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BRIEF ARTICLE

MELD score, insulin-like growth factor 1 and cytokines on bone density in end-stage liver disease

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Abstract

AIM: To determine the contributions of insulin-like growth factor 1 (IGF-1), cytokines and liver disease severity to bone mineral density in patients pre-transplantation.

METHODS: Serum IGF-1, tumor necrosis factor-α (TNFα) and interleukin 6 (IL-6) were measured and the Model for End-Stage Liver Disease (MELD) score calculated in 121 adult patients referred to a single centre for liver transplantation. Bone mineral density (BMD) of the lumbar spine and femoral neck were assessed via dual energy X-ray absorptiometry. Demographics, liver disease etiology, medication use and relevant biochemistry were recorded.

RESULTS: A total of 117 subjects were included, with low BMD seen in 68.6%, irrespective of disease etiology. In multivariable analysis, low body mass index (BMI), increased bone turnover and low IGF-1 were independent predictors of low spinal bone density. At the hip, BMI, IGF-1 and vitamin D status were predictive. Despite prevalent elevations of TNFα and IL-6, levels did not correlate with degree of bone loss. The MELD score failed to predict low BMD in this pre-transplant population.

CONCLUSION: Osteopenia/osteoporosis is common in advanced liver disease. Low serum IGF-1 is weakly predictive but serum cytokine and MELD score fail to predict the severity of bone disease.

Key words: Hepatic osteodystrophy; Insulin-like growth factor-1; Cytokines; Bone mineral density; MELD score

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INTRODUCTION

Low bone mineral density (BMD) is a known complication of chronic liver disease[1,2], demonstrated in diverse etiologies, including cholestasis[3,4], alcohol[5-7] and viral hepatitis[8,9]. However, the mechanism by which chronic liver disease mediates bone loss is not clearly defined and is likely to be multifactorial.

Declining serum insulin-like growth factor-1 (IGF-1) has been shown to play a role in the pathogenesis of bone loss in elderly normal subjects[10,11] and in males with idiopathic osteoporosis[12,13]. While known to decline in hepatic disease, correlating with the degree of dysfunction[14,15], the contribution of reduced IGF-1 to bone loss is controversial in this population. A positive correlation between IGF-1 and BMD has been reported in males with viral cirrhosis[8,9] but refuted in subjects with early hepatic disease[16]. Its role in the pathogenesis of hepatic osteopenia in advanced liver failure has not been ascertained.

Elevated levels of serum cytokines, including tumor necrosis factor-α (TNFα), interleukin-6 (IL-6) and interleukin-1, are seen in liver disease from both alcohol[17,18] and viral hepatitis[9,19], with levels shown to correlate with disease severity[19,20]. In the general population, TNF is known to stimulate formation and activity of osteoclasts, with a resultant increase in bone resorption[21,22]. A recent study supports the role of soluble TNF receptor p55 (sTNFR-55), a marker of TNF function, in mediating bone loss in males with viral cirrhosis[9]. However, little is known about the contribution of TNFα to hepatic osteopenia in other groups, including females and non-viral disease. IL-6 is also involved in bone remodeling through stimulation of osteoclast formation and, in conjunction with IL-1, stimulation of bone resorption[23,24]. Its contribution to bone loss in end-stage liver disease has not been determined.

Finally, the Model for End-Stage Liver Disease (MELD) score has been prospectively developed and validated to predict the severity of chronic liver disease[25] and has been adopted by United Network for Organ Sharing (UNOS) as the basis for cadaveric liver allocation. It is being considered for adoption in many other transplant programs worldwide. Despite its increasing utility, to our knowledge, only one study has examined the relationship between the MELD score and bone density and it was limited to primary sclerosing cholangitis[26]. The ability of the MELD score to predict low bone density in advanced liver failure warrants further study.

The aim of the present study was to investigate the relationship between advanced chronic liver disease and low bone density in a pre-transplant population, examining specifically the roles of serum IGF-1, TNF, IL-6 and the predictive ability of disease severity reflected by the MELD score. Other factors known to affect bone mass, including serum 25-hydroxyvitamin D (25OHD), parathyroid hormone (PTH), testosterone and body mass index (BMI), were included in the analysis.

MATERIALS AND METHODS

Patients

The study was conducted according to the Declaration of Helsinki and approved by the University of Alberta Health Research Ethics Board. A total of 121 adult patients were evaluated for orthotopic liver transplantation at the University of Alberta, Edmonton, Canada, between 1998 and 2000. 117 subjects were included in the analysis; 4 subjects were excluded because of acute fulminant hepatic failure.

Methods

The etiology of liver failure was determined by biochemical, serological and liver biopsy data (where available), and patients were classified according to disease etiology, including viral (hepatitis B or C), alcohol, cholestasis [primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC)] and other (hemochromatosis, Wilson's disease, alpha-1 anti-trypsin deficiency).

The main explanatory variables of interest included serum IGF-1, measured *via* radioimmunoassay (Nichols Institute Diagnostics Inc., San Juan Capistrano, CA), serum IL-6 and TNFα, measured via chemiluminesence (Diagnostic Products Corp., Los Angeles, CA) and MELD score, calculated using an internet-based calculator (http://www.mayoclinic.org/gi-rst/mayomodel7.html). Serum bilirubin, INR and creatinine were used in the calculation.

The covariates included in the analysis were those that may influence BMD, including age, gender, body mass index (BMI)(based upon measured height and weight), smoking status (current *vs* former or never smoker) and self-reported fracture history. Data on family history of osteoporosis or maternal hip fracture was not available. Medication use prior to bone densitometry was recorded, including use of osteoporosis therapy (bisphosphonates, raloxifene, calcitonin and hormone replacement therapy), nutritional measures (calcium and/or vitamin D supplementation) and corticosteroids, due to its known deleterious effects on bone. Additional biochemical data included indices of calcium and vitamin D metabolism (serum calcium, albumin, 25OHD, PTH), thyroid stimulating hormone (TSH) and gonadal function (total testosterone in males only). 24-hour urine for N-telopeptides (NTx) was measured *via* enzyme-linked immunosorbent assay (Diagnostic Products Corp., Los Angeles, CA), serving as a marker of bone turnover. Biochemical and clinical data measured closest to the time of bone densitometry were used in the analysis.

The outcome variable was BMD of the lumbar spine (L1-L4) and femoral neck, measured via dual energy X-ray absorptiometry (DXA) (Hologic QDR1000, Hologic Inc, Waltham, MA) using standard protocols. Vertebral BMD were standardized using the Hologic reference database; hip BMD values were standardized using the National Health and Nutrition Examination Study Ⅲ (NHANES Ⅲ) database. BMD values were expressed as the T-score, the number of standard deviations of the patients' BMD from the mean peak value for a reference population of the same race and gender. According to World Health Organization criteria, osteopenia was defined as a T-score between -1.0 and -2.5 and osteoporosis as a T-score less than -2.5[27]. Abnormal BMD was defined as a T-score less than -1.0 at either site.

Statistical analysis

All statistical analyses were performed using SPSS for Windows, version 14.0 (SPSS Inc., Chicago, IL). All results were expressed as the mean ± SD unless indicated otherwise.

Table 1 Patient demographics and biochemical data

Variable	*n* = 117
Age in years	50.4 (10.5)
Male gender - no. (%)	74 (63%)
Etiology of liver disease - no. (%)	
Viral	46 (39%)
Alcohol	20 (17%)
Cholestasis	25 (21%)
Other	26 (22%)
BMI (kg/m^2)	24.8 (5.0)
Current smoking - no. (%)	43 (37%)
History of fracture - no. (%)	10 (9%)
MELD score	15.2 (6.0)
Calcium[a] (N 2.1 - 2.6 nmol/L)	2.41 (0.22)
PTH (N 1.1 - 6.8 ng/L)	2.86 (2.44)
25 OHD (N 40 - 200 μg/mL)	32.2 (19.5)
Total testosterone (N 10 - 29.5 nmol/L)	12.0 (9.9)
IGF-1 (ng/L) (N, age and sex dependent)	41.3 (54.0)
TNFα (N < 8.1 ng/L)	14.8 (8.7)
IL-6 (N < 9.7 ng/L)	17.1 (46.2)
UNTx (N < 81 nmol BCE/ mmol creatinine)	57.3 (36.4)

[a]Corrected calcium presented; Values are presented as mean (SD) unless indicated otherwise, N: normal range. BCE: bone collagen equivalents; PTH: Parathyroid hormone; BMI: Body mass index; 25OHD: 25-hydroxyvitamin D; IGF-1: Insulin-like growth factor-1; TNFα: Tumor necrosis factor-α; IL-6: Interleukin-6

Subjects were grouped by etiology of liver disease, with continuous variables compared *via* one-way ANOVA with post-hoc testing, and dichotomous variables *via* χ^2 testing. Where variables were non-normally distributed, data were transformed (IGF-1, IL-6). Subjects were then grouped by severity of bone disease (normal, osteopenia and osteoporosis), comparing groups by one-way ANOVA. Univariate regression (correlation) was performed with Pearson standard linear regression analysis (normal distribution) or the Spearman test (non-normal distribution) to assess the association and prediction of BMD by continuous variables. Multivariable linear regression was then completed to adjust for the influence of covariates on the relationship between IGF-1, serum cytokines and disease severity on bone density. Covariates of clinical and statistical significance were included, including age, gender, BMI, 25OHD, testosterone, IGF-1, TNFα, IL-6 and MELD score. A *P*-value less than 0.05 was considered significant.

RESULTS

Clinical and biochemical data are summarized in Table 1 (all subjects) and Table 2, where subjects are grouped by etiology of liver disease. The mean age was 50.4 years (range 18-73) and 63.2% of subjects were male. None were receiving treatment for osteoporosis (bisphosphonates, raloxifene, calcitonin or hormone replacement therapy) at the time of bone densitometry. No significant differences were seen between disease groups with respect to age or gender, while a significantly higher number of subjects with viral disease were current smokers ($P < 0.001$) (data not shown).

Table 2 Clinical and Biochemical Data by Etiology of Cirrhosis

Variable	Viral	Alcohol	Cholestasis	Other
	n = 46	*n* = 20	*n* = 25	*n* = 26
BMI (kg/m^2)	25.4 (5.1)	24.4 (5.3)	23.3 (3.2)	25.8 (5.9)
MELD score	15.1 (6.14)	16.2 (6.14)	14.2 (5.06)	15.6 (6.51)
Corrected calcium (nmol/L)	2.39 (0.28)	2.44 (0.21)	2.37 (0.11)	2.41 (0.22)
PTH (ng/L)	2.14 (1.2)[a]	3.73 (2.7)	2.83 (1.5)	3.48 (3.9)
25OHD (μg/L)	30.6 (16.1)	34.4 (20.1)	37.0 (20.2)	28.7 (17.0)
Testosterone (nmol/L)	12.7 (11.2)	7.0 (4.5)[b]	15.7 (7.4)	12.2 (11.5)
IGF-1 (μg/L)	34.5 (47.3)	28.3 (27.1)	45.9 (47.7)	59.5 (79.2)
TNFα (ng/L)	16.1 (10.9)	13.7 (6.7)	15.0 (8.4)	13.0 (5.0)
IL-6 (ng/L)	26.7 (72.4)	19.3 (20.7)	7.1 (5.3)	9.9 (12.2)
UNTx (nmol BCE/ mmol creatinine)	54.9 (38.0)	69.3 (25.2)	56.5 (41.6)	53.7 (36.2)

Values are presented as mean (SD). [a]PTH significantly lower in viral group than in alcohol and other ($P < 0.05$); [b]Testosterone significantly lower in alcohol group than in cholestasis ($P < 0.05$). BCE: bone collagen equivalents; PTH: Parathyroid hormone; BMI: Body mass index; 25OHD: 25-hydroxyvitamin D; IGF-1: Insulin-like growth factor-1; TNFα: Tumor necrosis factor-α; IL-6: Interleukin-6.

PTH was significantly lower in the viral group ($P = 0.015$), while total testosterone was significantly lower in males with alcohol-induced disease than in those with cholestasis ($P = 0.027$)(Table 2). No other significant differences were seen between disease groups.

Prevalence of abnormal bone mineral density

Low BMD was seen in 80 (68.4%) patients, including 55 (47.0%) with osteopenia and 25 (21.4%) with osteoporosis. Low bone density was common at both the lumbar spine (56.4%) and femoral neck (57.8%). Table 3 summarizes T-scores and prevalence of low BMD by disease etiology. No differences were seen with respect to T-scores and prevalence of low bone density between liver disease groups.

Relationship between BMD, bone turnover, and variables of interest

Serum IGF-1: Serum IGF-1 was below that expected for age and gender in 96/109 (88%) of subjects, including 58/109 (53%) of subjects in whom the level was below the detection limit of 15 μg/L and assigned a value of 15 μg/L (Figure 1). A significant positive correlation was seen between IGF-1 and bone density at both sites (Table 4). However, when grouped by severity of bone disease (normal *vs* osteopenia *vs* osteoporosis), IGF-1 did not significantly differ (Table 5).

Serum cytokines

TNFα values exceeded the reference range (< 8.1 pg/L) in 89/110 (80.9%) subjects in whom values were available (Figure 1). However, there was no correlation between TNFα and BMD or bone turnover (Table 4). When only those with viral cirrhosis were included (data not shown), the lack of correlation persisted at both BMD sites (Lumbar

Table 3 T-scores and prevalence of abnormal BMD between disease groups

	Viral n = 46	Alcohol n = 20	Cholestasis n = 25	Other n = 26	P value
T-score lumbar spine mean (SD)	-1.08 (1.35)	-1.51 (1.35)	-1.43 (1.23)	-1.30 (1.43)	0.552
T-score femoral neck mean (SD)	-1.11 (1.07)	-1.31 (1.02)	-1.30 (0.81)	-1.03 (1.05)	0.706
Low BMD at 1 or both sites number (%)	31 (67.4%)	13 (65.0%)	18 (72.0%)	18 (69.2%)	0.963
Low BMD lumbar spine number (%)	22 (47.8%)	11 (55.0%)	15 (60.0%)	18 (69.2%)	0.556
Low BMD femoral neck number (%)	26 (56.5%)	12 (60.0%)	15 (60.0%)	14 (53.8%)	0.993

T-score values represent the mean (SD); BMD: Bone marrow density.

Table 4 Correlation between BMD, bone turnover and variables of interest

Variable	T-score (lumbar spine)		T-score (femoral neck)		Urine NTx	
	r Value	P Value	r Value	P Value	r Value	P Value
BMI	0.324[a]	< 0.001	0.360[a]	< 0.001	-0.249[a]	0.013
MELD	-0.255[a]	0.016	-0.038	0.692	0.311[a]	0.002
25OHD	0.278[a]	0.016	0.227[a]	0.003	-0.426[a]	< 0.001
Testosterone (males only)	0.13	0.273	0.003	0.978	-0.377[a]	0.003
IGF-1	0.215[a]	0.024	0.209[a]	0.029	-0.07	0.5
TNFα	-0.139	0.15	-0.084	0.39	0.07	0.51
IL-6	-0.137	0.19	-0.073	0.49	0.276[a]	0.015
Urine NTx	-0.346[a]	< 0.001	-0.102	0.319		

[a]Significant at P < 0.05. BMI: Body mass index; 25OHD: 25-hydroxyvitamin D; IGF-1: Insulin-like growth factor-1; TNFα: Tumor necrosis factor-α; IL-6: Interleukin-6.

Table 5 Clinical and biochemical parameters ranked by severity of bone loss

	Normal	Osteopenia	Osteoporosis	P value
BMI	26.8 (5.1)	24.4 (5.1)[a]	22.9 (3.6)[a]	0.006
MELD	15.5 (5.9)	14.2 (5.7)	16.9 (6.5)	0.18
25OHD	33.9 (15.7)	33.4 (20.2)	27.9 (15.3)	0.25
Testosterone	11.1 (9.8)	13.7 (10.8)	10.1 (8.3)	0.41
IGF-1	38.3 (35.5)	44.4 (67.5)	39.2 (46.1)	0.86
TNFα	14.3 (10.7)	15.2 (7.6)	14.7 (8.0)	0.89
IL-6	11.8 (12.9)	12.4 (14.0)	15.6 (17.4)	0.64
UNTx	47.2 (27.3)	59.4 (38.7)	70.2 (41.6)[b]	0.08

Values are presented as mean (SD); [a]Significantly lower than in subjects with normal BMD; [b]Significantly higher than UNTx in subjects with normal BMD (P=0.027) (Using post-hoc test of ANOVA). BMI: Body mass index; 25OHD: 25-hydroxyvitamin D; IGF-1: Insulin-like growth factor-1; TNFα: Tumor necrosis factor-α; IL-6: Interleukin-6.

spine: r = 0.249, P = 0.102; Femoral neck: r = 0.098, P = 0.526). Additionally, the mean value of TNFα did not differ between subjects with normal *vs* low BMD (Table 5). IL-6 values were abnormally elevated above the lab reference range (< 9.7 ng/L) in 27/92 (29.3%) of subjects (Figure 1). Again, there was no significant association between IL-6 and BMD, although IL-6 did correlate with bone turnover (Table 4). The mean value of IL-6 did not differ between subjects with normal and low BMD (Table 5).

MELD Score

A significant inverse correlation was seen between the MELD score and spinal bone density. There was no association at the hip (Table 4). However, when grouped by severity of bone disease, the MELD score did not significantly differ between groups (Table 5) but a significant positive correlation was noted between MELD score and bone turnover (Table 4).

Other covariates

In bivariate analysis, a significant positive correlation was seen between lumbar spine bone density, BMI and vitamin D status. At the femoral neck, BMI and vitamin D status again correlated significantly with bone density (Table 4). Low total testosterone was seen in 43.8% of our male subjects, the prevalence of which did not differ by disease group. There was no association between testosterone and BMD, although levels did inversely correlate with bone turnover (Table 4). Bone turnover was inversely correlated with spinal bone density, while there was no association at the hip (Table 4). As expected, bone turnover was significantly higher in those with osteoporosis compared to those with normal BMD (Table 4). BMI was significantly lower in those with low BMD compared to those with normal BMD (Table 5).

Multivariable linear regression

Variables approaching statistical significance (P < 0.2) in univariate regression or that are clinically relevant in affecting bone density were included in a multivariate model attempting to predict changes in BMD. Model inclusion variables included age, BMI, MELD score, 25OHD, testosterone, IGF-1, TNF, IL-6 and UNTx. At the lumbar spine, the model of best fit included BMI, UNTx and IGF-1 as independent predictors of spinal T-score (r = 0.523, adjusted r^2 = 0.249, P < 0.01). TNF, IL-6 and MELD score were not independent predictors. At the hip, BMI, age and 25OHD remained as independent predictors of bone density (r = 0.502, adjusted r^2 = 0.232, P < 0.001). Again, TNF, IL-6 and MELD score were not predictive and at this site, there was no effect from IGF-1.

DISCUSSION

Patients with end stage liver disease have complex hormonal and cytokine profiles. These changes can affect bone mineral density. Low BMD was seen in nearly 70% of subjects in a heterogeneous population referred for evalua-

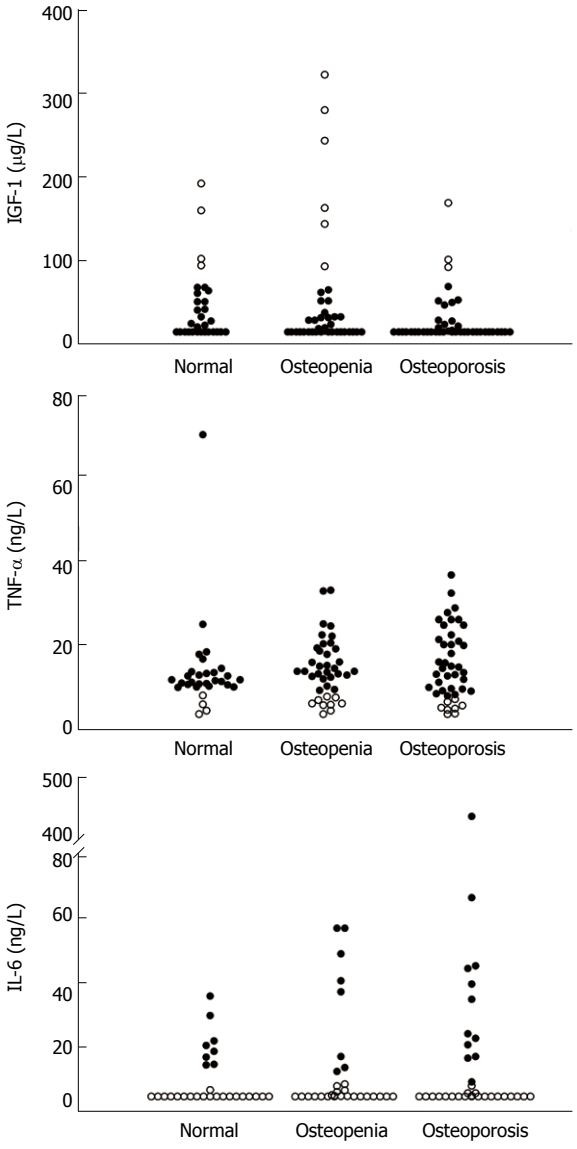

Figure 1 Individual IGF-1, TNFα and IL-6 values grouped according to severity of bone loss. ○ depicts individuals with values within the normal range and ● depicts individuals with values below (IGF-1) or above (TNFα and IL-6) the normal range. IGF-1: Insulin-like growth factor-1; TNFα: Tumor necrosis factor-α; IL-6: Interleukin-6

tion of liver transplantation. Prevalence did not differ by disease etiology and was common in sites of both trabecular and cortical bone. Serum IGF-1 was subnormal in nearly 90% of subjects and levels correlated directly with bone density. When adjusted for potential confounders, IGF-1 remained predictive of low spinal BMD. Despite elevated levels of the osteoclastogenic cytokines TNFα and IL-6, levels failed to correlate with bone density and were not independently predictive of bone loss. The MELD score was inversely associated with spinal bone density but lost predictive value when adjusted for potential confounders.

The prevalence of abnormal BMD in our population with end-stage liver disease is similar to that which has been previously reported[8,9,28]. Our patients had extremely low levels of serum IGF-1 which did not differ by disease etiology. Given the advanced stage of disease, this is not surprising and is in accordance with previous findings[14,15]. IGF-1 is known to play an important role in bone formation and in mineralization of bone surface through stimulation of bone cell proliferation and collagen synthesis[29,30]. Declining levels in hepatic disease would be expected to contribute to reduced bone density. Gallejo-Rojo *et al*[8,9] reported a significant association between serum IGF-1 and spinal bone density in a smaller group of male subjects with viral cirrhosis. Conversely, Ormarsdottir *et al*[16] showed no association in male and female subjects with non-viral disease. However, 78% of these patients were Child-Pugh A and subjects with viral disease were excluded. Our study expands upon existing literature as the first to report a significant association and independently predictive, albeit small, role for serum IGF-1 in hepatic osteopenia among a diverse population with advanced liver disease. Low serum IGF-1 may play an increasingly prominent role in the pathogenesis of low bone mass with advancing liver failure. A longitudinal study design which incorporates the role of a declining IGF-1 and that of its more stable IGF binding proteins on its relationship to bone loss may provide further insight.

Hypogonadism is a risk factor for reduced BMD[31] and is a known complication of advanced cirrhosis, irrespective of etiology[32,33]. While common in our male subjects, there was no significant association between total testosterone and BMD, with no difference in levels of testosterone between subjects with and without reduced BMD. While supporting previous results[9], interpretation is limited by the lack of measurement of free testosterone. Sex hormone binding globulin is known to increase in advanced cirrhosis[33], elevating total testosterone, whereas it is unbound testosterone that is available for tissue binding, including at the bone. We likely under report true hypogonadism and may under represent the importance of bioavailable testosterone levels on bone mass in this population.

To our knowledge, our study is the first to expand upon the contribution of TNFα to bone loss beyond males with viral cirrhosis. In this limited population, an inverse correlation was recently reported between bone density and soluble TNF receptor p55 (sTNFRp55), a modulator of the biological function of TNF[9]. In our expanded population, we failed to detect an association between TNFα and BMD or bone turnover and levels of TNF did not differ between those with and without reduced bone density. TNFα is rapidly cleared from circulation and, while elevated in liver disease, its levels are known to fluctuate widely[34]. The lack of an apparent role for TNFα elevation in low BMD in our population may relate to limitations in its direct quantification. sTNFRp55 is more stable, correlates well with TNFα[35] and may serve as a more accurate marker in this population. The measurement of this soluble receptor and its ability to predict reduced bone density in this population warrants further study.

IL-6 has been shown to mediate osteoclastogenesis through stimulation of osteoclast formation and, in conjunction with IL-1, stimulation of bone resorption[23,24]. In

post-menopausal women, serum levels of IL-6 have been found to predict bone loss[36]. The biological effects of IL-6 are dependent on soluble IL-6 receptors (sIL-6r) and both IL-6 and sIL-6r are increased in chronic liver disease, correlating with disease severity[37]. However, the contribution of IL-6 to hepatic osteopenia has not been previously reported. To our knowledge, our study is the first to report a lack of significant association between serum IL-6 and BMD. Numerous studies have noted an association between IL-6 polymorphisms and lower BMD in postmenopausal women[38], healthy males[39] and in inflammatory bowel disease[40]. The lack of significant association in our study may reflect the importance of gene polymorphisms and the role of more stable IL-6 receptors in affecting bone loss.

To date, only one study has previously explored the association and predictive ability of the MELD score on metabolic bone disease. Restricted to primary sclerosing cholangitis and limited by a small sample size and lack of biochemical measures of vitamin D and gonadal function, this study revealed no association between MELD score and spinal bone density[26]. We expand upon the literature to include larger patient numbers and diverse disease, and describe a significant inverse association between MELD score and spinal bone density. However, in multivariate analysis, this lacks predictive ability. This relationship may be better examined with a longitudinal study design whereby progression of hepatic dysfunction is followed in parallel with changes in bone density. However, it is important to note that as part of a pre-transplant work-up, the MELD score does not appear to be a useful marker for the presence or absence of metabolic bone disease.

Limitations to our study include the cross-sectional study design, where examination of causation is not possible. The absence of accurate data on the gonadal status of women limits examination of its contribution in female subjects. Finally, the lack of measurement of more stable serum cytokine receptors may lead to an under representation of their effects on mediating bone loss.

In conclusion, this study confirms the high prevalence of low bone density in advanced liver disease, regardless of underlying disease etiology. The pathogenesis of low BMD is multifactorial. Low serum IGF-1 is common in all disease groups, is associated with low BMD in both trabecular and cortical bone, and is a weak but significant predictor of low spinal bone density. Serum cytokine elevation is common, reflecting advanced hepatic disease, but levels do not predict the presence or absence of bone disease. While the MELD score is a useful predictor of survival in end-stage liver disease, it does not appear to serve a predictive function for the presence of low bone density.

COMMENTS

Background

Low bone mineral density (BMD) is a known complication of chronic liver disease of diverse etiologies. Little is known about the contributions of serum insulin growth factor 1 (IGF-1) and pro-inflammatory cytokines to low bone density or the ability of the Model for End Stage Liver Disease (MELD) score to predict bone loss in end-stage liver disease.

Research frontiers

Reduced serum IGF-1 and elevation of interleukin 6 (IL-6) and tumor necrosis factor α (TNF α) are markers of osteopenia in some hepatic disorders. The MELD score can predict the severity of chronic liver disease and may be a good predictor of hepatic osteopenia.

Innovations and breakthroughs

Low serum IGF-1 which is common in end-stage liver disease of various etiologies can predict low spinal bone density. Neither serum cytokine elevation nor MELD score can predict low bone density.

Applications

As part of a pre-transplant work-up, the MELD score does not appear to be a useful marker for the presence or absence of low BMD. Low serum IGF-1 may play a prominent role in the pathogenesis of low BMD in end-stage liver disease. A longitudinal study design may provide further insight.

Terminology

MELD score has been validated to predict the severity of chronic liver disease and adopted by United Network for Organ Sharing as the basis for cadaveric liver allocation.

Peer review

The study examines an issue important to the management of pre-transplant end stage liver disease (ESLD) patients. Post-liver transplant fracture is a very concerning problem in this patient population and screening patients for hepatic osteopenia is crucial. The authors have selected pathologically relevant potential predictors: the MELD score. The study revealed, interestingly and contrary to presumptions about the MELD score, that the score is not a good predictor of severity of hepatic osteopenia.

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