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Original Article

Association between nutritional screening via the Controlling Nutritional Status index and bone mineral density in chronic liver disease of various etiologies

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Aim: Bone density disorders are prevalent in patients with chronic liver disease (CLD), who commonly present with hepatic osteodystrophy. However, the relationship between nutritional status and bone mineral density (BMD) has been scarcely studied in CLD.

Methods: This single-center, cross-sectional study included outpatients consecutively diagnosed with CLD during a 1.5-year period. The nutritional status was assessed with the Controlling Nutritional Status (CONUT) index; dual-energy X-ray absorptiometry scans and parameters of bone mineral metabolism were carried out. Bone fracture risk was estimated with the World Health Organization FRAX tool.

Results: Among the 126 patients recruited (58.7% male), osteopenia and osteoporosis were present in 31.1% and 10.7%, respectively. The 10-year fracture risk was significantly higher among women. Malnutrition estimated with the CONUT index was present in 29.9% of patients and was significantly more frequent in cirrhotic patients, 63.4% of whom were malnourished. Malnutrition stage directly correlated with hepatic function as expressed by the Model for End-Stage Liver Disease index. A non-significant relationship between CONUT-assessed nutritional status and BMD was documented. 25-Hydroxyvitamin-D3 (25[OH]-D3) and fracture risk correlated positively with the CONUT stage, and total cholesterol had an inverse relationship with BMD.

Conclusion: Malnutrition assessed by the CONUT was very frequent in patients with liver cirrhosis. The CONUT score inversely correlated with liver function, while malnutrition stage directly correlated with BMD, fracture risk and 25(OH)-D3. Total cholesterol showed a negative association with BMD in this population.

Key words: bone mineral density, chronic liver disease, cirrhosis, Controlling Nutritional Status index, nutritional status, osteoporosis

INTRODUCTION

METABOLIC BONE DISEASE is a common complication in the clinical course of chronic liver disease (CLD), presenting as osteopenia and osteoporosis.[1,2] The generic term "hepatic osteodystrophy" has been used to refer to this type of disorder, although this term also includes osteomalacia, which is infrequent in liver disease.[3]

The World Health Organization (WHO) defines osteoporosis as a systemic skeletal disease characterized by a decrease in bone mineral density (BMD), leading to increased morbidity and mortality due to fractures.[4] Its diagnosis is based on BMD measurements through dual-energy X-ray absorptiometry (DEXA or bone densitometry) at the lumbar spine and femoral neck. A

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BMD under 2.5 standard deviations from the mean for young adults (T-score, ≤–2.5) is defined as osteoporosis, while a T-score between –1 and –2.5 indicates the presence of osteopenia. Severe or established osteoporosis is diagnosed for T-scores of –2.5 or less if there is also radiological evidence of one or more fractures due to fragility.[5]

Loss of BMD has been observed in chronic cholestatic disease, alcoholic cirrhosis, viral hepatitis, hemochromatosis and also in liver transplant patients.[6] The prevalence of osteoporosis and osteopenia described in different series of patients with CLD of various etiologies ranges between 11–45% and 18–48%, respectively.[7–10]

The pathogenesis of BMD loss secondary to CLD is multifactorial and only partially understood. The concomitant presence of an imbalance between bone formation and resorption involves osteoblast dysfunction and osteoclast activation to various degrees, although most of the published work agrees on a predominance of the former.[11] This alteration in bone turnover is mediated by hormonal, metabolic, inflammatory and genetic factors which often coincide in CLD.[12]

Patients with CLD may present various risk factors for bone loss, including low body mass index (BMI), vitamin D deficiency, sarcopenia or protein–calorie malnutrition.[13] Alterations in nutritional status are common in CLD and can affect approximately 20% and 50% of patients with compensated and decompensated cirrhosis, respectively.[13,14] For this reason, the European Society for Clinical Nutrition and Metabolism (ESPEN) recommends carrying out a nutritional assessment in all patients with CLD. The test recommended for assessing nutritional status is the Subjective Global Assessment (SGA), but anthropometric methods also can be used.[15]

Several recent studies have examined the possibility of assessing nutritional status in patients with CLD with other protocols, such as the Prognostic Nutritional Index (PNI) or Controlling Nutritional Status (CONUT) index, which are comprised exclusively of analytical data.[16,17] However, the relationship between nutritional status and changes in BMD has not been extensively studied and there is little data on the applicability of the CONUT in patients with compensated liver disease. This paper aims to investigate the relationship between nutritional status as measured by the CONUT screening method, the risk of bone fracture and changes in BMD in a population consisting of patients with CLD of various etiologies.

METHODS

THIS IS A transversal, descriptive study of adult (aged ≥18 years) patients with CLD of various etiologies who were prospectively recruited between January 2012 and June 2013. Diagnoses of CLD were based on clinical, analytical, histological and/or radiological criteria. The prevalence of the etiologies of CLD in the studied population is summarized in Table 1.

We recorded the epidemiological characteristics of the study subjects, including age, sex, cardiovascular risk factors, pharmacological treatment and postmenopausal status. Twenty-nine patients (23%) had a previous diagnosis of type 2 diabetes, 51 (40.5%) had hypertension and 18 (14.3%) had hypercholesterolemia. Menopause was present in 36 (72%) of female patients. Eleven diabetic patients (8.7%) received treatment with insulin, 17 (13.5%) with metformin, 5 (4%) with sulfonylureas and three (2.4%) with dipeptidyl-peptidase IV inhibitors. Sixteen patients with hypercholesterolemia (12.7%) were treated with statins. Forty-one subjects took diuretics: 13 furosemide (10.3%), 14 spironolactone and 14 thiazides (11.1% for each agent). Beta-blockers were used in 25 cases (19.8%) and angiotensin-converting enzyme inhibitors in 20 (15.9%). Only two patients received corticosteroids (5 mg of oral prednisone daily).

In addition, each patient underwent an analysis comprised of a hemogram; a basic biochemistry analysis (including albumin, prealbumin and cholesterol); a hormonal profile with vitamin D3, parathyroid

Table 1 Etiology of chronic liver disease

Etiology of liver disease	*n* (%)
Alcoholic liver disease*	23 (18.3)
Chronic hepatitis B	24 (19)
Chronic hepatitis C	33 (26.2)
Primary biliary cirrhosis	7 (5.6)
Primary sclerosing cholangitis	1 (0.8)
Hereditary hemochromatosis**	17 (13.5)
Wilson's disease	5 (4)
Autoimmune hepatitis	6 (4.8)
Cryptogenic	3 (2.4)
Non-alcoholic steatohepatitis***	17 (13.5)

*, ** and *** denote cases of mixed etiology. **n* = 3, alcoholic and chronic viral hepatitis (two hepatitis B virus [HBV] and one hepatitis C virus [HCV]); ***n* = 3 hemochromatosis and non-alcoholic steatohepatitis; ****n* = 4 non-alcoholic steatohepatitis and chronic viral hepatitis (three HBV and one HCV).

Table 2 Controlling Nutritional Status index score : assessment of undernutrition degree

Parameter	Normal	Undernutrition degree Light	Moderate	Severe
Serum albumin (g/dL)	3.5–4.5	3.0–3.49	2.5-2.9	<2.5
Score	0	2	4	6
Total lymphocytes (mL)	>1600	1200–1599	800–1199	<800
Score	0	1	2	3
Cholesterol (mg/dL)	>180	140–180	100–139	<100
Score	0	1	2	3
Total score	0–1	2–4	5–8	9–12

Adapted from de Ulíbarri *et al.*[17]

hormone and vitamin A levels; and a determination of calcium excretion in urine over a 24-h period. The BMI of each patient was calculated, and BMD was determined with a DEXA scan. The risk of hip and osteoporotic fractures over 10 years was also estimated with the World Health Organization FRAX-OMS tool. Finally, the CONUT index was calculated for each patient based on the score of three analytical parameters: albumin, total cholesterol and total lymphocyte count. The results were then used to classify the nutritional status of each patient as either normal (CONUT score, 0–1) or one of light (2–4), moderate (5–8) or severe malnutrition (9–12) (Table 2).

A descriptive study of patient characteristics and the study variables was also carried out, with the results expressed as percentages or as a mean plus or minus the standard deviation. The relationship between the presence of cirrhosis of the liver and malnutrition was analyzed with a χ^2-test, and linear multiple regression models were constructed to assess the association between the BMD parameters and the variables making up the CONUT index. The level of statistical significance was set at $P < 0.05$. All statistical analyses were carried out with the PAWS version 18.0 program (SPSS, Chicago, IL, USA). The registry supporting this study was approved by the institutional research and ethics committee.

RESULTS

THE STUDY SUBJECTS included 126 patients, 74 men (58.7%) and 52 women (41.3%), with an average age of 55.3 years (range, 25–83). One fourth of the study subjects (32 patients, 25.4%) presented with cirrhosis of the liver. The most frequent causes of CLD were chronic hepatitis C and B in 33 and 24 cases (26.2 and 19%), respectively. The median BMI was 29.3 kg/m^2 (range, 21–46). Twenty-four patients (20%) presented a normal BMI while 53 patients (44.9%) were overweight and 41 (34.7%) were obese. The median values of all analytical parameters used are given in Table 3. The mean level of fasting plasma glucose was 113.3 ± 35.6 mg/dL (range, 65–269). Seventy-seven patients (62.6%) had a glucose level below 110 mg/dL, 22 (17.9%) between 111 and 125 mg/dL, and 24 (19.5%) had 126 mg/dL or more. There was a high proportion of diabetic patients with fasting glucose above 126 mg/dL ($n = 22$, 75.9%). Among the subjects with a previous diagnosis of hypercholesterolemia ($n = 18$), 14 (77.8%) had a total cholesterol level lower than 250 mg/dL and 12 (66%) had a low-density lipoprotein (LDL) fraction below 175 mg/dL. With regard to BMD determined by means of DEXA, the median t-score was −0.26 in the lumbar spine and −0.28 in the femoral neck. The median risk for major osteoporotic or hip fractures at 10 years was 0.80 and 3.13, respectively, with a significantly greater risk observed in female patients. No significant differences were observed regarding osteopenia and osteoporosis between cirrhotic and non-cirrhotic patients (25.8% of osteopenia and 9.7% of osteoporosis vs 3% and 11%, respectively; $P = 0.70$). Table 4 summarizes the densitometric and fracture risk data of the study population.

With regard to nutritional status assessment, the CONUT index was applied to a total of 117 patients for whom data on the three analytical parameters comprising this scale were available: albumin, total cholesterol and absolute number of lymphocytes. Thirty-five cases (29.9%) showed signs of malnutrition, 25 light (24.8%) and six moderate (5.1%). Cirrhosis of the liver was significantly associated with the presence of malnutrition; in fact, 63% of cirrhotic patients were undernourished as measured with the CONUT index in contrast to 20% of non-cirrhotic patients (Fig. 1).

Table 3 Demographic data and laboratory parameters

	Global ($n = 126$)	Men ($n = 74$)	Women ($n = 52$)	P
Age (years)	55.3 ± 13.4	53.7 ± 12.2	57.6 ± 14.9	n.s.
BMI (kg/m^2)	29.3 ± 5.0	28.8 ± 3.8	30.0 ± 6.3	n.s.
Hemoglobin (g/dL)	14.3 ± 1.8	14.9 ± 1.7	13.4 ± 1.5	<0.001
Hematocrit (%)	42.0 ± 5.0	43.4 ± 4.8	39.2 ± 4.1	<0.001
Calcium (mg/dL)	9.22 ± 0.46	9.30 ± 0.44	9.11 ± 0.46	0.03
Phosphorus (mg/dL)	3.0 ± 1.0	3.2 ± 0.6	3.4 ± 0.5	n.s.
Pre-albumin (g/dL)	21.8 ± 8.5	22.9 ± 9.2	20.3 ± 7.2	n.s.
Albumin (g/dL)	4.3 ± 0.7	4.3 ± 0.7	4.2 ± 0.6	n.s.
Total cholesterol (mg/dL)	193 ± 47	193 ± 48	192 ± 46	n.s.
Lymphocytes (μL)	2213 ± 832	2317 ± 867	2056 ± 770	n.s.
25(OH)-D3 (ng/dL)	19.7 ± 10.7	20.3 ± 10.3	18.8 ± 11.4	n.s.
PTH (pg/mL)	47.0 ± 18.0	45.4 ± 19.4	50.2 ± 16.6	n.s.
Urinary calcium (mg/24 h)	173 ± 125	187 ± 128	153 ± 118	n.s.

Results expressed as mean ± standard deviation.
25(OH)-D3, 25-hydroxyvitamin-D3; BMI, body mass index; n.s., non significant; PTH, parathyroid hormone.

A comparison of the correlations between nutritional status according to the CONUT, liver function and BMD parameters showed that the degree of malnutrition is more directly and significantly correlated with the Model for End-Stage Liver Disease (MELD) values in the group of cirrhotic patients ($r = 0.624$, $P < 0.01$). In addition, the CONUT results were directly associated with the various indicators of BMD, with this correlation being significant for the z-score at the femoral neck ($r = 0.211$, $P < 0.05$). In addition, the CONUT values correlated positively with both vitamin D3 levels and fracture risk (Table 5).

Of the three parameters making up the CONUT scale, total cholesterol presented a negative correlation with both the degree of liver function and BMD (lumbar spine, $r = -0.251$, $P < 0.05$; femoral neck, $r = -0.203$, $P < 0.05$), as well as with the lumbar and femoral z-scores and with the spinal t-score. These correlations were also more significant in patients with liver cirrhosis (Table 6).

Table 4 Densitometric characteristics, bone mineral density and fracture risk

	Global ($n = 126$)	Men ($n = 74$)	Women ($n = 52$)	P
Bone densitometry†				
Normal	71 (58.2%)	52 (71.2%)	19 (38.8%)	<0.001
Osteopenia	38 (31.1%)	20 (27.4%)	18 (36.7%)	<0.001
Osteoporosis	13 (10.7%)	1 (1.4%)	12 (24.5%)	<0.001
BMD (L), g/cm^2	1.02 ± 0.19	1.06 ± 0.16	0.96 ± 0.21	0.002
BMD (FN), g/cm^2	0.86 ± 0.14	0.91 ± 0.12	0.79 ± 0.15	<0.001
z-score (L)	0.35 ± 1.34	0.36 ± 1.18	0.34 ± 1.54	n.s.
z-score (FN)	0.69 ± 1.11	0.73 ± 1.01	0.64 ± 1.25	n.s.
t-score (L)	–0.26 ± 1.69	0.17 ± 1.35	–0.87 ± 1.94	0.002
t-score (FN)	–0.28 ± 1.15	–0.13 ± 0.97	–0.49 ± 1.36	n.s.
Hip fracture risk‡ (%, 10 years)	2.10 (1.45–3.15)	1.8 (1.20–2.50)	2.8 (2.0–7.1)	<0.001
Global Osteoporotic Fracture Risk‡ (%, 10 years)	0.20 (0.10–0.90)	0.20 (0.10–0.60)	0.60 (0.10–2.1)	0.002

Results expressed as mean ± standard deviation.
†Number of cases (%), ‡median (range).
25(OH)-D3, 25-hydroxyvitamin-D3; BMD, bone mineral density; FN, femoral neck; L, lumbar spine; n.s.: non significant.

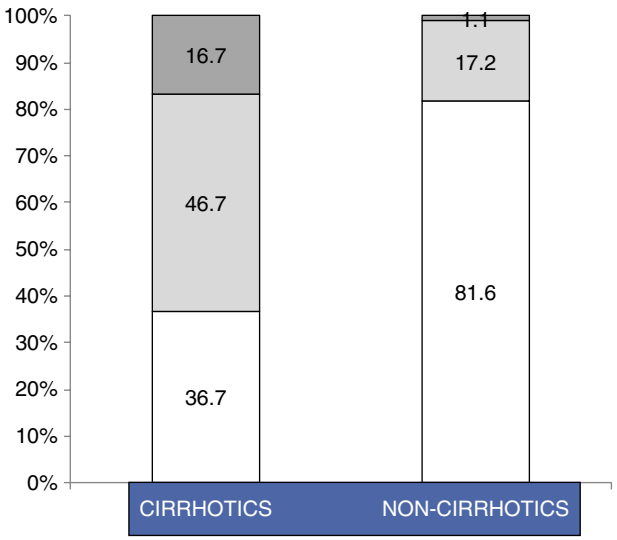

Figure 1 Nutritional status measured with the Controlling Nutritional Status index in patients with and without liver cirrhosis. ■, moderate; □, light; □, normal.

Total cholesterol values adjusted for age and sex were inversely and significantly correlated with BMD and directly but not significantly associated with the risk for both hip fracture and overall osteoporotic fracture (Table 7). Furthermore, a significant interaction was observed between plasma cholesterol and cirrhosis with regard to bone density in the lumbar spine ($P = 0.03$). The BMD values were thus significantly lower in cirrhotic patients with higher total cholesterol levels (Fig. 2).

Table 5 Correlations of the Controlling Nutritional Status (CONUT) index score with liver function, bone density parameters and fracture risk

	Global ($n = 126$)	Non-cirrhotics ($n = 94$)	Cirrhotics ($n = 32$)
MELD score	0.353**	0.079	0.624**
25(OH)-D3	0.236*	0.212	0.082
BMD (L)	0.123	0.049	0.221
BMD (FN)	0.097	0.044	0.098
z-score (L)	0.165	0.050	0.315
z-score (FN)	0.211*	0.166	0.157
t-score (L)	0.130	0.056	0.212
t-score (FN)	0.069	0.045	0.082
Hip fracture risk	0.074	0.091	0.057
Major fracture risk	0.069	0.090	−0.035

*$P < 0.05$; **$P < 0.01$.
25(OH)-D3, 25-hydroxyvitamin-D3; BMD, bone mineral density; FN, femoral neck; L, lumbar spine; MELD, Model for End-Stage Liver Disease.

Table 6 Correlations of total cholesterol with liver function, bone density parameters and fracture risk

	Global ($n = 126$)	Non-cirrhotics ($n = 94$)	Cirrhotics ($n = 32$)
MELD score	−0.182*	−0.079	−0.391*
25(OH)-D3	−0.145	−0.135	−0.066
BMD (L)	−0.251*	−0.155	−0.478*
BMD (FN)	−0.203*	−0.139	−0.345
z-score (L)	−0.258*	−0.132	−0.513*
z-score (FN)	−0.243*	−0.164	−0.390*
t-score (L)	−0.258*	−0.161	−0.478*
t-score (FN)	−0.179	−0.127	−0.300
Hip fracture risk	0.045	−0.005	0.130
Major fracture risk	0.112	0.047	0.306

*$P < 0.05$; **$P < 0.01$.
25(OH)-D3, 25-hydroxyvitamin-D3; BMD, bone mineral density; FN, femoral neck; L, lumbar spine; MELD, Model for End-Stage Liver Disease.

DISCUSSION

OUR FINDINGS SHOW a higher prevalence of BMD changes and malnutrition (as assessed with the CONUT index) among patients with CLD, especially those with liver cirrhosis. The degree of malnutrition was significantly correlated with liver function as determined by the MELD score. The CONUT values were directly related to densitometric data as well as to the risk for osteoporotic fractures and vitamin D levels, with the latter being statistically significant.

The loss of BMD is a frequent complication in patients with CLD, who present osteopenia rates close to 50% and osteoporosis rates ranging 10–45%.[10,18–23] The deterioration of bone mass in these patients is due to a set of etiopathogenic factors that give rise predominantly to osteoblastic dysfunction,[24–28] although there also may be a certain degree of osteoclastic hyperactivity.[29–31]

Factors that favor osteoblastic dysfunction include low levels of osteocalcin and insulin-like growth factor, both of which have been observed in patients with CLD,[26,32] as well as hyperbilirubinemia and the retention of bile acids.[27,33] The activation of osteoclasts has been associated with various conditions described in CLD, such as hyperparathyroidism secondary to calcium and vitamin D deficiency,[34] hyperactivation of the receptor activator of nuclear factor-κB ligand (RANKL)/osteoprotegerin system,[35] and the liberation of several

Table 7 Relationship between cholesterol level adjusted by age and sex, bone density and fracture risk

	BMD (FN)	BMD (LS)	Fracture Risk (hip)	Fracture Risk (major)
Cholesterol (10-mg/dL increments)	−0.007 (−0.012 to −0.002)	−0.011 (−0.018 to −0.004)	0.051 (−0.035 to 0.138)	0.025 (−0.022 to 0.072)
Age (1-year increments)	−0.004 (−0.005 to −0.002)	−0.001 (−0.003 to 0.002)	0.115 (0.083 to 0.147)	0.058 (0.041 to 0.076)
Female sex	−0.104 (−0.15 to −0.057)	−0.111 (−0.178 to −0.044)	2.33 (1.480 to 3.180)	0.78 (0.320 to 1.250)

Results expressed as changes of dependent variable (95% confidence interval) related to increasing of independent variable.
BMD, bone mineral density; FN, femoral neck; L, lumbar spine.

cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF)-α or the p55 receptor of TNF.[23]

In our study, the overall rates of osteoporosis and osteopenia were 10.7% and 31.1%, respectively, with a significantly higher prevalence of both in female patients. Previous series have described a prevalence of osteoporosis similar to that found in our work,[21,36] although other authors have reported higher incidence rates. Thus, Ninkovic *et al*. analyzed 243 patients in the advanced stages of CLD and found that 36.6% suffered from osteoporosis and 48.1% presented osteopenia.[37] The incidence rates reported by Choudhary *et al*. were even higher at 38% and 57.3%, respectively, in their study of 115 patients with cirrhosis of various etiologies.[38] It is worth noting that the majority of these studies have been carried out on populations consisting exclusively of cirrhotic patients and those in the advanced stages of chronic liver failure, in which bone mass loss is more frequent.[13,39] In contrast, in our study population, only 25% of the patients presented with advanced CLD, which may explain the lower BMD loss observed overall.

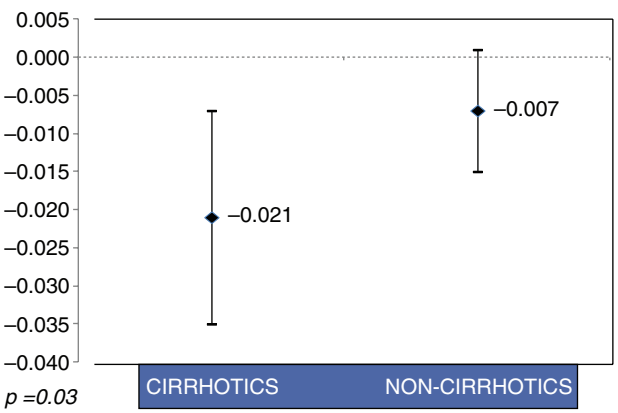

Figure 2 Changes in spinal bone mineral density associated with a 10-mg/dL increase in total cholesterol levels in patients with and without liver cirrhosis.

Protein–calorie malnutrition is quite prevalent among patients with CLD, especially in advanced stages of liver failure.[9,12,14] The causes of nutritional alterations, which are present in a significant percentage of patients with cirrhosis, are multiple and include metabolic disorders, malabsorption and poor digestion of nutrients, intestinal bacteria overgrowth, changes in motility, or enteropathy due to portal hypertension, among others.[14,40–43]

Nutritional deficiencies have been proposed as a risk factor that may contribute to osteoporosis in the evolution of CLD.[12,13,39] Nevertheless, little is known about the specific pathogenic mechanisms underlying the relationship between changes in nutritional status and loss of BMD in these patients. Leptin, a hormone synthesized by adipocytes, favors osteoblast proliferation; its deficiency in CLD could be a negative factor in the formation of bone tissue, although its role in this process remains unclear.[44] Sarcopenia or loss of skeletal muscle mass is also frequent in advanced CLD, and although it has been associated with osteoporosis in both men[45] and postmenopausal women,[46] its relationship with alterations in BMD has yet to be studied in liver disease.

Our study attempts to assess the nutritional status of patients with CLD with the aid of the CONUT in order to determine the association between malnutrition, loss of BMD and bone fracture risk. Recognizing nutritional deficiencies in CLD is paramount, given the fact that dietary supplementation has been associated with improvements in liver function, as well as with a lower rate of hospital infections and mortality.[47,48] The ESPEN recommends the SGA for those patients with CLD. The SGA is a standardized and validated tool which uses clinical data and information taken from physical examinations of patients to classify their degree of

malnutrition.[15] Nevertheless, several recently published studies have used other tools to assess nutritional status in these patients because they are simpler to carry out. The CONUT is a nutritional screening system designed in 2005 by Ulibarri *et al*. as an automated tool for early detection of malnutrition in a hospital setting. It uses three analytic parameters (albumin, cholesterol and total lymphocytes) to define three degrees of malnutrition (light, moderate or severe). The CONUT index was validated by taking other methods of assessment, including the SGA and Full Nutritional Assessment as a reference; the CONUT showed a high degree of agreement with both of these more established methods.[17] The validity of the CONUT was subsequently evaluated by its developers, who constructed logistical regression models using the SGA as a reference and calculated a kappa index of 0.680 for the comparison between the two methods.[49] The clinical experience with the CONUT in liver disease is scarce, but some studies have indicated its potential usefulness as it correlates significantly with both the severity of CLD and with anthropometric data.[16] The prognostic ability of the CONUT also has been studied in a small population of patients with advanced stages of liver failure awaiting a liver transplant, in which it proved to be a good indicator of long-term survival.[50]

In our study, the CONUT found malnutrition rates of 63% and 18.3% in cirrhotic and non-cirrhotic patients, respectively. Previously published series also showed a high incidence of malnutrition in patients suffering from liver disease. Lautz *et al*. observed a malnutrition rate of 65% in their study of 123 cirrhotic transplant candidates.[51] This incidence may be higher in hospitalized patients, as demonstrated by Caregaro *et al*. in their study of 120 patients with liver cirrhosis mostly due to alcoholism. In this case, protein deficiencies were detected in 81% of the study subjects.[52] The same authors found that the degree of malnourishment correlated positively with the severity of CLD. Recently, Kawabe *et al*. used various assessment methods to carry out a nutritional study on 86 patients with cirrhosis due to hepatitis C, finding malnutrition rates ranging from 25.6% as measured with the SGA up to 76.7% when the Maastrich Index was used.[53]

It is worth noting that in our study, none of the patients presented with severe malnutrition. This may be due to the fact that our study population, including cirrhotic patients, was made up entirely of outpatients with compensated liver disease.

The nutritional status of our patients significantly correlated with their liver function as determined with the MELD index, that is, those with a higher degree of malnutrition presented higher MELD values. In this way, we observed how this association is more marked in cirrhotics, suggesting that malnutrition is more common in the advanced stages of CLD, as demonstrated in several previous studies.[16,54,55] It is also noteworthy that no inverse relationship was found between nutritional status, BMD parameters and vitamin D3 levels. Based on these findings, it may seem paradoxical that malnutrition as detected with the CONUT does not necessarily imply a lower BMD, higher fracture risk or D3 hypovitaminosis. From this it could be deduced that nutritional status per se is not a principal factor in BMD loss in patients with CLD, but that it plays a part, together with other pathogenic mechanisms, in the development of osteopenia, as has been described in the majority of studies on this subject to date.[12,13,39,56–58]

As noted above, the CONUT uses three laboratory values to assess nutritional status. Upon analyzing the relationship of each parameter with those related to liver function and bone density, we observed that total cholesterol levels had an inverse association with the MELD index, lumbar spine BMD and the z-score, with more marked correlations in cirrhotic patients. Once adjusted for age and sex, plasma cholesterol also showed an inverse relationship with BMD and a direct non-significant relationship with bone fracture risk. The relationship between cholesterol levels and BMD has been previously studied, but the results have been contradictory, with no conclusive elucidation of the pathogenic mechanisms behind this relationship. The influence of cholesterol levels on BMD could be mediated by the oxidized particles of LDL cholesterol, which may induce apoptosis of osteoblasts, with this effect being neutralized by high-density lipoprotein (HDL) cholesterol.[59] In a similar vein, it also has been suggested that the capture of osteoclastic cholesterol by HDL may favor the apoptosis of these cells while an increase in LDL cholesterol would promote their survival.[60,61] Furthermore, several genetic mechanisms which could influence both BMD as well as lipoprotein levels have been described. In this way, Apo $e^{-/-}$ murine models with low levels of cholesterol present high bone density,[62] although this association is not clear in humans.[61,3] Other researches have found that exposure of T lymphocytes to oxidized LDL particles increases the production of RANKL by the former, thus activating osteoclastic function and the process of bone resorption.[64] In this context, T lymphocytes in the bone marrow of rats fed a diet rich in lipids have been demonstrated to produce a significantly greater amount of

RANKL, and their splenic lymphocytes overexpress the LOX-1 receptor for oxidized LDL, with the subsequent production of osteoclastogenic cytokines such as IL-6, TNF-α, IL-1β and γ-interferon.[65]

The association between cholesterol and BMD has been studied in various series of postmenopausal women. Sarkis *et al*. found that subjects with a greater BMD presented a more favorable LDL profile, although there were no significant differences between them and women with a BMD considered normal for their age (femoral neck t-score, 0.9 vs −0.2, $P < 0.001$; LDL cholesterol, 114 vs 124 mg/dL, $P = 0.18$).[66] Tarakida *et al*. observed an inverse relationship between cholesterol and BMD assessed with calcaneal ultrasound; the bone mass loss was significantly greater for plasma cholesterol levels over 240 mg/dL, independently of pro-resorptive cytokine levels.[67] Moreover, the effect of hypercholesterolemia on bone turnover expressed as concentrations of remodeling markers was studied by Majima *et al*. in a group of 281 patients with hypercholesterolemia whose bone alkaline phosphatase and N-terminal telopeptide of type 1 collagen (NTX) levels directly correlated with total cholesterol and LDL levels, especially in the subgroup of postmenopausal women. Additionally, NTX levels were significantly higher in both men and women with hypercholesterolemia in comparison with the control group.[68] Thus, the association between total cholesterol and BMD observed in our series agrees with previously published findings, although it should be noted that prior to our study, the effect of an unfavorable lipid profile on BMD had not been specifically examined in populations of patients with CLD.

Conversely, other authors have found no direct association between lipid profile and BMD. Thus, cholesterol levels were not associated with the loss of bone density in the Framingham cohort study on osteoporosis, which included 712 women and 450 men in a prospective study with over 30 years of follow up.[69] Go *et al*. likewise found no significant variations in the spinal or femoral BMD as a result of changes in LDL cholesterol levels in 958 postmenopausal women after a follow-up period of 7 years.[70] In fact, Tanko *et al*. suggested that the weak association observed between plasma cholesterol and spinal BMD after menopause may be mediated more by hypoestrogenism than by the direct effect of cholesterol on osteoblast function,[71] a possibility which should be taken into consideration in populations like the one in our study, in which the female subjects had a mean age above 55 years.

Our study has several limitations, including its uncontrolled design, small sample size, absence of other anthropometric parameters apart from BMI and heterogeneous population with regard to disease etiology. Furthermore, although the CONUT index was designed for use in a hospital setting, we used it in a group of outpatients with compensated liver disease, which might have led to an underestimation of the presence of malnutrition in our study population. Finally, it should be noted that albumin levels, which constitute one of the parameters used in the CONUT index and score double the rating than cholesterol and lymphocytes, are of limited use for nutritional screening of patients with changes in extracellular volume. This is generally the case in CLD and cirrhosis,[14] where it may be difficult to distinguish whether low serum albumin is due to the liver disease itself or to the impaired nutritional status of the patient.

In conclusion, in our study population, which included 126 outpatients with CLD of mixed etiologies, the CONUT index found a global incidence of malnutrition of 30%. These rates were higher in the subgroup of cirrhotic patients, in whom the incidence of malnutrition was 60%. Nutritional impairment was directly correlated with liver dysfunction as measured by the MELD index. A direct association between bone density and nutritional status was observed, so that the higher CONUT scores correlated positively with BMD; malnutrition was thus not associated with a lower bone density. No significant correlations were observed between the level of malnutrition and bone fracture risk. However, total cholesterol levels, which comprise one of the components of the CONUT index, were inversely correlated with BMD, a finding described in previously published studies on postmenopausal women.

Therefore, taking into account that the CONUT has not been validated as a reliable marker of nutritional status in CLD, conclusions about its relationship with bone density and liver function should be carefully drawn. Future research should include multicenter studies on the usefulness of the CONUT index for nutritional assessment in liver disease, taking as a reference those tools considered to be methods of choice by clinical guidelines. There should also be more emphasis on determining the relationship between lipid profiles and BMD in groups of patients suffering from CLD with a homogeneous etiology and with a similar degree of hepatocellular failure.

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