteoporosis, risk factors

1. Introduction

It is estimated that 240 million people are chronically infected with hepatitis B virus (HBV) worldwide.[1] In Asia-Pacific region, such as China, Japan and South Korea accounts for nearly 50% of chronic hepatitis B (CHB) patients worldwide.[2–4] Patients with chronic HBV infection have an increased risk of many diseases, including cirrhosis, liver failure, and hepatocellular carcinoma.[5,6] Hepatic related osteopathy is one of the complications of chronic infection with HBV. Hepatic osteopathy including hepatic osteopenia and hepatic osteoporosis. Hepatic osteoporosis can lead to a decrease in Bone mineral density, which increases the risk of fracture. Hepatic osteoporosis and its related fractures reduce the quality of life and prognosis of patients with CHB related cirrhosis.

Although study reported before found that chronic liver disease is closely related to hepatic related osteopathy. The pathophysiological mechanism and risk factors are still not fully recognized.[7] Since the best strategy for hepatic related osteopathy is early diagnosis and intervention. A comprehensive and systematic analysis of the risk factors for hepatic osteopathy in patients with CHB related cirrhosis is needed to effectively screen high-risk patients for early treatment to prevent fractures, thereby improving the quality of life and prognosis of patients.[8,9]

In our study, a retrospective cohort was conducted and used to analyze the bone mineral density (BMD) of patients with CHB related cirrhosis and healthy controls. We also analyzed the risk factors associated with hepatic osteopathy, thereby to provide evidences of prevention and management of hepatic related osteopathy.

2. Subjects and methods

2.1. Subjects

All patients were enrolled at the Shandong Provincial Qianfoshan Hospital between August 2015 and September 2017. A total of

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The Institutional Review Board of Shandong Provincial Qianfoshan Hospital had approved this study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent was obtained from all patients for inclusion in the study.

The authors declare that they have no financial or personal relationships with other people or organizations that could inappropriately influence this work.

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396 patients were enrolled. Among them, there are 189 patients diagnosed with CHB related cirrhosis (Cirrhosis group) and 207 as health control (Controls group). The criteria for enrollment in the cirrhosis group were as follows:

1. The diagnostic criteria for CHB was that HBsAg persisted positive for more than 6 months [10];
2. Patients diagnosed as CHB-associated cirrhosis with Child-Pugh Stage A.[11]

Patients were excluded if:

1. Patient with HCV/HIV infection, or other chronic liver disease, such as hepatolenticular degeneration, alcoholic liver disease, cholestatic liver disease;
2. Patients with long-term use of glucocorticoids;
3. Patients are receiving anti-osteoporosis drugs.

2.2. Bone mineral density assessment

The BMD of the lumbar spine and hip was measured using a Discovery A dual-energy X-ray absorptiometry (Hologic, US). The testing process is carried out by a professional physician. All subjects were examined for BMD using a uniform position to minimize the interference of individual position. According to the WHO diagnostic criteria, $-2.0 < T$ value < -1.0 is defined as osteopenia, and T value ≤ -2.0 is defined as osteoporosis. Hepatic related osteopathy is defined as the presence of cirrhosis-related osteopenia or osteoporosis.

2.3. Liver stiffness measurement

All patients enrolled in our study were HBV related cirrhosis diagnosed by liver stiffness >12 Kpa.[12] The value of liver stiffness was measured by Fibroscan (Echosens Corp., Paris, France). A total of 10 measurements were carried out, and the liver stiffness value was record only if the interquartile range did not exceed 40% in any of the measurements. The results were expressed in kilopascals. The median value was taken as representative.

2.4. Statistical analysis

In this study, the continuous variables are expressed as the mean ± standard deviation (SD), and the categorical variables are expressed as a percentage. The χ^2 test and the t test were used to detect whether the 2 sets of data were statistically different. One-way ANOVA was used to detect whether there was a statistical difference in clinical characteristics between the 3 groups of patients with cirrhosis. Univariate and multivariate analysis were used to explore the risk factors associated with the hepatic osteopathy. The data analysis and quality control were assessed by SPSS for windows, version 13.0.

3. Results

3.1. Demographic data

A total of 396 patients were included, including 189 in the cirrhosis group. The average age is 56.89 ± 10.26 years old. The control group consisted of 207 people with an average age of 56.67 ± 9.45 years. The range of liver stiffness among all the patients were 4.92 to 24.59 Kpa. There was no significant difference in sex and age between the 2 groups. There was no statistical difference in age, height, weight, and body mass index (BMI) between the 2 groups. The BMD of patients with cirrhosis was significantly lower than that of the control group (spine: 1.02 ± 0.16 vs 1.08 ± 0.13, $P < .001$; hip: 0.86 ± 0.14 vs 0.91 ± 0.14, $P < .001$). As shown in Table 1.

Table 1

Characteristics of cirrhosis group and health control group.

Variables	Cirrhosis group (N=189)	Controls group (N=207)	*P* value
Sex, M/F	141/48	145/62	.312
Age, years	56.89 ± 10.26	56.67 ± 9.45	.818
Height, cm	161.08 ± 7.76	162.86 ± 12.85	.098
Weight, Kg	58.38 ± 9.02	59.87 ± 10.67	.135
BMI	22.48 ± 2.98	22.64 ± 3.72	.621
BMD at spine	1.02 ± 0.16	1.08 ± 0.13	<.001
BMD at hip	0.86 ± 0.14	0.91 ± 0.14	<.001
Liver stiffness	17.92 ± 4.98	6.77 ± 2.14	<.001

BMD = bone mineral density, BMI = body mass index.

3.2. Sub-population analysis of BMD among CHB patients with cirrhosis

The sub-population analysis of BMD is shown in Figure 1.

Sex: the bone density of male patients is higher than that of female patients regardless patients were in the cirrhosis group or in the control group. When we compared the BMD of the cirrhosis group with control group, we observed that the BMD of the control group was higher than that of the cirrhosis group except for the lumbar spine BMD of the male patient.

Age: Both the cirrhosis group and control group showed a trend of decreasing BMD with age. However, when the cirrhosis group was compared with the control group, there was no statistical difference in BMD between the 2 groups when the patient was <40 years old. However, when the patient was >60 years old, the bone density of the cirrhosis group was significantly lower than that of the control group.

BMI: Both the cirrhosis group and the control group showed an increase in BMD with an increase in BMI. The comparison between the cirrhosis group and the control group indicated that when BMI <18, the BMD of patients with cirrhosis was significantly lower than that of the control group. However, when BMI >24, no statistical difference was found in BMD between the 2 groups.

3.3. Differences in CHB related cirrhosis patients with or without osteopathy

The clinical features of hepatic related osteopathy in patients with CHB related cirrhosis are shown in Table 2. Among them, 62 people were diagnosed with normal BMD, 95 were osteopenia, and 32 were osteoporosis. There were statistical differences in gender distribution, age, height, weight, and BMI between the 3 groups. The proportion of women in osteoporosis group was higher ($P < .001$), the mean age was longer ($P < .001$), and the BMI was lower ($P = .037$).

3.4. Risk factors associated with osteopenia among CHB related cirrhosis

Univariable and multivariable analysis were conducted and the results are shown in Table 3. Univariate analysis showed that

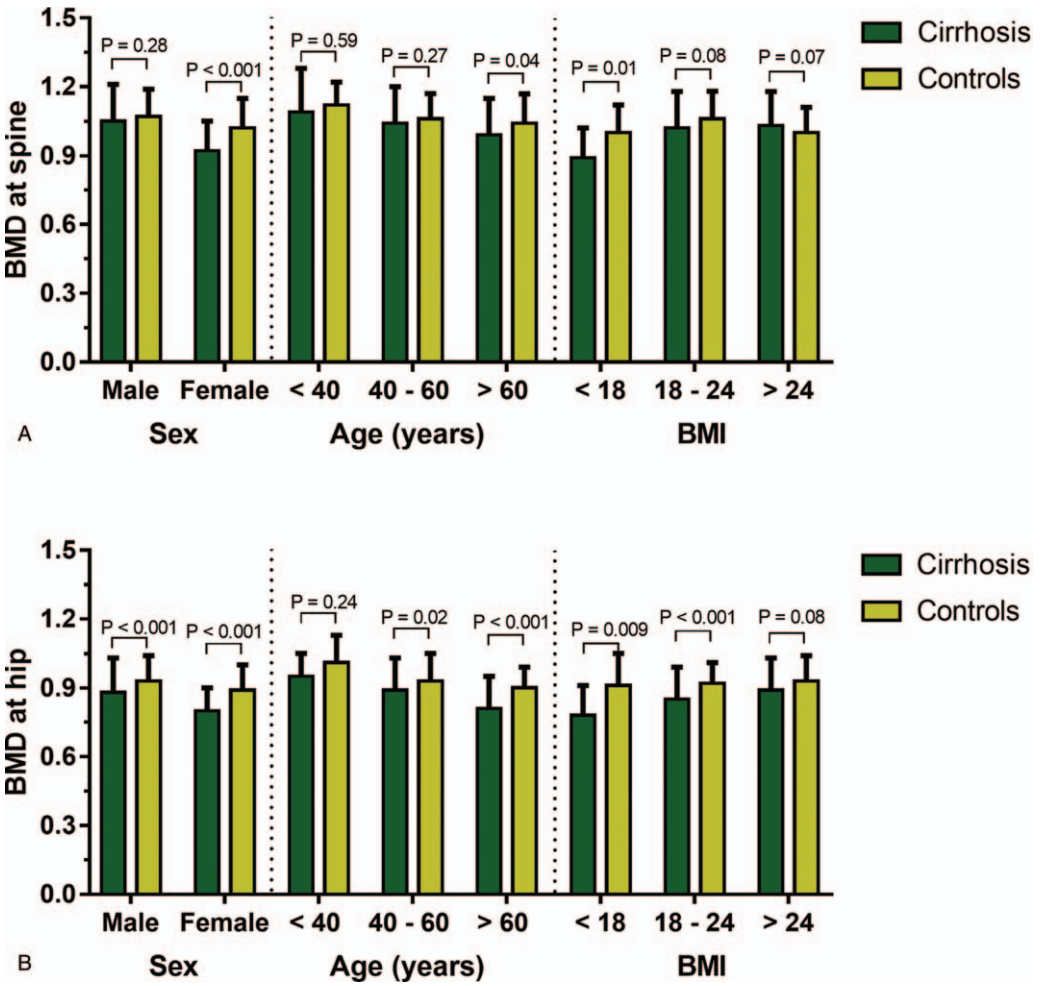

Figure 1. Sub-analysis of BMD among CHB patients with cirrhosis and controls. Spine (A): 1.05 ± 0.16 in cirrhosis group vs 1.07 ± 0.12 in controls (Male, $P < .001$); 0.92 ± 0.13 in cirrhosis group vs 1.02 ± 0.13 in controls (Female, $P < .001$); 1.09 ± 0.19 in cirrhosis group vs 1.12 ± 0.10 in controls (Age <40 years, $P < .001$); 1.04 ± 0.16 in cirrhosis group vs 1.06 ± 0.11 in controls (40 < Age < 60 years, $P < .001$); 0.99 ± 0.16 in cirrhosis group vs 1.04 ± 0.13 in controls (Age >60 years, $P < .001$); 0.89 ± 0.13 in cirrhosis group vs 1.00 ± 0.12 in controls (BMI <18, $P = .001$); 1.02 ± 0.16 in cirrhosis group vs 1.06 ± 0.12 in controls (18 < BMI < 24, $P < .001$); 1.03 ± 0.15 in cirrhosis group vs 1.07 ± 0.11 in controls (BMI >24, $P < .001$). Hip (B): 0.88 ± 0.15 in cirrhosis group vs 0.93 ± 0.11 in controls (Male, $P < .001$); 0.80 ± 0.10 in cirrhosis group vs 0.89 ± 0.11 in controls (Female, $P < .001$); 0.95 ± 0.10 in cirrhosis group vs 1.01 ± 0.12 in controls (Age <40 years, $P < .001$); 0.89 ± 0.14 in cirrhosis group vs 0.93 ± 0.12 in controls (40 < Age < 60 years, $P < .001$); 0.81 ± 0.14 in cirrhosis group vs 0.90 ± 0.09 in controls (Age >60 years, $P < .001$); 0.78 ± 0.13 in cirrhosis group vs 0.91 ± 0.14 in controls (BMI <18, $P = .001$); 0.85 ± 0.14 in cirrhosis group vs 0.92 ± 0.09 in controls (18 < BMI < 24, $P < .001$); 0.89 ± 0.14 in cirrhosis group vs 0.93 ± 0.11 in controls (BMI >24, $P < .001$). BMI, body mass index; BMD, bone mineral density.

Table 2

Demographic data in CHB related cirrhosis with hepatic osteopathy.

Variables	Normal (N=62)	Osteopenia(N=95)	Osteoporosis(N=32)	*P* value
Sex, M/F	58/4	65/30	18/14	<.001
Age, years	51.92 ± 9.29	58.48 ± 10.51	59.62 ± 9.67	<.001
Height, cm	163.02 ± 7.58	160.74 ± 7.09	158.28 ± 9.19	.016
Weight, Kg	61.56 ± 8.85	57.77 ± 8.31	54.05 ± 9.41	<.001
BMI	23.17 ± 3.07	22.33 ± 2.71	21.56 ± 3.37	.037
ALT, U/L	108.08 ± 78.48	107.73 ± 74.14	108.72 ± 81.77	.998
AST, U/L	129.34 ± 89.90	119.84 ± 89.89	136.19 ± 88.38	.624
PLT, G/L	110.87 ± 23.98	108.45 ± 17.65	110.25 ± 9.61	.720
HBV DNA	1.90 ± 2.46	2.08 ± 2.46	2.73 ± 2.65	.305
Liver stiffness	17.53 ± 3.06	18.11 ± 3.94	19.67 ± 3.66	.026

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMD = bone mineral density, BMI = body mass index, HBV = hepatitis B virus, PLT = platelet.

Table 3

Factors associated osteopenia among patients with CHB related cirrhosis.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Sex	1.631	1.030–2.580	.037	6.931	2.087–23.017	.002
Age	1.041	1.018–1.065	<.001	1.096	1.051–1.142	<.001
Height	0.976	0.956–0.996	.018			
Weight	0.946	0.888–1.008	.086			
BMI	0.965	0.944–0.986	.002	0.874	0.771–0.992	.037
ALT	1.000	0.996–1.004	.993			
AST	0.999	0.996–1.003	.697			
PLT	0.995	0.979–1.011	.502			
HBV DNA	1.056	0.934–1.196	.384			
Liver stiffness	1.071	1.014–1.098	.012	1.125	1.092–1.344	.046

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, HBV = hepatitis B virus, PLT = platelet.

women, older age, low height, low weight, and low BMI were factors associated with osteopenia in patients with CHB related cirrhosis. However, multivariate analysis showed that only women (OR = 6.931, $P = .002$), older age (OR = 1.096, $P < .001$), low BMI (OR = 0.874, $P = .037$), high liver stiffness value (OR = 1.125, $P = .046$) were independent risk factors of osteopenia in patients with CHB related cirrhosis.

3.5. Risk factors associated with osteoporosis among CHB related cirrhosis.

We also explore the risk factors for osteoporosis. The results are shown in Table 4. Univariate analysis found that women, low height and low body weight were risk factors of osteoporosis in patients with CHB related cirrhosis. However, multivariate correlation analysis suggested that only low weight (OR = 0.934, $P = .006$) and high liver stiffness value (OR = 1.246, $P = .034$) were an independent risk factor for osteoporosis in patients with CHB related cirrhosis.

4. Discussion

Patients chronically infected with HBV have an increased risk of liver fibrosis, cirrhosis and other end-stage liver disease.[13–18] Hepatic related osteopathy is one of the serious complications of patients with CHB related cirrhosis. Rapid loss of BMD in patients with hepatic related osteopathy is the most reliable predictor of late pathological fractures.[19] In patients with cirrhosis, once a pathological fracture occurs, it will bring serious adverse prognosis and a decline in quality of life. However, due to the insidious symptoms of hepatic related osteopathy, it is difficult to identify those hepatic osteopathy patients. Previous reports suggested that patients with cirrhosis have a higher prevalence of osteoporosis.[20] Low BMD occurs in at least 20% of patients with chronic liver disease.[21] The prevalence of osteoporosis in patients with chronic liver disease is 12%5 to 5%.[22,23] Osteoporosis and its related fractures are still common in patients with cirrhosis than in the general population.[24] In this study, we demonstrated that the lumbar spine and hip BMD were significantly lower in patients with cirrhosis than in the control population. Especially in elderly and low BMI patients. In addition, our study showed that among the cirrhosis population, women, older age, and low BMI are independent risk factors for osteopenia and low body weight is the independent risk factor for osteoporosis in patients with CHB related cirrhosis. Hence, BMD monitoring should be given timely in those high-risk population and timely intervention should be taken into consideration to reduce the risk of pathological fracture.

Previous studies have reported that age is one of the most important factors associated with bone loss,[25] but how age affects bone metabolism is not entirely clear. Genetic factors may play an important role. Epidemiological surveys show that more than 10 million people in the US who are older than 50 have osteoporosis, and about 1.5 million osteoporotic pathological

Table 4

Factors associated osteoporosis with CHB related cirrhosis.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Sex	2.171	1.040–4.534	.039			
Age	1.020	0.982–1.059	.309			
Height	0.966	0.934–0.998	.040			
Weight	0.944	0.909–0.980	.003	0.934	0.889–0.980	.006
BMI	0.905	0.808–1.013	.084			
ALT	1.000	0.995–1.005	.954			
AST	1.002	0.997–1.006	.467			
PLT	1.002	0.982–1.023	.818			
HBV DNA	1.121	0.964–1.303	.139			
Liver stiffness	1.159	1.054–1.277	.007	1.246	1.065–1.588	.034

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, HBV = hepatitis B virus, PLT = platelet.

fractures occur each year. In addition, there are 27.6 million people with age-related osteoporosis in Europe, with more than 3.5 million fractures per year.[26] The results of this study suggest that aging not only accelerates bone loss in patients with cirrhosis, but also is an independent risk factor for predicting osteopenia in patients with cirrhosis. Low BMI is another risk factor associated with bone loss.[27] Weight loss is closely associated with an increased risk of fracture, and weight gain is associated with a reduced risk of hip fracture.[28,29] Based on our findings, we found that bone loss was more severe in patients with low BMI. Low BMI was an independent risk factors for osteopenia in patients with cirrhosis. In addition, low body weight and high liver stiffness value were independent risk factors for osteoporosis in patients with cirrhosis. It suggests that CHB related cirrhosis patients with low BMI and low weight should be given sufficient attention in BMD. Our study also found that patients with higher liver stiffness values are more likely to have hepatic osteopathy. This results suggests, for patients with high liver stiffness values, attention should be paid to BMD. Moreover, our results show that maybe liver stiffness value measured by Fibroscan could be used to predicted decreased BMD among HBV related cirrhosis and be regarded as a monitoring method for bone nutrition among those population.

There are some limitations in this study. First, the sample size is relatively small, so the results may be biased. The data collected in this study came from a single center and may lead to some enrollment bias. A multicenter prospective study is needed for further validate the risk factors in screening and early diagnosis of hepatic osteopathy in CHB related cirrhosis patients.

Author contributions

Conceptualization: Shujuan Cao, Wei Zhang.
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Writing – original draft: Shujuan Cao, Wei Zhang, Zengcun Su, Xuping Zhang.
Writing – review & editing: Shujuan Cao, Zengcun Su, Xuping Zhang.

References

[1] Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10:1–98.
[2] Cai S, Cao J, Yu T, et al. Effectiveness of entecavir or telbivudine therapy in patients with chronic hepatitis B virus infection pre-treated with interferon compared with de novo therapy with entecavir and telbivudine. Medicine (Baltimore) 2017;96:e7021.
[3] Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63:261–83.
[4] Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009;50:661–2.
[5] Cai SH, Lu SX, Liu LL, et al. Increased expression of hepatocyte nuclear factor 4 alpha transcribed by promoter 2 indicates a poor prognosis in hepatocellular carcinoma. Therap Adv Gastroenterol 2017;10:761–71.
[6] Geier A. Hepatitis B virus: the "metabolovirus" highjacks cholesterol and bile acid metabolism. Hepatology 2014;60:1458–60.
[7] Han H, Wang B, Wang B. Progression of hepatic osteodystrophy: pathogenesis, diagnosis and treatment. Zhonghua Gan Zang Bing Za Zhi 2014;22:75–7.
[8] Cai S, Ou Z, Liu D, et al. Risk factors associated with liver steatosis and fibrosis in chronic hepatitis B patient with component of metabolic syndrome. United European Gastroenterol J 2018;6:558–66.
[9] Zheng JP, Miao HX, Zheng SW, et al. Risk factors for osteoporosis in liver cirrhosis patients measured by transient elastography. Medicine (Baltimore) 2018;97:e10645.
[10] Cai S, Li Z, Yu T, et al. Serum hepatitis B core antibody levels predict HBeAg seroconversion in chronic hepatitis B patients with high viral load treated with nucleos(t)ide analogs. Infect Drug Resist 2018;11:469–77.
[11] Cai S, Yu T, Jiang Y, et al. Comparison of entecavir monotherapy and de novo lamivudine and adefovir combination therapy in HBeAg-positive chronic hepatitis B with high viral load: 48-week result. Clin Exp Med 2016;16:429–36.
[12] Chen YP, Liang XE, Zhang Q, et al. Larger biopsies evaluation of transient elastography for detecting advanced fibrosis in patients with compensated chronic hepatitis B. J Gastroenterol Hepatol 2012;27:1219–26.
[13] Xue X, Cai S, Ou H, et al. Health-related quality of life in patients with chronic hepatitis B during antiviral treatment and off-treatment. Patient Prefer Adherence 2017;11:85–93.
[14] Zeng J, Cai S, Liu J, et al. Dynamic changes in liver stiffness measured by transient elastography predict clinical outcomes among patients with chronic hepatitis B. J Ultrasound Med 2017;36:261–8.
[15] Cai SH, Lv FF, Zhang YH, et al. Dynamic comparison between Daan real-time PCR and Cobas TaqMan for quantification of HBV DNA levels in patients with CHB. BMC Infect Dis 2014;14:85.
[16] Lai W, Cai S. Comment on "Prevalence of Anxiety and Depression in Patients with Inflammatory Bowel Disease". Can J Gastroenterol Hepatol 2018;2018:6747630.
[17] Xue X, Cai S. Comment on "Assessment of Liver Stiffness in Pediatric Fontan Patients Using Transient Elastography". Can J Gastroenterol Hepatol 2016;2016:9343960.
[18] Zheng C, Yan H, Zeng J, et al. Comparison of pegylated interferon monotherapy and de novo pegylated interferon plus tenofovir combination therapy in patients with chronic hepatitis B. Infect Drug Resist 2019;12:845–54.
[19] Guarino M, Loperto I, Camera S, et al. Osteoporosis across chronic liver disease. Osteoporos Int 2016;27:1967–77.
[20] Guanabens N, Pares A. Osteoporosis in liver cirrhosis. Gastroenterol Hepatol 2012;35:411–20.
[21] Rouillard S, Lane NE. Hepatic osteodystrophy. Hepatology 2001;33:301–7.
[22] Matloff DS, Kaplan MM, Neer RM, et al. Osteoporosis in primary biliary cirrhosis: effects of 25-hydroxyvitamin D3 treatment. Gastroenterology 1982;83:97–102.
[23] Suzuki H . Bone complications in chronic liver disease (hepatic osteodystrophy). Clin Calcium 2015;25:1619–24.
[24] Giouleme OI, Vyzantiadis TA, Nikolaidis NL, et al. Pathogenesis of osteoporosis in liver cirrhosis. Hepatogastroenterology 2006;53:938–43.
[25] Jilka RL, O'Brien CA. The role of osteocytes in age-related bone loss. Curr Osteoporos Rep 2016;14:16–25.
[26] Hernlund E, Svedbom A, Ivergard M, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 2013;8:136.
[27] Jang DG, Kwon JY, Choi SK, et al. Prevalence of low bone mineral density and associated risk factors in Korean Puerperal Women. J Korean Med Sci 2016;31:1790–6.
[28] Ensrud KE, Lipschutz RC, Cauley JA, et al. Body size and hip fracture risk in older women: a prospective study. Study of osteoporotic fractures research group. Am J Med 1997;103:274–80.
[29] Crandall CJ, Yildiz VO, Wactawski-Wende J, et al. Postmenopausal weight change and incidence of fracture: post hoc findings from Women's Health Initiative Observational Study and Clinical Trials. BMJ 2015;350:h25.