

AGA Technical Review on Osteoporosis in Hepatic Disorders

This literature review and the recommendations therein were prepared for the American Gastroenterological Association Clinical Practice Committee. The paper was approved by the Committee on March 1, 2003, and by the AGA Governing Board on July 25, 2003.

Bone disease is a major complication of chronic liver disease (CLD) and liver transplantation and can result in spontaneous or low-trauma fracturing that significantly impacts on morbidity, quality of life, and even survival. The etiology of these disorders is complex and multifactorial. The general biology and pathogenesis of osteoporosis, including its relationship with inflammatory states, diagnostic tools, and clinical utility of bone densitometry, has been reviewed elsewhere in the AGA Technical Review on Osteoporosis in Gastrointestinal Diseases.¹ In this review, issues specific to osteoporosis and hepatic disease will be discussed.

Methods routinely used in skeletal assessment and relevant terminology will be briefly summarized. The development of bone densitometry has made it possible to measure bone mass and assess its contribution to fracture risk. It is generally accepted that bone mass is the single best predictor of in vitro skeletal strength²⁻⁴ and fracture risk.⁵ The most widely available bone density technology is dual-energy x-ray absorptiometry (DXA), which is currently the gold standard for measurement of bone mass. Conventional DXA (also known as central DXA) is able to measure all skeletal structures, including those in the thicker body regions such as the lumbar spine and hip. The related isotopic method, dual-photon absorptiometry (DPA), is now rarely used. Other methods are available for measuring bone in the extremities using radionuclide sources, x-ray, or ultrasonography. Quantitative computed tomography can be used to measure bone density but is infrequently used outside of research settings. Conventional diagnostic radiographs are still an important component in the assessment of osteoporosis because the presence of fragility fractures (such as vertebral compression fractures) indicates osteoporosis and high fracture risk independent of bone mineral density (BMD).

Bone density measurements follow a bell-shaped (Gaussian) distribution. Therefore, they are described as the number of standard deviations (SD) that the value deviates from the mean for normal controls. Age-related changes in bone density must be taken into account. The Z-score refers to the number of SD above or below the mean for an age-matched population. The T-score refers

to the number of SD above or below the mean for a young adult population (corresponding to peak bone mass). A World Health Organization report formulated diagnostic ranges for osteoporosis based on T-score⁶: normal is a T-score greater than -1.0 (i.e., the patient's BMD is no more than 1 deviation below the young adult mean), osteopenia (low bone mass) is a T-score between -1.0 and -2.5 , and osteoporosis is a T-score less than -2.5 . The data reviewed for these recommendations were derived almost exclusively from postmenopausal white women. Caution must be exercised in extrapolating the World Health Organization diagnostic criteria to other groups because BMD and fracture risk are strongly affected by age, sex, and ethnicity. BMD and calcaneal ultrasound measurements predict clinical fractures in older men and women.⁷⁻⁹ Risk of fracture shows a continuous gradient relationship with bone density; there is no true "fracture threshold." Results are usually stated in terms of relative risk of fracture per SD change in bone density. Although any measured site provides fracture risk information about other sites, the best site for characterizing hip fracture risk is a measure of the proximal femur (with a relative risk of 2.6 per SD change in bone density).⁷ It must be remembered that many factors important in the pathophysiology of fracture (such as predisposition to falling) are not measurable with bone densitometry.

Bone cell activity can be evaluated through the measurement of biochemical markers.¹⁰ Osteoblasts produce type I collagen (the primary collagen of bone tissue), noncollagenous proteins (such as osteocalcin or bone Gla protein [BGP]), and enzymes (such as serum alkaline phosphatase). Biochemical markers reflect bone turnover but are not useful in predicting BMD. Higher levels of

Abbreviations used in this paper: BGP, bone Gla protein; BMD, bone mineral density; CLD, chronic liver disease; DPA, dual-photon absorptiometry; DXA, dual-energy x-ray absorptiometry; 25-OHD, 25-hydroxyvitamin D; OLT, orthotopic liver transplantation; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; PTH, parathyroid hormone.

Table 1. Quality of Evidence on Which Recommendation Is Based

Grade	Definition
A	Homogeneous evidence from multiple well-designed randomized (therapeutic) or cohort (descriptive) controlled trials each involving a number of participants to be of sufficient statistical power
B	Evidence from at least one large well-designed clinical trial with or without randomization, cohort or case-control analytic studies, or well-designed meta-analysis
C	Evidence based on clinical experience, descriptive studies, or reports of expert committees
D	Not rated

Adapted from Heathcote.¹⁷

bone markers are associated with more rapid bone loss, although the correlation is relatively poor and limits their use in individual patients.¹¹ Higher rates of bone turnover have been shown to predict greater fracture risk independent of BMD.^{10,12,13} The findings that markers can show a dramatic and early reduction within weeks of starting antiresorptive therapy suggest they may be helpful in confirming therapeutic effect, because a nadir is usually reached between 2 and 3 months after initiation of treatment.^{14,15} This change is much more rapid than can be seen with serial BMD measurements. The clinical role of biochemical markers is still unclear.

Transiliac bone biopsy has been a useful research tool for characterizing bone metabolism in normal and disease states. However, the invasiveness, cost, and complexity of this technique markedly limit its widespread clinical application. The most important clinical role in hepatic disorders is for the diagnosis of osteomalacia. This diagnosis is based on increased mineralization lag time and increased osteoid seam thickness (both criteria have to be present).

Materials and Methods

A systematic literature review was conducted, and studies were critically appraised using published methods.¹⁶ Evidence was graded using guidelines adapted from the Practice Guideline Committee of the American Association for the Study of Liver Diseases¹⁷ as summarized in Table 1. Results were the basis for evidence-based conclusions and recommendations for the hepatic disorders covered in this review.

We searched Medline and ISI Web of Science using general terms related to osteoporosis and metabolic bone disease (osteopor* OR osteopen* OR bone density OR fractures OR "bone loss" OR "bone mineral" OR "bone metabolism" OR DXA [TITLE] OR DEXA [TITLE] OR "bone densitometry") and combined these with specific terms for the relevant hepatic disorders (liver/transplantation[MAJR] OR "liver diseases"[MAJR] OR "liver transplantation"[MAJR]). Recently pub-

lished reviews, references from retrieved articles, and expert committee reports were manually searched for additional studies.

Point estimates of prevalence of osteoporosis and mean bone density were extracted and combined (weighted for patient numbers) to give pooled estimates. Although not a formal meta-analysis, results can be taken to reflect general trends in the published data and should be useful for assessing the overall magnitude of the impact of various hepatic disorders on bone metabolism. Pooling of data was site specific but combines related technologies, different vendors, reference ranges, and sexes. Our analysis did not show any major difference in results restricted to a technology or vendor. Against the many other assumptions inherent to bone densitometry, this simplification is not unreasonable.

This review excludes skeletal disorders unrelated to osteoporosis such as avascular necrosis, hepatitis C-associated osteosclerosis, and hypertrophic osteoarthropathy. Hepatobiliary rickets and liver disorders of infancy and early childhood (such as extrahepatic biliary atresia) are quite different from skeletal disorders that present in adults and older children and have also been excluded.

CLD

Metabolic bone disease occurring in individuals with CLD, known as hepatic osteodystrophy, is a common complication among individuals with long-standing hepatic disease, particular those with cholestasis. Special care is required to prevent the development of clinical bone disease in individuals with advanced hepatic disease.

Pathogenesis

Complex metabolic changes in liver disease create multiple mechanisms for alterations in bone metabolism, and in any given patient it is likely that multiple factors are operating simultaneously. Most studies indicate that markers of bone formation are reduced in both cholestatic and noncholestatic liver disease.¹⁸ The consistent observation of decreased bone formation with CLD raises the possibility that retained substances may impair osteoblast function, and it has been shown that unconjugated bilirubin impairs osteoblast proliferative capacity in a dose-dependent fashion.¹⁹ Serum bilirubin levels are typically normal during a prolonged asymptomatic phase in most forms of cholestatic liver disease. Diamond et al.²⁰ compared dynamic bone histomorphometry in 80 patients with mixed CLDs and 40 healthy controls. The prevalence of osteoporosis (defined as trabecular bone volume less than the lower limit of normal) was 21% and increased with increasing age and reduced body mass index. Cirrhotic patients had reduced osteoid thickness, osteoblast surface, and bone formation rate as well as

higher mineralization lag time, all of which are consistent with an osteoblast defect. Cirrhotic patients also had reduced serum BGP or osteocalcin levels, which correlated with bone formation rate ($r = 0.59$) and osteoblast surface ($r = 0.43$).

Insulin-like growth factor 1 is known to play a key role in the process of bone remodeling and maintenance of bone mass and is reduced in advanced cirrhosis.²¹ Patients with cirrhosis and osteoporosis have significantly lower levels of insulin-like growth factor 1 than nonosteoporotic cirrhotic patients.²² Osteoprotegerin is produced by the liver and its role in liver disease is still speculative, but reductions would be expected to result in increased osteoclast-mediated bone resorption.

Bone loss in women with cholestatic and noncholestatic liver diseases is more rapid than in healthy controls, and postmenopausal status seems to be a contributing factor.^{23,24} Reduced trabecular bone volume in primary biliary cirrhosis (PBC) appears to be largely confined to postmenopausal women and more specifically to those with longer duration of disease and decreased calcium absorption.²⁵ Because testosterone is metabolized to estrogen, men with hypogonadism have a relative decline in serum estrogen levels; recent data show that estrogen is very important for maintenance of skeletal health in men. Nutritional deficiencies are very frequent in patients with advanced cirrhosis due to a wide array of metabolic disturbances associated with this disease, as recently reviewed by Cabré and Gassull.²⁶ Renal tubular acidosis is more common in patients with liver disease and may also play a role in the development of metabolic bone disease.²⁷ A role for malabsorption of vitamin K in cholestatic disorders also remains speculative.

Medications used in the treatment of liver disease can also have an adverse effect on bone and calcium metabolism. Corticosteroids are frequently used in patients with autoimmune hepatitis and other inflammatory disorders. Even budesonide, a corticosteroid with minimal systemic availability, may lead to accelerated bone loss in cirrhotic patients and postmenopausal women,^{28,29} although not all studies have shown a deleterious effect of budesonide on BMD.³⁰ Some studies suggest that cyclosporin A increases biochemical parameters of bone remodeling and paradoxically prevents bone loss in patients with PBC.³¹ Interferon alfa reduces markers of bone turnover and may inhibit the formation of osteoblasts,³² but the effect on BMD has not been directly studied. One cross-sectional study suggested that ribavirin may induce bone loss when administered for 12 months to patients with chronic hepatitis C (Z-score -1.5 lower than in non-ribavirin-treated patients),³³

but the mechanism of this effect is unclear and has subsequently been contradicted by a longitudinal study.³⁴ Therapy with the bile acid-binding agent cholestyramine may further decrease absorption of vitamin D and 25-hydroxyvitamin D (25-OHD), whereas extended exposure to loop diuretics can further promote renal calcium loss.³⁵

Many series have evaluated bone metabolism in patients with PBC and most indicate a high turnover state even when trabecular bone volume and distal forearm BMD are still normal,^{36,37} although some reports indicate low bone turnover.²⁵ Reduced trabecular wall thickness and increased bone turnover is proportional to severity of hepatic dysfunction and cholestasis.³⁸ Increased serum parathyroid hormone (PTH) level has been implicated, possibly in response to reductions in 25-OHD.³⁹ The increased fractional resorption surface is independent of vitamin D status but paradoxically appears to resolve with parenteral vitamin D₂.³⁷ An osteoblast defect may also exist in PBC,³⁸ although other studies show increased osteoblast activity.⁴⁰ One retrospective study did not find any osteomalacia or osteoporotic condition in women with PBC aged 45–54 years, although indices of bone turnover were increased and similar findings were shown in women with PBC aged 65–74 years and those with age-related osteoporosis.⁴¹ This suggests that some of the osteoporosis attributed to PBC may be the result of the concomitant aging process. Finally, it has been suggested that precipitation of calcium salts by unabsorbed fats within the intestinal lumen may contribute to the calcium malabsorption in chronic cholestasis. Other chronic cholestatic disorders such as primary sclerosing cholangitis (PSC) have not been as thoroughly studied, but histologic examination in advanced cases again shows increased bone resorption, reduced formation, and no osteomalacia.⁴²

Osteoporotic patients without fractures typically have a normal serum alkaline phosphatase level, and an increased value in a patient with osteoporosis may be a clue to the presence of PBC. The prevalence of occult celiac disease is substantially increased in patients with PBC.^{43–46} Patients with autoimmune cholangitis, PSC, and autoimmune hepatitis may also have an increased prevalence of celiac disease.^{47,48} Routine serologic screening for celiac disease has been suggested in these patients, although a high prevalence of false-positive anti-gliadin and anti-tissue transglutaminase antibodies have been reported in patients with CLD.^{49–51} Anti-endomyssial antibodies are probably the preferred screening test. Although no studies have specifically assessed the impact of coexistent liver disease and celiac disease on osteopo-

rosis or fractures, the effect is likely to be greater than if these disorders occur in isolation.

Twin studies suggest that up to 85% of the variation in peak bone mass is determined by genetic factors.⁵² Several candidate gene polymorphisms have been associated with alteration in BMD. There is some suggestion that PBC may be associated with a higher frequency of the BB genotype for the vitamin D receptor locus *BsmI* and rare haplotypes,^{53,54} although others have not confirmed any difference in the prevalence of polymorphisms for the vitamin D receptor or α_1 chain of type 1 collagen (COLIA1).⁵⁵ In healthy populations, the BB allele pair has been associated with reduced BMD. A trend for lower BMD in patients with PBC carrying a B allele has also been reported,⁵³ although other studies found no difference⁵⁵ or even the opposite effect.⁵⁴ The s allele for the COLIA1 Fnu4HI restriction site was associated with reduced spine (but not hip) BMD but did not correlate with subsequent BMD loss or prevalence of vertebral fracture.⁵⁵

Viral cirrhosis is associated with significant reductions in serum BGP, PTH, testosterone (in men), 25-OHD, and 1,25(OH)₂-vitamin D levels, increased bone specific alkaline phosphatase and carboxy-terminal telopeptide of type I collagen, and a picture of uncoupled high bone turnover.^{56–58} BMD has shown significant positive correlations with 25-OHD level, insulin-like growth factor 1 level, and preserved liver function but inverse correlations with BGP and collagen breakdown products.^{22,56,58} Lower levels of 25-OHD, testosterone (in men), and insulin-like growth factor 1 in more advanced Child-Pugh stages may contribute to the correlation between BMD and disease severity.^{22,56} Together, these data indicate a possible role for vitamin D deficiency and hypogonadism (in men).

Alcoholic patients with cirrhosis show a pattern of low-turnover osteoporosis; however, in “abstainers” or when the liver biopsy specimen shows only steatosis, histologic and biochemical markers of osteoblast function are normal.^{59–62} Among 56 male alcoholic patients, 18 (32%) had both low serum 25-OHD and decreased BMD levels.⁶³ A baseline transiliac biopsy specimen with double-tetracycline labeling showed reduced bone formation and trabecular mean wall thickness but did not show any cases of overt osteomalacia. Dramatic short-term increases in BMD of the distal radius with vitamin D supplementation, up to +27.4%, implicate vitamin D in the pathogenesis of this disorder. Reduced serum testosterone levels, present in both actively drinking alcoholic patients and “abstainers” with CLD, probably contributes to the skeletal deficit.⁶⁴ Actively drinking alcoholic

patients show reduced BGP levels, but this recovers after 10 days of abstinence, whereas collagen breakdown products are elevated in both actively drinking and abstaining alcoholic patients.⁶⁵ These data indicate that excessive alcohol intake can have a direct action on bone, leading to imbalance in formation and resorption and favoring the development of osteopenia.

Although the overwhelming majority of people with genetic hemochromatosis are asymptomatic, late-stage (cirrhotic) disease is frequently associated with hypogonadism,⁶⁶ probably explaining why all subjects in one cohort with a lumbar T-score less than -2.5 were men (6 of 9 with symptomatic hypogonadism).⁶⁷ In univariate analysis, the risk of osteoporosis is significantly increased by liver cirrhosis but highly influenced by the degree of iron overload.⁶⁷ Bone biopsy specimens in patients with the lowest BMD did not show evidence of osteomalacia, and mean levels of bone formation and resorption markers were normal.⁶⁶ Iron may exert an inhibitory effect on osteoblast function, although conclusive evidence is still lacking.^{20,66}

Osteomalacia. The essential role of the liver in bile salt secretion, absorption of dietary vitamin D₃, and subsequent 25-hydroxylation to 25-OHD led to the incorrect belief that osteomalacia would be the primary skeletal disorder. Early estimates of the prevalence of osteomalacia in chronic cholestatic liver disease ranged from 0% to 64%.^{61,68} This enormous variation has been attributed to patient selection bias, variability in the severity of liver disease, and differences in histologic criteria for the diagnosis, with the highest rates seen when the diagnosis did not use the strict criteria. At one time, it was claimed that osteomalacia occurred in cirrhotic patients despite adequate vitamin D₂ replacement, possibly from 1- α hydroxylase failure or differential effect of vitamin D₂ and D₃, but subsequent studies have conclusively disproved this.⁶⁹ Malabsorption of vitamin D in cholestatic liver disease has been clearly shown and may be aggravated by the use of cholestyramine.⁷⁰ This requires an increased dose of vitamin D to compensate for reduced intentional absorption of 25-OHD undergoing enterohepatic circulation, but there is normal metabolism and target tissue responsiveness with adequate dosing.⁷¹ PBC-associated osteomalacia can be healed with oral or parenteral vitamin D therapy despite ongoing use of cholestyramine, and serum 25-OHD is a good indicator of effective treatment.^{70,72}

It is now widely accepted that, although the potential for osteomalacia exists, osteoporosis is the primary metabolic bone disease found in association with CLD and vitamin D plays a minor role.^{38,73,74} Metabolism of vi-

Table 2. Uncontrolled Cross-sectional Studies of Bone Density in Chronic Liver Disease

Reference	BMD instrument	Subjects	Mean bone density	Prevalence of reduced bone density and definition used
Angulo et al. ⁹⁴	DPA	81 PSC	Lumbar: 95% AM	Lumbar T < -2.5: 8.6%
Crippin et al. ⁹⁵	DPA	203 female PBC	Lumbar: 93% AM	
Guañabens et al. ³¹	DPA	38 female PBC		Lumbar < 0.979 g/cm ² ("fracture threshold"): 45%
Hay et al. ⁴²	DPA	18 new-diagnosis PSC 30 pre-OLT PSC 185 healthy controls	Lumbar: 96.0% AM at diagnosis 77.6% AM pre-OLT	Lumbar BMD < 0.900 g/cm ² ("fracture threshold"): 0% at diagnosis 50% pre-OLT
Lindor et al. ⁹¹	DPA	88 PBC		Lumbar BMD < 0.85 g/cm ² ("fracture threshold"): 35%
Olsson et al. ⁹³	SPA	39 AIH 32 PBC	Distal forearm: AIH 93.8% AM PBC 97.8% AM	
Pereira et al. ⁴⁰	DXA	36 female PBC	Total body BMC/lean body mass: 76% AM	Lumbar T < -2.5: 17% Femoral neck T < -2.5: 14%
Shiomi et al. ⁸⁵	DXA SPA	41 PBC 56 VC	Lumbar: Normal < 60 yr 77% AM in PBC > 60 yr 89% AM in VC > 60 yr Radius: Normal < 60 yr reduced for > 60 yr	
Sinigaglia et al. ⁶⁷	DXA	31 HHC		Lumbar T < -2.5: Non-cirrhotic 7% Cirrhotic 47%
Springer et al. ⁵⁴	DXA	72 female PBC	Lumbar T: -1.4 Lumbar Z: -0.2 Femoral neck T: -1.9 Femoral neck Z: -0.5	Lumbar T < -2.5: 24% Lumbar Z < -2: 11% Femoral neck T < -2.5: 32% Femoral neck Z < -2: 10%
Stellon et al. ⁶¹	SPA	36 PBC or PSC	Distal radius Z: -0.3 male -0.7 female Mid-radius Z: +0.6 male -0.3 female	Radius Z < -2: 14%
Wolfhagen et al. ¹⁰¹	DXA	12 PBC	Lumbar Z: -0.3 Femoral neck Z: -0.3	

AM, age-matched healthy controls; AIH, autoimmune hepatitis; VC, viral cirrhosis; HHC, hereditary hemochromatosis; SPA, single photon absorptiometry.

tamin D is normal in hepatic osteodystrophy,⁷⁵⁻⁷⁸ but malabsorption of both calcium and vitamin D may occur and contribute to skeletal effects. Adults derive most of their vitamin D from photoconversion in the skin, and patients with cholestasis appear to have normal photoconversion.^{75,79} Serum vitamin D binding protein may be reduced in liver disease, but it is unlikely that this will significantly affect serum 25-OHD concentration because saturation of serum vitamin D binding protein is normally very low (2%-3%).³⁵

In the largest and most complete assessment to date of vitamin D metabolism in CLD, Diamond et al.⁸⁰ studied 107 patients with CLD of various causes (including 19 with primary cholestatic disorders) and compared static and dynamic bone histomorphometry with 40 age-matched controls. Levels of vitamin D metabolites were normal in noncirrhotic patients and were independent of

the underlying diagnosis. Cirrhotic patients showed a significant decrease in 25-OHD and 1,25(OH)₂-vitamin D, but this was largely explained by variations in the carrier proteins, albumin, and serum vitamin D binding protein. Although 21% of the patients also had a reduction in serum-free 1,25(OH)₂-vitamin D, none of these showed histologic features of osteomalacia. Osteoblast dysfunction, as measured by BGP response to oral supplementation with calcitriol (1,25[OH]₂-vitamin D₃), produced a subnormal result in 44 patients with histologic abnormalities compared with 20 healthy controls. Together, these findings indicate that osteoblast dysfunction in CLD cannot be explained by abnormalities in vitamin D metabolites or their effects. Bone histomorphometry showed similar changes in cirrhotic and non-cirrhotic patients, although there was a higher prevalence of low trabecular bone area and reduced bone formation

Table 3. Controlled Cross-sectional Studies of Bone Density in Chronic Liver Disease

Reference	BMD instrument	Subjects	Mean bone density	Prevalence of reduced bone density and definition used
Bagur et al. ³⁹	DXA	23 female PBC 100 healthy controls	Lumbar Z: -1.3 Total body Z: -1.3	Lumbar T < -2.5: 56%
Bonkovsky et al. ⁸¹	DPA	133 mixed CLD 300 healthy women	Lumbar: 95% AM Femoral neck: 94% AM	Lumbar Z < -2: 26% Femoral neck Z < -2: 13%
Chen et al. ⁵⁸	DPA	30 male VC 10 healthy controls	Lumbar: VC 90.6% AM	Lumbar Z < -2: VC 20% Controls 10%
Conte et al. ⁸⁸	SPA	6 cirrhotic HHC 8 cirrhotic ALD 30 healthy controls	Forearm metaphysis: HHC 78% AM ALD 101% AM	
Corazza et al. ⁵⁶	DXA	31 VC 37 healthy controls	Lumbar T: -1.6 VC -0.3 controls Femoral neck T: -1.5 VC -0.9 controls	Lumbar T < -2.5: 21% VC 8% controls Femoral neck T < -2.5: 10% VC 3% controls
Diamond et al. ⁸⁷	SPA QCT	115 mixed CLD 113 healthy controls		Lumbar Z < -2: 16% CLD 7% controls Forearm Z < -2: 23% CLD 5% controls
Diamond et al. ⁸⁰	SPA QCT	54 mixed cirrhotic CLD 53 mixed noncirrhotic CLD 113 healthy controls	Lumbar QCT: Noncirrhotic 94.9% AM Cirrhotic 81.6% AM Forearm: Noncirrhotic 102% AM Cirrhotic 91.0% AM	
Eastell et al. ⁹⁰	DPA	210 female PBC 139 healthy women	Lumbar Z: -0.66	
Floreani et al. ¹⁸	DPA	38 PBC 11 noncholestatic CLD 20 healthy controls	Lumbar: PBC 88.2% AM Noncholestatic 86.0% AM	
Gallego-Rojo et al. ²²	DXA	32 male VC 24 healthy controls	Lumbar Z: -1.27 Femoral neck Z: -0.48	Any site T < -2.5: 53%
Halmos et al. ⁵³	DXA	30 new-diagnosis PBC 51 healthy controls	Lumbar T: PBC -2.2 Controls -2.3 Lumbar Z: PBC -1.0 Controls -0.8	
Hay et al. ⁴²	DPA	18 new-diagnosis PSC 30 pre-OLT PSC 185 healthy controls	Lumbar: 96.0% AM at diagnosis 77.6% AM pre-OLT	Lumbar BMD < 0.900 g/cm ² ("fracture threshold"): 0% at diagnosis 50% pre-OLT
Kalef-Ezra et al. ⁹²	DXA SPA	27 mixed AIH 17 mixed cirrhotic CLD 180 healthy controls	Lumbar: AIH 102% AM Cirrhotic 90.9% AM Distal third forearm: AIH 99.3% AM Cirrhotic 90.8% AM	
Masaki et al. ²³	DXA	184 VC 905 healthy controls	Lumbar Z: Normal in males Normal in females age < 60 yr Reduced in women age ≥ 60 yr	
Mitchison et al. ³⁶	SPA	33 new-diagnosis PBC local healthy controls	Distal forearm: PBC = controls Distal femur: PBC = controls	Distal forearm Z < -2: 9% Distal femur Z < -2: 0%

(continued on following page)

Table 3 (continued).

Reference	BMD instrument	Subjects	Mean bone density	Prevalence of reduced bone density and definition used
Ormarsdóttir et al. ⁸⁴	DXA	72 mixed CLD 122 healthy controls	Lumbar Z: -0.35 CLD +0.26 controls Femoral neck Z: -0.18 CLD +0.1 controls	Lumbar or femoral neck T < -2.5: 30% CLD 15% controls
Pares et al. ⁵⁵	DXA	61 female PBC local healthy controls	Lumbar T: -1.4 Lumbar Z: -0.3 (est.) Femoral neck T: -1.4 Lumbar Z: -0.6 (est.)	Lumbar T < -2.5: 19%
Pietschmann et al. ⁸³	SPA	49 mixed cirrhotic CLD 35 healthy controls	Distal forearm: 80% AM	
Resch et al. ⁵⁹	SPA	18 male steatotic ALD 22 male cirrhotic ALD 23 healthy controls	Distal forearm: Steatosis 91.2% AM Cirrhosis 78.0% AM	
Riggio et al. ⁹⁹	DXA	22 mixed cirrhotic CLD 16 healthy controls	Total body: 91.5% AM	
Stellon et al. ⁹⁸	SPA	36 AIH	Radial metaphysis: Reduced (P = 0.05) Radial diaphysis: Normal	Radial metaphysis or diaphysis Z < -2: 14%
Tsuneoka et al. ⁵⁷	DXA	40 VC 20 VH 40 healthy controls	Lumbar: VC 75.8-81.1% AM VH 80.8-89.3% AM	Lumbar BMD <90% AM: VC 40% VH 20%
Van Berkum et al. ⁸⁶	DPA SPA	55 female PBC 55 healthy controls	Lumbar: 92% AM Distal forearm: 92% AM Proximal forearm: 95% AM	BMD <5th percentile for age: 9% lumbar 5% distal forearm 4% proximal forearm

AM, age-matched healthy controls; VC, viral cirrhosis; HHC, hereditary hemochromatosis; ALD, alcoholic liver disease; AIH, autoimmune hepatitis; est, estimated from graphical data; QCT, quantitative computerized tomography; VH, viral hepatitis.

rate in the cirrhotic patients. Greater age and hypogonadism independently correlated with reduced trabecular bone area. A low bone formation rate was present in 51% of the cirrhotic patients, and this correlated with age, hypogonadism, and serum albumin levels but not with levels of vitamin D metabolites.

Other recent studies have confirmed the rarity of osteomalacia in cholestatic and noncholestatic disorders.^{25,38} Calcium malabsorption has been reported in both hepatocellular and biliary liver disease. Fractional calcium absorption is frequently reduced in chronic cholestasis, and this correlates with low serum 25-OHD levels.^{25,68} Some reports indicate normal levels of serum vitamin D metabolites,⁸¹ whereas others suggest a high prevalence of deficiency.^{68,82} Even if frank osteomalacia is rare, vitamin D insufficiency may contribute to hepatic osteodystrophy. Pietschmann et al.⁸³ reported significantly reduced BGP, reduced 25-OHD, and normal serum PTH levels in 49 mixed cirrhotic patients with a 6-year mean duration of disease. There was moderate correlation between 25-OHD and corrected serum calcium ($r = 0.47$; $P < 0.03$) and between 25-OHD and BGP ($r = 0.62$; $P < 0.001$) levels. These find-

ings suggest that vitamin D deficiency and decreased bone formation contribute to the skeletal deficit in cirrhosis.

Prevalence of Bone Disease in CLD

Results from uncontrolled (Table 2) and controlled (Table 3) studies of bone mineral content (BMD) in CLD are summarized. DXA and DPA data from the spine and hip were pooled after excluding data related to newly diagnosed cases (where specified) because this may underestimate the impact of CLD on bone metabolism. The mean pooled lumbar spine Z-score was -0.68, with severely reduced BMD (Z-score less than -2) in 21% and osteoporosis (T-score less than -2.5) in 21%. The equivalent values for the hip were a mean Z-score of -0.44, with severely reduced BMD (Z-score less than -2) in 12% and osteoporosis (T-score less than -2.5) in 23%.

Tables 2 and 3 indicate marked heterogeneity in BMD findings in CLD, ranging from no effect to a large BMD deficit. When healthy controls are included, the mean T-score from DXA is often negative,^{53,56} with rates of osteoporosis (T-score less than -2.5) up to 15%.⁸⁴ Uncontrolled studies may therefore exaggerate the apparent

severity of hepatic osteodystrophy, especially in older subjects who are expected to show "normal" age-related BMD loss. For example, Ormarsdóttir et al.⁸⁴ found a 15% prevalence of osteoporosis among 122 healthy age-matched controls. Technical factors, including the method and site of skeletal assessment, are also important because cortical sites appear to be much less sensitive than the vertebral trabeculae.^{22,85,86} Finally, patient populations vary greatly in terms of average age, gonadal status, diagnosis, duration of disease, severity of liver dysfunction, and previous exposure to bone-active treatments (such as calcium, vitamin D, and corticosteroids).

There was no consistent relation between diagnosis and skeletal deficit. Importantly, cholestatic disorders (PBC and PSC) are reported to show a greater reduction than noncholestatic liver disease in some studies^{18,81,85} but not in others.^{84,87} Separate pooling of the studies in Tables 2 and 3 suggests that a difference probably exists but that it is quite mild (mean Z-score for the spine: -0.7 cholestatic, -0.5 noncholestatic; for the hip: -0.6 cholestatic, -0.4 noncholestatic). Alcohol-associated cirrhosis (but not steatosis) was associated with normal BMD in 2 of 3 studies.^{59,81,88} Habitual alcohol consumption (more than 80 g/day) was shown to worsen bone disease in patients with viral cirrhosis²³ but not with hemochromatosis.⁶⁷ No difference has been found between hepatitis B and hepatitis C.^{22,23}

Osteoporosis may appear more striking in patients with PBC because the disease usually affects elderly women, who are naturally prone to osteoporosis. Osteoporosis can be the first clinical manifestation underlining cholestatic liver disease, so it may be worthwhile to screen for anti-mitochondrial antibody in osteoporotic patients with both an elevated γ -glutamyltransferase and serum alkaline phosphatase level.⁸⁹ In the largest controlled study of PBC to date, lumbar Z-scores were moderately reduced (mean Z-score, -0.66).⁹⁰ Lumbar Z-score correlated significantly with a calculated risk score based on age, bilirubin level, prothrombin time, serum albumin level, and edema ($r = -0.36$, $P < 0.001$). This inverse relationship between BMD and liver dysfunction has been confirmed by other groups.⁹¹ BMD is strongly affected by estrogen status in PBC. It is usually normal in premenopausal women and shows the greatest skeletal deficit in premature menopause.³⁹ Patients with newly diagnosed PBC have a BMD similar to healthy controls, but the finding of a Z-score SD significantly greater than 1 shows greater than normal heterogeneity and may indicate a more susceptible subpopulation.⁵³

Established cirrhosis was generally associated with lower BMD than noncirrhotic liver disease (with a single exception⁹³).^{57,59,67,80,87,92} Bone density in patients with newly diagnosed PBC and PSC is similar to healthy controls.^{36,42,53} Duration of liver disease does not correlate with BMD.^{18,42,54,56,57,83,84,93,94} Among cirrhotic patients, more advanced clinical stage (Child-Pugh), composite scores (Mayo risk score), and histologic stage (Scheuer) generally showed progressively more severe skeletal deficit (with 3 exceptions^{39,58,83}).^{40,42,56,85,86,90,91,94,95} Single biochemical indicators of liver disease (serum albumin level, bilirubin level, liver enzyme levels, prothrombin time) do not correlate as consistently.^{18,23,39,42,54,57,59,61,81,84,90,91,93,94,96} Ascites^{23,57} but not edema, gastroesophageal varices, or hepatoma⁹⁰ appears to be a clinical marker for lower BMD. Coexisting gastrointestinal disease (such as inflammatory bowel disease in PSC) may be an additional risk factor.⁹⁴ Osteoporotic lumbar BMD in hereditary hemochromatosis was associated with the amount of iron accumulation (in addition to serum-free testosterone, lack of HLA-A3, and body mass index).⁶⁷ Biochemical markers of bone metabolism have shown variable correlations with BMD. Studies that have examined this for serum PTH,^{18,22,56,58,81,93,96} 25-OHD,^{22,23,42,56,58,80,81,84,85,93,95,96} and BGP^{18,22,23,56,58,81,83,93,96,97} have been largely negative. Bone resorption markers appear more promising with significant inverse correlations in most,^{22,56,57,97} but not all,^{18,81} studies.

Many studies have attempted to identify clinical predictors of BMD. An inverse correlation between older age and age-adjusted BMD is found in most,^{18,23,57,80,84,85,87,94} but not all,^{42,56,67,81,90,96} series. As expected, women showed reductions in age- and sex-matched BMD that were equal^{93,94} or greater than in men.^{23,84} Menopause (especially premature menopause) and male hypogonadism adversely affected BMD in some,^{18,23,39,54,80,87} but not all,^{80,93,98} series. Serum testosterone levels in men correlated with BMD in 2 studies^{56,67} but not in 2 others.^{58,84} Greater body mass and weight may be associated with greater BMD,^{54,84,99} but the correlation is inconsistent.^{56,67,93} Use of corticosteroids in mixed liver disorders (including autoimmune hepatitis, PBC, and PSC) has been associated with reduced BMD in some,^{61,84,86,93} but not other,^{42,54,87,94,98} studies. Cholestyramine was not associated with reduced BMD in one study of patients with PBC.¹⁸ Use of multiple clinical variables may be more useful. A relatively simple prediction rule, relying on body mass index, corticosteroid history, age, and sex, appeared to predict the presence of osteoporosis with an accuracy of 83%.⁸⁴

Table 4. Longitudinal Studies of Bone Density in Chronic Liver Disease

Reference	BMD instrument	Subjects	Mean follow-up (yr)	Change (annual %)
Angulo et al. ⁹⁴	DPA	42 PSC (placebo arm)	Up to 5	Lumbar: -1%
Eastell et al. ⁹⁰	DPA	105 female PBC	2	Lumbar: -1.98%
Floreani et al. ¹⁸	DPA	38 PBC	0.5	Lumbar PBC: -6.2%
		11 noncholestatic CLD		Lumbar noncholestatic: no change
		20 healthy controls		Lumbar controls: no change
Guañabens et al. ³¹	DPA	19 female PBC (placebo arm)	2	Lumbar: -3.5%
Guañabens et al. ¹⁰⁰	DPA	11 PBC (placebo arm)	2	Lumbar: -3.3%
Herlong et al. ⁸²	SPA	15 women PBC	1	Distal radius: -6.1%
Leuschner ³⁰	DXA	18 PBC (placebo arm)	2	Lumbar: -0.5%
Lindor et al. ⁹¹	DPA	38 PBC (placebo arm)	2.3	Lumbar: -0.7%
		30 PBC with lumbar T < -2 (placebo arm)		
Lindor et al. ⁹⁷	DXA	< -2 (placebo arm)	1	Lumbar: -0.9%
				Total hip: +0.9%
Masaki et al. ²³	DXA	61 VC	0.8-6	Lumbar: -0.6% males -2.8% females
Pares et al. ⁵⁵	DXA	61 female PBC	1	Lumbar: -1.2%
Shiomi et al. ²⁴	DXA	38 PBC (control arm)	2.5	Lumbar: -0.4% males -2.3% females
Shiomi et al. ⁹⁶	DXA	17 PBC (control arm)	1-3.5	Lumbar: -3.1%

SPA, single photon absorptiometry; VC, viral cirrhosis.

Longitudinal Studies of Bone Density in CLD

Most published longitudinal studies of BMD in CLD have focused on cholestatic disorders, and many of these have been limited by small patient numbers, short follow-up, measurement at peripheral sites with poor site-responsiveness, and instrumentation with suboptimal precision (Table 4). Other studies failed to replace vitamin D-deficient patients; therefore, bone loss may not be representative of nutritionally replete individuals.^{24,96} Most of the available data concern the lumbar spine, and the general absence of hip data is a significant shortcoming.

In general, rates of bone loss are similar to expected,^{23,30,55,91,94,97} although 2 often-quoted studies of women with PBC or viral cirrhosis have shown accelerated bone loss.^{23,90} Some data suggest that women had more rapid bone loss than men,^{23,24} but another study found no gender difference.⁹⁴ Age, menopause, diagnosis (cholestatic vs. noncholestatic), corticosteroid use, body mass and weight, serum bilirubin level (with a single exception⁵⁵), Mayo risk score, and presence or duration of inflammatory bowel disease (in PSC) have not been shown to affect the rate of bone loss, although data are quite limited.^{18,90,94,100}

Data concerning BMD loss in primary cholestatic disease are contradictory. The largest PBC cohort evaluated women only (age range, 27-77 years; 38% postmenopausal) and found annual rates of spine bone loss in PBC significantly greater than predicted (PBC, -1.9%

vs. predicted -0.96%; $P < 0.02$).⁹⁰ All of the women were taking calcium supplements (1300 mg/day) and vitamin D supplements (if serum 25-OHD was reduced), but none of the postmenopausal women received hormone replacement therapy. There was no correlation between the rate of bone loss and markers of liver disease severity. Other studies have found that bone loss in PBC is similar to predicted normal age-dependent loss.^{30,55,91,97} One study even failed to find evidence of rapid bone loss in a high-risk group with preexisting osteoporosis (initial lumbar spine T-score less than -2) in up to 2 years of follow-up.⁹⁷ Bone loss is accelerated in corticosteroid-treated PBC.¹⁰¹ One study of BMD loss in PSC found similar rates for patients and healthy controls over follow-up of up to 5 years.⁹⁴ Ursodeoxycholic acid did not affect the rate of bone loss in a treated subgroup.

One longitudinal study in patients with viral cirrhosis (largely hepatitis C related) was identified.²³ Sixty-one male and female Japanese patients with lumbar spine DXA were followed up for 10-72 months. The annual change in men was not significantly different from healthy controls (-0.6% per year), whereas women showed significantly greater bone loss than expected (-2.8% per year). These data are consistent with the cross-sectional results discussed earlier and are similar to findings in Japanese patients with PBC,²⁴ although once again the high prevalence of untreated vitamin D deficiency raises concerns over the ability of these results to reflect the natural history of bone loss in vitamin D-replete patients.

Table 5. Fracture Prevalence and Incidence in Chronic Liver Disease

Reference	Subjects	Prevalent fractures (%)	Mean follow-up (yr)	Incident fractures (%)
Angulo et al. ⁹⁴	81 PSC		Up to 5	Vertebral: 2%
Chen et al. ⁵⁸	30 male VC	Vertebral: 7%		
Diamond et al. ⁸⁷	115 mixed CLD 113 healthy controls	Vertebral: 14% male CLD 6% male controls 6% female CLD <60 yr 4% female controls <60 yr 67% female CLD ≥60 yr 33% female controls ≥60 yr Peripheral: 15% male CLD 4% male controls 20% female CLD <60 yr 8% female controls <60 yr 67% female CLD ≥60 yr 33% female controls ≥60 yr		
Guañabens et al. ²⁵	20 PBC	Vertebral: 20%		
Guañabens et al. ³¹	38 female PBC (placebo arm)	Vertebral: 13%	2	Vertebral: 5%
Hay et al. ⁴²	18 new-diagnosis PSC 30 pre-OLT PSC	Vertebral: At diagnosis 0% Pre-OLT 7%		
Kalef-Ezra et al. ⁹²	27 mixed hepatitis 17 mixed cirrhosis	Vertebral: Hepatitis 7% Cirrhosis 12%		
Lindor et al. ⁹⁷	30 PBC with lumbar T < -2 (placebo arm)	Vertebral: 10%	1-2	Vertebral: 13%
Olsson et al. ⁹³	39 hepatitis 32 PBC	Vertebral: Hepatitis 44% PBC 7%		
Ormarsdóttir et al. ⁸⁴	72 mixed CLD	Vertebral: 15%		
Pares et al. ⁵⁵	61 female PBC	Vertebral: 13% Peripheral: 10%		
Stellon et al. ⁹⁸	36 AIH on corticosteroids	Vertebral: 3%		
Stellon et al. ⁶¹	36 PBC or PSC	Vertebral: 14%		

VC, viral cirrhosis; AIH, autoimmune hepatitis.

Many of the published longitudinal studies are flawed and may explain the inconsistent findings, even from the same group.^{31,55,100} The very high rates of bone loss reported in some studies, if sustained over many years, would be predicted to cause extreme levels of demineralization, but this is not supported by the cross-sectional data.

Fracture Prevalence and Incidence in CLD

Population differences in terms of age, sex, and corticosteroid exposure probably contribute to the wide reported range (3%–44%) in prevalent vertebral fracture rates (Table 5).^{93,98} Fracture rates increase dramatically in older subjects, and this expected pattern is seen in patients with CLD.⁸⁷ In the largest cohort to date, Diamond et al.⁸⁷ found prevalent vertebral and peripheral fracture rates among patients with mixed liver disorders that were approximately twice the rate of matched controls. Postmenopausal women were at much greater risk than men or younger women (fracture rates of 67%,

14%–15%, and 6%–20%, respectively). In regression analysis, vertebral fractures were independently related to lower spine BMD, severity of liver dysfunction, and hypogonadism. Peripheral fractures were related to established cirrhosis, hypogonadism, and alcohol abuse. Fracture rates were minimal in eugonadal noncirrhotic patients.^{64,87}

Other smaller studies have confirmed higher fracture rates in patients with more severe dysfunction (with a single exception⁹²)^{42,58} and lower BMD (with a single exception³⁹).^{64,87,94,97} No association has been seen with serum PTH, 25-OHD, or biochemical markers of liver and bone metabolism.³⁹

Cholestatic disease has been reported to be associated with fracture rates both greater than⁹³ and similar to⁸⁷ noncholestatic disorders. Interestingly, the highest rate of prevalent fractures (44%) was seen in patients with autoimmune hepatitis, and this was much greater than in patients with PBC (7%).⁹³ Most of the patients with

autoimmune hepatitis had been treated with corticosteroids. These limited data suggest that fractures may not be a major clinical problem in early-stage PBC, as distinguished from patients with PBC undergoing liver transplantation or those with more advanced disease who are probably at significantly increased fracture risk. This area is still quite controversial, and larger studies are needed.

Incident fracture rates have been even less well characterized. One study in patients with PSC reported only 2% symptomatic vertebral fractures in up to 5 years of follow-up,⁹⁴ and another study of women with PBC found 5% with new radiographic vertebral fractures over 2 years of follow-up.³¹ In the control arm of a treatment study in patients with PBC with established osteoporosis (lumbar T-scores less than -2), 9% had prevalent vertebral fractures and 13% experienced new radiographic vertebral deformities over the next 1–2 years (similar to the rate of 14% in the etidronate-treated arm).⁹⁷ Reduced lumbar spine BMD (below the fourth percentile) appeared to be a marker for increased risk of vertebral fracture.

Summary of Bone Disease in CLD

1. On average, there is a mild BMD deficit in CLD, but considerable patient heterogeneity exists (level B evidence).
2. In the absence of concurrent corticosteroid therapy, rates of BMD loss are similar to predicted (level B evidence).
3. Vertebral and nonvertebral fracture rates are increased in CLD, especially in postmenopausal women (level A evidence).
4. Markers of greater osteoporosis and fracture risk include older age, hypogonadism, corticosteroid therapy, and established cirrhosis (level B evidence).
5. Eugonadal noncirrhotic patients generally have a low incidence of osteoporotic fractures (level A evidence).
6. Patients with PBC are at increased risk for osteoporosis due to predominant female sex and older age, but cholestatic disease per se does not differ significantly from noncholestatic disorders in terms of osteoporosis and fracture risk (level A evidence).
7. Prediction rules relying on multiple variables (such as body mass index, corticosteroid history, age, and sex) may be a useful aid in predicting the presence of osteoporosis and for risk stratification (level B evidence).

Liver Transplantation

As the long-term survival of patients undergoing orthotopic liver transplantation (OLT) increases, osteoporosis is becoming a major cause of morbidity.¹⁰² The etiology is multifactorial, and pretransplant bone disease and posttransplant factors both contribute to the problem. Of these, the most important factor in the development of posttransplant bone disease is the degree of osteopenia at the time of OLT.⁷⁴ The use of high-dose corticosteroids and other immunosuppressive agents such as cyclosporin A and tacrolimus (FK506), immobility, and poor nutrition are believed to contribute to the excessive bone loss after OLT. Postoperative regimens are changing, and patients now spend much less time immobilized in the hospital. Newer immunosuppressive regimens are also less reliant on corticosteroids. An important but unanswered question is whether these undesirable effects of liver transplantation on bone can be avoided.

Pathogenesis

Immunosuppressive therapy used to prevent rejection of the transplanted liver undoubtedly contributes to rapid loss of bone mass after OLT. The deleterious effect of high-dose corticosteroids is well known, and maximum bone loss occurs during the first 3–6 months, when the corticosteroid dose is the highest. Bone loss decreases as corticosteroids are tapered down to maintenance levels. A similar temporal relationship holds for cyclosporine and tacrolimus. An early decrease in lumbar spine BMD (between baseline and 4 months) is followed by partial recovery at 12 months in patients treated with either cyclosporine or tacrolimus.¹⁰³ It is difficult to separate the effects of corticosteroids from those of cyclosporine and tacrolimus because both are elements of most standard immunosuppressive regimens. Because these agents are also corticosteroid sparing, their overall role in posttransplant osteopenia is obviously complex. Animal studies suggest that both agents can lead to high-turnover osteoporosis with accelerated bone resorption^{104–106} and have been implicated in the osteopenia of patients undergoing cardiac transplantation, but there are currently no human data to confirm these findings in OLT recipients.¹⁰⁷ Greater loss of lumbar spine BMD may occur with cyclosporine than with tacrolimus, possibly related to earlier withdrawal of corticosteroids and lower cumulative doses with the latter, although the degree of hip loss is similar.^{103,108} Paradoxically, one randomized study found that most of the fractures actually occurred in the tacrolimus group.¹⁰³ A larger study will be needed to resolve these discordant findings.

Table 6. Uncontrolled Cross-sectional Studies of Bone Density in OLT

Reference	BMD instrument	Subjects	Mean bone density	Prevalence of reduced bone density and definition used
Arnold et al. ¹¹⁵	DXA SPA	80 mixed pre-OLT 48 mixed post-OLT	Lumbar Z: -0.59 pre-OLT -0.95 at 6 mo -1.13 at 12 mo -0.91 at 24 mo -0.89 after 24 mo Cortical radius Z: -0.66 pre-OLT -0.07 at 6 mo -0.92 at 12 mo -1.25 at 24 mo -0.75 after 24 mo	
Crosbie et al. ¹¹¹	DXA	27 mixed pre-OLT	Lumbar T: -1.48 Femoral neck T: -1.36	Lumbar T < -2.5: 41% Femoral neck T < -2.5: 37%
Feller et al. ¹¹²	QCT	28 mixed pre-OLT	Lumbar Z: -0.82 pre-OLT -2.04 at 3 mo -1.68 at 12 mo -1.00 at 85 mo	
Floreani et al. ¹²²	DXA	54 end-stage CLD (26 transplanted)	Lumbar Z: -1.5 end-stage CLD -1.4 pre-OLT -1.6 at 3 mo -1.4 at 12 mo	Lumbar BMD < 0.800 g/cm ² ("fracture threshold"); all end-stage CLD 41%
Giannini et al. ¹²⁹	DXA	46 mixed post-OLT (1-48 mo)	Lumbar Z: Males -1.7 Females -1.7 Total hip Z: Males -1.1 Females -1.9	Lumbar T < -2.5: 30% Femoral neck T < -2.5: 46%
Hamburg et al. ¹²³	DXA	45 post-OLT 1 yr 17 post-OLT 5 yr 4 post-OLT 10 yr	Lumbar Z: -1.6 at 1 yr -1.0 at 5 yr -0.3 at 10 yr Total hip Z: -1.2 at 1 yr -2.0 at 5 yr -1.4 at 10 yr	
Hawkins et al. ¹³²	DXA	82 mixed post-OLT (median 1.6 yr)		Lumbar Z < -2: 43%
Hay et al. ¹³³	DXA	63 pre-OLT PBC/PSC 33 post-OLT 1 yr		Lumbar BMD < 0.98 g/cm ² ("fracture threshold"); 75% pre-OLT 85% post-OLT
Isoniemi et al. ¹⁵⁴	DXA	33 post-OLT (mean 4.1 yr), menopausal females (mostly PBC)	Lumbar T: -2.11 Lumbar Z: -0.90 Femoral neck T: -2.29 Femoral neck Z: -0.89	Lumbar T < -2.5: 50% Femoral neck T < -2.5: 44%
Keogh et al. ¹²¹	DXA	41 mixed pre-OLT	Lumbar Z: -0.76 Femoral neck Z: -2.14 Total body Z: -0.78	
Leidig-Bruckner et al. ¹⁴¹	DXA	130 mixed pre-OLT	Lumbar T Males -0.79 Females -2.14	Lumbar T < -2.5: Males 16% Females 55%
Lopez et al. ¹²⁷	DXA	71 mixed post-OLT (mean 1.75 yr)		Lumbar Z < -2: 41%
Ninkovic et al. ¹⁴⁰	DXA	37 mixed pre-OLT		Lumbar T < -2.5: 22% Femoral neck T < -2.5: 20% Either site T < -2.5: 39%
Reeves et al. ¹³⁰	DXA	90 mixed pre-OLT	Lumbar: 85.5-96.3% AM	

(continued on following page)

Table 6 (continued).

Reference	BMD instrument	Subjects	Mean bone density	Prevalence of reduced bone density and definition used
Riemens et al. ¹³⁶	DXA	53 pre-OLT	Lumbar Z <0: 79% Hip Z <0: 77%	
Trautwein et al. ¹¹³	pQCT	193 mixed pre-OLT and post-OLT	Forearm Z: Pre-OLT -1.1 cholestatic -0.4 noncholestatic Post-OLT <24 mo -1.9 cholestatic -0.6 noncholestatic Post-OLT >24 mo -2.0 cholestatic -1.0 noncholestatic	Forearm T <-2.5: Pre-OLT 24% cholestatic 14% noncholestatic Post-OLT <24 mo 48% cholestatic 25% noncholestatic Post-OLT >24 mo 44% cholestatic 12% noncholestatic

pQCT, peripheral quantitative computerized tomography; QCT, quantitative computerized tomography; SPA, single photon absorptiometry.

Pre-OLT bone histomorphometry most commonly shows a low turnover pattern with reduced bone formation rate, reduced osteoid area and osteoblast surface, and osteoporosis without osteomalacia.^{109,110} In 27 mixed cirrhotic patients hospitalized for transplantation, assessment resorption markers were increased with little change in formation markers, implying a negative “uncoupling index.”¹¹¹ BGP is often low before transplantation but normalizes after OLT in conjunction with an increase in serum PTH level.^{112,113} Some find that PTH level starts to decline toward normal by 3 months,¹¹⁴ but others report that elevations persist for many years.^{113,115,116} The uncoupling index appears to correlate positively with subsequent BMD recovery.¹¹⁶ In a study by Crosbie et al.,¹¹⁶ the uncoupling index was negative during the first 3 months after OLT but was positive between 6 and 24 months after OLT.

Histologic studies performed 3 months after OLT show an increase in osteoblast surface and increased bone formation, and this parallels an increase in serum BGP level.¹⁰⁹ It has been suggested that this may reflect recovery as high-dose corticosteroid therapy is reduced.¹¹⁷ Although bone formation rate and activation frequency increase and mineralization lag time shortens, there is no overall change in indices of remodeling balance or trabecular microstructure.¹¹⁰ This suggests one possible mechanism for the high incidence of fractures in the early post-OLT period disproportionate to the relatively small reduction in BMD. As discussed previously, increased bone turnover has been implicated in fracture risk independent of BMD and offers a rationale for perioperative antiresorptive therapy. This is supported by the finding in one small study that higher levels of urinary collagen cross-links before OLT are a marker of increased fracture risk after transplantation.¹¹⁸

Vitamin D insufficiency is present in up to 96% of patients before OLT.^{112,114,116} Serum 25-OHD level was

lower in patients with osteoporosis than those with normal BMD.¹¹⁶ Men with the BB genotype for the vitamin D receptor may be relatively protected against post-OLT bone loss. Guardiola et al.¹¹⁹ did not observe any baseline difference in BMD before liver transplantation; however, 3 months after OLT, there was 3.7% greater loss in BB/Bb genotypes than with bb, and this difference was statistically significant after adjustment for hospitalization and corticosteroid exposure. The difference persisted to 24 months.

Greater physical activity in OLT recipients may be associated with slightly higher BMD,¹²⁰ but this finding needs to be confirmed in a larger cohort. Postoperative bone loss is accompanied by a decrease in lean body mass that can predispose to falls and may contribute to the increase in frequency of fractures after OLT.¹²¹

Prevalence of Bone Disease After Liver Transplantation

Many cross-sectional studies confirm that patients undergoing assessment for OLT have a significant reduction in BMD and a high prevalence of frank osteoporosis (Tables 6 and 7). Pooling of the DXA-DPA data in these tables (weighted for patient numbers) gives a mean lumbar spine Z-score of -0.88, with severely reduced BMD (Z-score less than -2) in 20% and osteoporosis (T-score less than -2.5) in 32%. The equivalent values for the hip are a mean Z-score of -0.31, with severely reduced BMD (Z-score less than -2) in 11% and osteoporosis (T-score less than -2.5) in 27%. In general, there is less severe involvement of the hip and forearm than the spine, which is consistent with the general principle that predominantly cortical sites are less susceptible than sites rich in trabecular bone.

Most cross-sectional studies show that post-OLT patients have a slightly lower BMD than pretransplant patients, especially during the first year. The pooled

Table 7. Controlled Cross-sectional Studies of Bone Density in OLT

Reference	BMD instrument	Subjects	Mean bone density	Prevalence of reduced bone density and definition used
Abdelhadi et al. ¹³⁴	DPA SPA	25 mixed pre-OLT 25 healthy controls	Femoral neck: 96% AM Distal radius: 95% AM Proximal radius: 100% AM	
Hay et al. ⁴²	DPA	30 pre-OLT PSC 185 healthy controls	Lumbar: 77.6% AM	Lumbar BMD <0.9 g/cm ² ("fracture threshold"): 50% pre-OLT
Hussaini et al. ¹²⁸	DXA	56 mixed pre-OLT 329 healthy controls		Lumbar Z <-2: 13% Femoral neck Z <-2: 13% Total body Z <-2: 14% Any site Z <-2: 23%
McDonald et al. ¹⁰⁹	QCT	35 mixed pre-OLT 127 healthy controls	Lumbar trabecular: 83.7% AM males 92.9% AM females	
Meys et al. ¹²⁴	DXA	33 mixed pre-OLT 31 mixed post-OLT 200 healthy controls	Lumbar Z: -0.9 pre-OLT -0.9 post-OLT	
Monegal et al. ¹²⁶	DXA	58 mixed pre-OLT 832 healthy controls	Lumbar Z: -1.0 (est.) Femoral neck Z: -0.3 (est.)	Lumbar Z <-2: 26% Femoral neck Z <-2: 9%
Valero et al. ¹²⁵	DXA	100 mixed post-OLT 1368 healthy controls	Lumbar Z: -1.63	Lumbar Z <-2: 33%

AM, age-matched healthy controls; est, estimated from graphical data; SPA, single photon absorptiometry; QCT, quantitative computerized tomography.

mean lumbar spine Z-score in transplanted patients was -1.34 for the lumbar spine and -1.36 for the hip. There was a corresponding increase in the prevalence of osteoporosis (T-score less than -2.5) at the lumbar spine to 38% and at the hip to 45%. When the study population contains a wide range in time since transplantation, the most severe reduction in BMD usually occurs during the first year, with subsequent improvement to levels that can be similar to before transplantation.^{112,115,116,122-124} Some studies find an SD for the Z-score that is substantially greater than 1 and may indicate variation in individual susceptibility.¹¹⁵

Pretransplant factors that have not shown an association with reduced BMD include patient age, serum PTH level, serum 25-OHD level, bone markers (with one exception in which BGP showed a weak negative correlation with vertebral BMD¹²⁵), biochemical measures of liver function (with one exception⁹⁰), and renal function.^{42,90,109,112,116,122,125-128} Floreani et al.¹²² reported that age, serum PTH level, and serum creatinine level were associated with vertebral BMD, but this finding was only present through multiple regression analysis, and the lack of univariate associations greatly reduces its credibility. One study reported lower hip (but not spine) BMD in Child-Pugh class C than class B,¹²⁶ but other studies have failed to confirm an association with disease severity.^{109,128} Body mass showed a positive correlation with BMD in 2 studies^{122,129} but no significant correlation in 2 other studies.^{109,127} Pre-OLT corticosteroid exposure did not appear to affect BMD in pretransplant PSC.⁴²

Whether the specific liver diagnosis is an important factor is uncertain. Primary cholestatic disorders may show more severe reductions in pretransplant and posttransplant BMD than parenchymal disorders,^{109,111,113,116,123-125,128-131} but this is far from a uniform finding.^{115,121,127,132} In part, disagreement relates to the fact that patients with PBC are often older women and therefore normal age-related bone loss will result in a lower absolute BMD or T-score despite a similar Z-score.^{112,122} Contradictory studies suggest that alcohol is a marker for greater¹²⁶ or minimal¹³⁰ bone effects. BMD was found to be normal in pretransplant autoimmune hepatitis.¹¹¹

The effect of sex is complicated by differences in BMD reference ranges for men and women. Some studies suggest that men are more susceptible to transplant-related bone disease than women,^{109,122,123} but BMD expressed relative to healthy men (whether as T-score, Z-score, or percent normal) can be misleading because absolute BMD is still typically greater in women. Conversely, one study suggested that women are more affected even when BMD is expressed as sex-referenced Z-scores,¹²⁹ whereas others find no sex difference.^{125,127,128} Absolute BMD is usually lowest in postmenopausal women, intermediate in premenopausal women, and highest in young men.¹²⁵ Male hypogonadism and reduced serum testosterone level have been associated with reduced BMD.¹¹²

Posttransplant factors that have not shown a correlation with BMD include time since procedure, duration of hospitalization, rejection episodes, graft function, daily or cumulative corticosteroid doses (aside from one study

that found a correlation for the hip but not the spine), and other immunosuppressive agents.^{112,116,124,125,127-129,132}

Longitudinal Studies of Bone Density After Liver Transplantation

Many short-term longitudinal studies of BMD after OLT have been performed (Table 8). There is rapid bone loss during the first 3–6 months after transplantation with subsequent stabilization^{123,129} or improvement^{90,112,124,131,133} after 6–12 months, which is consistent with the previously discussed cross-sectional studies. Measurement of predominantly cortical peripheral sites seems to be relatively insensitive in detecting loss in bone mass compared with the lumbar spine and hip.¹³⁴ Although annualized rates of spine bone loss as high as 18% per year over the first 3 postoperative months have been reported,⁹⁰ this is not sustained for the full year; therefore, this way of expressing change in BMD is misleading. Therefore, where possible, change in BMD has been expressed as overall change from baseline, an approach that is not affected by nonlinear rates of loss. Some studies suggest that the hip is reduced to a greater extent than the lumbar spine and shows less spontaneous recovery.^{121,129} If confirmed, this could have important implications for the preferred site of measurement, mechanism of fracture (fall being a critical event in hip fractures), and treatment (with a focus on fall prevention). It should be noted that not all studies have confirmed a significant loss of BMD after OLT. In 26 patients described by Floreani et al.,¹²² there was no significant change in BMD (lumbar Z-score before OLT, -1.4 ; 3 months, -1.2 ; 12 months, -1.4) in the absence of any skeletal protection (including calcium or vitamin D).

Few longitudinal studies of BMD and fracture after OLT include more than 2 years of follow-up, and many confine their observations to the first few months. Hamburg et al.¹²³ reported on 66 OLT recipients up to 15 years after transplantation. Most subjects received calcium (minimum dosage, 500 mg) and 1- α -hydroxycholecalciferol (minimum dosage, 0.25 mg). Average bone density was less than expected for the lumbar spine and hip, but this tended to improve over time in the lumbar spine and remain stable in the hip. Most fracture events also occurred early, with few late fractures despite minimal skeletal protection. Long-term follow-up data even suggest the possibility of continued recovery of BMD for as long as 7 years after OLT.¹¹²

Greater age was associated with more rapid bone loss in one study.¹²⁹ Men and women have similar rates of bone loss (one study reported greater loss in men from the hip but not the spine).^{109,121,123} Liver diagnosis did not affect early bone loss in most studies,^{121,123,125} al-

though one found greater loss with cholestatic disorders¹¹³ and another found less bone loss with cholestatic disorders than with postnecrotic cirrhosis.¹²⁹ Final recovery of BMD to above baseline may be more common with cholestatic disorders.¹³¹ Eastell et al.⁹⁰ followed up 20 women who underwent transplantation for PBC and observed an early decrease in lumbar spine BMD at 3 months, with recovery by 12 months and a significant increase by 24 months ($+5\%$ above baseline). Hypogonadism is common in male transplant recipients and predicts bone loss after heart transplantation (although this has not been confirmed after OLT).¹³⁵

The duration of hospitalization correlated with bone loss in one study¹⁰⁹ but not in 2 others.^{134,136} Daily or cumulative corticosteroid exposure and serum cyclosporin A levels were not associated with greater bone loss (with one exception¹²⁹).^{109,122,123,134} Rejection episodes were not associated with bone loss in one study.¹⁰⁹ Results with biochemical measures of liver function^{129,134} and bone markers^{116,134,136} have been inconclusive.

Fracture Prevalence and Incidence After Liver Transplantation

Low-trauma or atraumatic vertebral fractures most often occur within the first 6–12 months after OLT^{131,137,138} and have been reported to affect 0%–30% of the population (Table 9).^{114,122} This wide range probably reflects differences in patient selection and in diagnostic surveillance. Studies that do not routinely perform spine radiography report a much lower incidence of posttransplant vertebral fractures,^{121,128,130,139} although 2 studies found that most vertebral fractures were symptomatic.^{137,140} The spine was the most common fracture site in most studies^{90,103,109,130,131,133,137,140-142}; however, when spine x-rays were not routinely performed, one series found that hip fractures predominated¹²⁸ whereas another found that minor fractures of the extremities were the most common site.¹³⁹

Ninkovic et al.¹⁴⁰ reported a 27% incidence of vertebral fractures 3 months after OLT despite a nonsignificant reduction in lumbar BMD (-2.0%). Post-OLT fractures were related to pre-OLT fractures (present in 35%), which was in turn related to older age. This study suggests that factors other than BMD make a major contribution to the high fracture incidence and that prevention of posttransplant bone disease should focus on both optimizing bone health before transplantation and early preventive strategies after transplantation. Other studies have confirmed that pre-OLT prevalent vertebral fractures are the single strongest predictor of post-OLT vertebral fractures.^{137,142,143} BMD is clearly important,

Table 8. Longitudinal Studies of Bone Density in OLT

Reference	BMD instrument	Subjects	Mean follow-up	Change (overall %)
Abdelhadi et al. ¹³⁴	DPA SPA	9 mixed OLT	1 yr	Lumbar: -8.2% baseline-3 mo -5.5% baseline-12 mo Femoral neck: -4.9% baseline-3 mo -5.5% baseline-12 mo Distal radius: -4.7% baseline-3 mo -8.2% baseline-12 mo Proximal radius: +0.3% baseline-3 mo 0.0% baseline-12 mo
Crosbie et al. ¹¹⁶	DXA	12 mixed pre-OLT	2 yr	Lumbar T: -2.50 at 6 mo Femoral neck T: -2.27 at 6 mo
Eastell et al. ⁹⁰	DPA	20 female PBC	2 yr	Lumbar: -4.5% baseline-3 mo no change baseline-12 mo +5% baseline-24 mo
Feller et al. ¹¹²	QCT	28 mixed OLT	7 yr	Lumbar: -25.5% baseline-3 mo -17.9% baseline 12 mo -12.4% baseline-46 mo -14.4% baseline-7 yr
Floreani et al. ¹²²	DXA	26 mixed OLT	1 yr	Lumbar Z: -0.2 baseline-3 mo 0.0 baseline-12 mo
Giannini et al. ¹²⁹	DXA	21 mixed post-OLT (1-48 mo)	2 yr	Lumbar: +2.5% Total hip: -2.4%
Hamburg et al. ¹²³	DXA	45 post-OLT 1 yr 17 post-OLT 5 yr 4 post-OLT 10 yr	Up to 15 yr	Lumbar (annual %): +4.1% 1-2 yr +0.2% 2-5 yr +0.1% 5-10 yr +0.3% 10-15 yr Total hip (annual %): -1.0% 1-2 yr +0.3% 2-5 yr 0.0% 5-10 yr +0.2% 10-15 yr
Hay et al. ¹³³	DXA	63 pre-OLT PBC and PSC 34 controls	1 yr	Lumbar: -6.8% baseline-4 mo -5.7% baseline-12 mo
Hussaini et al. ¹²⁸	DXA	56 mixed pre-OLT 329 healthy controls	2 yr	Lumbar: Post-OLT < pre-OLT 1-12 mo Post-OLT = pre-OLT 18-24 mo Femoral neck: Post-OLT = pre-OLT 1-5 mo to 5 mo Post-OLT < pre-OLT 6-24 mo Total body: Post-OLT = pre-OLT 1-24 mo
Keogh et al. ¹²¹	DXA	24 mixed pre-OLT	1.6 yr	Lumbar -2.3% Femoral neck -7.7% Total body -1.9%
McDonald et al. ¹⁰⁹	QCT	11 mixed OLT		Lumbar trabecular: -24% baseline-3 mo No change 3-12 mo
Meys et al. ¹²⁴	DXA	16 mixed OLT	1 yr	Lumbar: -3.5% Total body: -3.5%
Ninkovic et al. ¹⁴⁰	DXA	37 mixed OLT	3 mo	Lumbar: -2.0% Femoral neck: -2.4%
Riemens et al. ¹³⁶	DXA	53 mixed pre-OLT	1 yr	Lumbar: -6% Hip: -7%
Valero et al. ¹²⁵	DXA	77 mixed OLT (lumbar Z > -2)	1 yr	Lumbar: -3.4%

QCT, quantitative computerized tomography; SPA, single photon absorptiometry.

Table 9. Fracture Prevalence and Incidence in OLT

Reference	Subjects	Prevalent fractures (%)	Mean follow-up (yr)	Incident fractures (%)
Arnold et al. ¹¹⁵	48 mixed OLT	Vertebral: 10%	1.25	Vertebral: 31%
Compston et al. ¹¹⁴	27 mixed post-OLT		0.3	Vertebral: 30%
Eastell et al. ⁹⁰	20 female PBC post-OLT		2	Any fracture: 65% Vertebral: 35% Hip: 10%
Floreani et al. ¹²²	26 mixed pre-OLT	Vertebral: 6%	1	Vertebral: 0%
Haagsma et al. ¹⁴⁴	26 mixed OLT	Vertebral: 0% pre-OLT	2	Vertebral: 28% 1 yr, 36% 2 yr
Hamburg et al. ¹²³	45 post-OLT 1 yr 17 post-OLT 5 yr 4 post-OLT 10 yr	33% 1 yr 47% 5 yr 25% 10 yr	Up to 15	9% 1–5 yr 5% 5–15 yr
Hay et al. ¹³³	63 pre-OLT PBC and PSC 34 controls	Vertebral: 13%	1	Vertebral: 29%
Hussaini et al. ¹²⁸	56 mixed pre-OLT 329 healthy controls			All sites: 11% Hip: 9%
Keogh et al. ¹²¹	41 mixed post-OLT		1.6	Vertebral: 5% Nonvertebral: 7%
Leidig-Bruckner et al. ¹⁴¹	130 mixed OLT	Vertebral: Males 5% Females 9%	3.3	Vertebral: 32% at 3 yr Nonvertebral: 7%
McDonald et al. ¹⁰⁹	35 mixed OLT		0.5	Vertebral: 17%
Meys et al. ¹²⁴	33 mixed pre-OLT 31 mixed post-OLT	Vertebral: 8.4% pre-OLT 29% post-OLT		
Monegal et al. ¹²⁶	58 mixed pre-OLT	Vertebral: 22%		
Navasa et al. ¹³⁷	91 mixed OLT		1.1	All sites: 24%
Navasa et al. ¹³⁸	26 PBC OLT	Any site: 8% pre-OLT	2	Any site: 31% first year 8% second year
Neuhaus et al. ¹⁰⁸	246 mixed post-OLT		>2	Atraumatic fractures: 2.8%
Ninkovic et al. ¹⁴⁰	37 mixed OLT	Vertebral: 35%	0.25	Vertebral: 27% Nonvertebral: 0%
Park et al. ¹⁰³	35 mixed OLT		1	All sites: 24% Vertebral: 16%
Porayko et al. ¹³¹	146 mixed pre-OLT	Any site: 4%	2	Any site: 22%
Ramsey-Goldman et al. ¹³⁹	49 mixed OLT		1.3	All sites: 10% Vertebral: 6% Hip: 6%
Reeves et al. ¹³⁰	45 mixed OLT (control arm)		Uncertain	Vertebral: 16%
Riemens et al. ¹³⁶	53 pre-OLT	Vertebral: 6% pre-OLT	1	Vertebral: 25%
Rust et al. ¹⁴²	28 PBC OLT	Any site: 32% pre-OLT	7.5	Vertebral: 28%
Sheiner et al. ¹⁴⁵	96 mixed OLT		5.5	Any fracture: 14%

however, because reduced BMD before and after OLT has been associated with higher fracture rates in most studies (with 2 exceptions^{112,140}).^{90,109,124,130,131,136,142} Pre-OLT BMD less than the “fracture threshold” (defined as the BMD value below which 90% of osteoporotic fractures are found) predicted post-OLT vertebral fractures with a sensitivity of 83% and specificity of 62%.⁹⁰

Liver diagnosis did not affect fracture rates in some studies,^{115,140,144} but others reported higher rates in cholestatic disorders (especially PBC)^{124,131,137,141} and alcohol abuse.¹²⁴ Greater age was a risk factor in some, but not all, studies.^{137,144} One group found that age correlated with pretransplant fractures but not with posttransplant fractures.¹⁴⁰ Most studies have found higher fracture rates in women (especially after age 45 years and menopause^{124,139,145}),^{124,128,139,141,145} but others have not

shown a gender effect^{137,140} and one found that men were at greater risk.¹³⁶ Low urinary calcium clearance before transplantation (but not after transplantation) was a risk factor in one isolated study.¹⁴⁴ One small study reported that higher levels of urinary collagen cross-links before OLT are a marker of increased fracture risk after transplantation.¹¹⁹

Posttransplant variables that have not been shown to affect fractures rate are serum PTH level,¹¹⁴ duration of hospitalization,^{130,137,144} immunosuppression doses,^{130,137,144} and acute rejection,^{114,123,130,140} although 2 small studies suggest that patients undergoing retransplantation are at higher risk.^{136,137}

Fracture rates after liver transplantation have also been compared with other solid organ transplants. In the series by Ramsey–Goldman et al.,¹³⁹ fractures were iden-

tified in patients with a variety of solid organ transplants (49 OLT, 490 non-OLT). Overall fracture incidence (adjusted for follow-up duration) was greatest with kidney/pancreas (0.11 per year of observation), least with isolated kidney and heart (0.38), and intermediate with OLT (0.78). For all organs, postmenopausal status (for women) or age older than 45 years (for men) identified most fractures. Women were significantly more likely than men to sustain fractures. The most common site of fracture was the foot, with a low rate of symptomatic vertebral fractures. A large study by Leidig-Bruckner et al.¹⁴¹ prospectively followed up 235 solid organ transplant recipients (130 liver and 105 cardiac) with lateral thoracolumbar spine radiographs performed before transplantation and annually after transplantation. Despite a high prevalence of low BMD in the pre-OLT subgroup (lumbar spine T-score less than -2.5 in 16% of men and 55% of women), there was a low prevalence of compression deformities as judged qualitatively and by quantitative criteria (men, 5%; women, 9%). Univariate analysis showed that female sex (hazard ratio, 1.79), older age (hazard ratio, 1.13 for every 5 years), cholestatic liver disease (hazard ratio, 1.99), and lumbar spine T-scores less than -2.5 (hazard ratio, 3.1) were predictors of fracture.¹⁴¹ Multivariate analysis showed that the only statistically significant pre-OLT predictor of an incident vertebral fracture was the presence of a pretransplant prevalent vertebral fracture (hazard ratio, 8.57). Nonvertebral fractures were infrequent (9 of 130 [7%]). Fracture rates were similar for liver and heart transplant recipients but predictors were different, with age the major independent predictor of vertebral fracture in the cardiac group.

Most studies in OLT recipients have been short-term and have focused on BMD and fractures of the spine. Comparatively little information is available on the hip, the site of fracture that is generally believed to be of greatest clinical significance.

Summary of Bone Disease After Liver Transplantation

1. All pre-OLT patients should be evaluated for osteoporosis and disorders of bone metabolism: history and physical examination with attention to risk factors for osteoporosis, thoracolumbar spine x-rays, serum calcium level, phosphate level, 25-OHD level, and free testosterone level (for men). Thoracolumbar spine radiographs should be repeated if the patient reports loss of height or severe back pain (level D evidence).
2. Bone loss after OLT follows a biphasic course, with the greatest decrease during the first 3–6 months and then spontaneous stabilization or even improvement (level A evidence).
3. Most fractures develop in the first year, and very few fractures occur after the first 3 years (level A evidence).
4. The small but statistically significant decrease in BMD after OLT is insufficient to completely account for the high early fracture risk and usually does not worsen over time (level A evidence).
5. Posttransplant BMD can recover to above baseline and appears to be more common with cholestatic liver disease (level B evidence).
6. Pretransplant insufficiency fractures and low BMD are markers of high fracture risk after OLT (level A evidence).

When to Measure Bone Density in Liver Disease

The path of least resistance is to simply order a DXA for all patients with hepatic disease. This would identify subjects with low BMD who do not have other obvious risk factors for osteoporotic fracture but would lead to a considerable number of unnecessary tests. However, there are subjects with BMD that fall within the normal range who may still have other risk factors rendering them susceptible to fracture. A clinician might be lulled into a false sense of security when a normal BMD is reported.

Clearly, patients with the hepatic disorders reviewed who have experienced a fragility fracture, who are postmenopausal, and who have been on long-term corticosteroid therapy (>3 months) should be tested. A fragility fracture may be defined as one that occurs as a result of minimal trauma, such as a fall from a standing height or less, or no identifiable trauma. Development and validation of a risk factor grading system for liver disorders is greatly needed. In the absence of an available scoring system, clinicians must use common sense in deciding when to pursue DXA testing. Patients who have some of the noted risk factors should likely be screened with DXA, with repeated screening after 2–3 years for those within the normal range to exclude significant bone loss. A shorter follow-up interval (approximately 1 year) is recommended for patients recently initiating high-dose corticosteroid therapy; however, in general, 1 year is not long enough to determine the effectiveness of any treatment of bone disease in adults.⁷³ An alternative approach is to screen all patients, but third-party payers will have to decide if this is cost-effective and clinicians will have to decide if the current state of therapy is sufficiently

evidence based to warrant intervention for borderline cases.

In liver disease, BMD should be assessed with DXA when the diagnosis of PBC is first made, in patients with cirrhosis, in those receiving long-term corticosteroid therapy, and before transplantation. Patients on long-term corticosteroid therapy should have measurement of BMD repeated yearly until stable. All pre-OLT patients should be evaluated for osteoporosis and disorders of bone metabolism: history and physical examination with attention to risk factors for osteoporosis, thoracolumbar spine x-rays, serum calcium level, phosphate level, 25-OHD level, and free testosterone level (in men). Thoracolumbar spine radiographs should be repeated if the patient reports loss of height or severe back pain.

Summary of Bone Density Testing in Liver Disease

1. Patients who have experienced a fragility fracture, who are postmenopausal, and who require long-term corticosteroid therapy (>3 months) should undergo BMD testing. BMD should also be assessed when the diagnosis of PBC is first made, in patients with cirrhosis, and before liver transplantation (level D evidence).
2. Patients with risk factors and a normal initial BMD result should be retested after 2–3 years to exclude significant bone loss. A shorter follow-up interval (approximately 1 year) is recommended for patients recently initiating high-dose corticosteroid therapy (level D evidence).
3. Osteoporosis can be the first clinical manifestation underlying cholestatic liver disease, and it may be worthwhile to screen for anti-mitochondrial antibody in osteoporotic patients with both an elevated γ -glutamyltransferase and serum alkaline phosphatase level (level D evidence).⁸⁹

Therapy in Liver Disease

Therapy of osteoporosis in general, including corticosteroid-induced osteoporosis, has been discussed in the AGA Technical Review on Osteoporosis in Gastrointestinal Diseases.¹

Therapy of Bone Disease in CLD

Factors that contribute to the development of osteoporosis and increased fracture risk in patients with hepatic osteodystrophy include older age, hypogonadism, use of corticosteroids, and cirrhosis. Although vitamin D deficiency and osteomalacia may occur in patients with

hepatic osteodystrophy from malnutrition, malabsorption, and reduced enterohepatic circulation of vitamin D, osteoporosis accounts for most of the metabolic bone disease in these patients. Early studies did not show beneficial effects of calcium alone in reversing osteoporosis in patients with hepatic osteodystrophy. However, in patients with PBC who were vitamin D replete, 2 studies showed that calcium improved bone mass.^{146,147} In controlled studies of vitamin D–deficient patients, high-dose vitamin D or 25-OHD increased bone mass and reversed some of the osteomalacic skeletal changes.^{63,148} Similarly, in patients with hepatic osteodystrophy, calcitriol increased bone mass.^{24,96} The beneficial skeletal effects of each of these vitamin D preparations in patients with hepatic osteodystrophy presumably result from correction of vitamin D deficiency. Because malabsorption of calcium may also occur in osteoporotic patients with PBC and other hepatic osteodystrophies, calcium and vitamin D supplementation should be standard care in these patients. Estrogen replacement therapy may protect bone in older women with hepatic osteodystrophy.⁹⁵ Use of transdermal estrogen may potentially be less hepatotoxic.¹⁴⁹ Bisphosphonates hold promise for the treatment of patients with hepatic osteodystrophy.^{149,150} Intermittent cyclic etidronate prevented bone loss in PBC during 1 year of treatment with immunosuppressive drugs.¹⁰¹ Prospective longitudinal studies are needed to evaluate the effects of newer potent bisphosphonates on PBC and other forms of hepatic osteodystrophy.

Therapy of Bone Disease After Liver Transplantation

To reduce the high fracture rate after OLT, education regarding the importance of lifestyle changes (e.g., regular exercise, smoking cessation), vitamin D, and calcium supplementation should be given. Although few prospective studies are available, all patients should receive 1000–1200 mg of elemental calcium daily (depending on their age) and at least 400–800 IU of vitamin D daily. Vitamin D deficiency should be corrected by increasing serum 25-OHD levels to at least 25–30 ng/mL.¹⁵¹ In patients with malabsorption, higher doses of calcium and vitamin D may be necessary. For vitamin D deficiency (25-OHD <15 ng/mL), 50,000 U/week of vitamin D for 8 weeks will restore serum levels to >30 ng/mL.¹⁵² In severe malabsorption, 50,000 IU of vitamin D 2 or 3 times a week and occasionally parenteral vitamin D may be necessary, with careful monitoring of the serum 25-OHD, serum calcium, and urinary calcium levels. Treatment of the underlying malabsorptive process should obviate the need for such supraphysiological doses of supplemental vitamin D.

Withdrawal of corticosteroids seems to accelerate the recovery of bone mass following successful liver transplantation.¹⁵³

The role of pharmacologic agents is much less clear. In 33 postmenopausal liver transplant recipients treated with estrogen for 2 years, Isoniemi et al.¹⁵⁴ showed that spinal bone density increased in the spine and hip sites similar to postmenopausal women not on immunosuppressive therapy. In 40 OLT recipients, antiresorptive therapy with either parenteral calcitonin or intermittent cyclic etidronate increased bone mass between 6.4% and 8.2%, respectively, at 1 year.¹²⁵ Because posttransplant BMD can recover spontaneously, particularly in patients with cholestatic liver disease, these increments in bone mass may also reflect reversal of the underlying hepatic process or recovery of gonadal function.¹⁵⁵ One nonrandomized trial found that cyclic etidronate and α -calcidiol did not prevent bone loss in 53 OLT recipients.¹³⁶ In another nonrandomized longitudinal study of patients with low bone mass before OLT, infusions of pamidronate every 3 months before and after liver transplantation for 9 months dramatically decreased the risk of fracture, an important end point.¹³⁰ A subsequent randomized controlled trial in 99 adults awaiting OLT did not find any benefit of a single preoperative infusion of pamidronate on BMD or fractures,¹⁵⁶ although bone histomorphometry showed that the increase in bone resorption usually seen after OLT was partially suppressed by treatment.¹⁵⁷ A controlled trial of subcutaneous salmon calcitonin for 6 months in 63 patients undergoing OLT also failed to affect BMD or incident fractures.¹³³

Although definitive data in favor of drug therapy in patients undergoing liver transplantation is obviously lacking, it must be acknowledged that the clinical trials that have been conducted to date have all been relatively small. Many of these agents are approved by the Food and Drug Administration for the prevention and/or treatment of osteoporosis in other settings, such as postmenopausal or corticosteroid-induced osteoporosis, where they have clearly shown beneficial effects on the skeleton. Therefore, these therapies should still be considered for the prevention and treatment of osteoporosis associated with OLT. In women with hypogonadism before age 45 years, therapy with hormone replacement therapy (best via the transdermal route in patients with malabsorption or liver disease) is advised. As in other organ transplant recipients, bone loss occurs rapidly, so therapy is optimally started before or at the time of OLT.¹⁵⁸ Intravenous administration of newer potent bisphosphonates (such as ibandronate and zoledronate) at

the time of transplantation may provide a sustained reduction of bone turnover and fractures, although this approach needs to be tested in large clinical trials in organ transplant recipients.

Summary of Therapy for Liver Disease

1. All patients require education regarding the importance of lifestyle changes (e.g., regular exercise, smoking cessation), vitamin D, and calcium supplementation (level D evidence).
2. All patients should receive 1000–1200 mg of elemental calcium daily (depending on their age) and at least 400–800 IU of vitamin D daily. Vitamin D deficiency should be corrected by increasing serum 25-OHD levels to at least 25–30 ng/mL (level D evidence). In patients with malabsorption, higher doses of calcium and vitamin D may be necessary.
3. If female hypogonadism or early menopause (before age 45 years) is evident, hormone replacement therapy (best via the transdermal route in patients with malabsorption or liver disease) is advised for the prevention of osteoporosis (level D evidence in hepatic disease, level A evidence for vertebral and nonvertebral fracture risk reduction in generally healthy postmenopausal women). Estrogen therapy is approved by the Food and Drug Administration for the prevention of osteoporosis in postmenopausal or hypogonadal premenopausal women but must be balanced against the significant risks. Non-estrogen-based therapy is generally preferred for older postmenopausal women.
4. Raloxifene, a selective estrogen receptor modulator, is approved by the Food and Drug Administration for the prevention and treatment of osteoporosis in postmenopausal women (level D evidence in hepatic disease, level A evidence for vertebral fracture risk reduction in osteoporotic postmenopausal women). A bone disease specialist should participate in the decision to choose raloxifene in patients with a hepatic disorder.
5. Testosterone should be used to treat hypogonadism in men (level D evidence).
6. Bisphosphonates should be considered in patients with known osteoporosis, with vertebral fractures, or who cannot withdraw from corticosteroids after 3 months of use (level D evidence). Bisphosphonates are approved by the Food and Drug Administration for the prevention and treatment of osteoporosis in patients with known osteoporosis, with fragility fractures, or on prolonged cortico-

steroid therapy (level D evidence in hepatic disease, level A evidence regarding vertebral and nonvertebral fracture risk reduction in postmenopausal women, level A evidence regarding vertebral fracture risk reduction in osteoporotic men and corticosteroid-treated patients).

7. Nasal or subcutaneous calcitonin can be considered as an alternative when the preceding antiresorptive agents are contraindicated or poorly tolerated (level D evidence in hepatic disease, level A evidence regarding fracture risk reduction in osteoporotic postmenopausal women).
8. As in other organ transplant recipients, bone loss occurs rapidly, so therapy is optimally started before or at the time of OLT. There is conflicting evidence that intravenous administration of a bisphosphonate at the time of transplantation may reduce bone turnover and fractures, but its use should be directed by a bone disease specialist (level C evidence).
9. PTH is approved by the Food and Drug Administration for the treatment of severe osteoporosis (level D evidence in hepatic disease, level A evidence in osteoporotic postmenopausal women). Its use should be directed by a bone disease specialist.
10. Fluoride is not recommended for treatment of osteoporosis associated with a hepatic disorder (level D evidence in hepatic disease, no consistent evidence for fracture risk reduction in other groups).

Conclusions

The recommendations from this review have been incorporated into a management algorithm (see Figure 1). It must be understood that evidence to support this is still incomplete and that the best clinical management of the patient requires an individualized approach rather than strict adherence to any algorithm. The choice of T-score at or below -2.5 for intervention is arbitrary but reflects the World Health Organization diagnostic threshold; some groups have recommended that a higher threshold for pharmacologic intervention may be cost-effective in high-risk patients (e.g., T-score less than -1.5 for a postmenopausal woman with additional clinical risk factors).

Bone disease has become an increasingly recognized problem among patients with hepatic disorders. With the increasing prevalence of patients with known CLD (many of whom have survived liver transplantation), there will be large numbers of patients within any hepatology practice with potential bone disease. The widespread accessibility to DXA testing has led to an increasing number of hepatology patients with diagnoses of osteopenia and osteoporosis. There is a clear need to better define the implications of a DXA diagnosis of "osteopenia" in these patients. It is the risk of fracture that is the critical end point, and this is frequently overlooked. Further research is urgently required to better define the magnitude of the excess fracture risk in gastrointestinal and hepatic disorders. Furthermore, it will be critical to define who among these disease groups

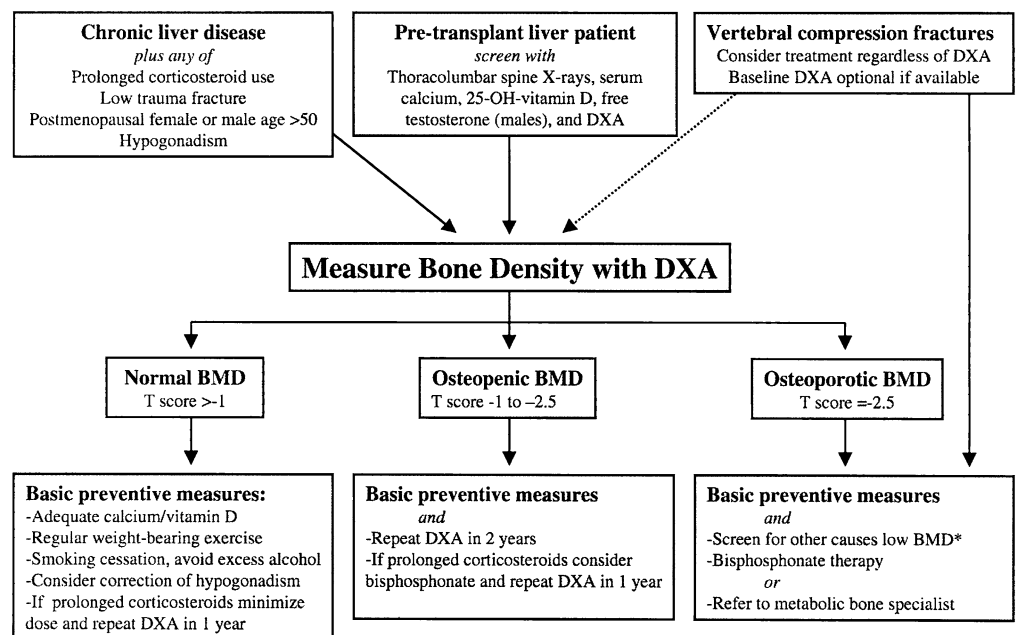


Figure 1. General approach to the clinical management of osteoporosis in patients with CLD. (*Laboratory screen for other causes of low BMD: complete blood count, serum calcium, alkaline phosphatase, creatinine, 25-OH-vitamin D, protein electrophoresis, and testosterone [in men].)

are at greatest risk for fracture because, as has been shown in inflammatory bowel disease, fracture risk may be only mildly increased.¹⁵⁹ Thus, prospective data are required to determine the relative importance of known risk factors in each disease group. This will lead to a more efficient use of screening with techniques such as DXA. Finally, there is a paucity of therapeutic intervention studies specifically aimed at bone health in hepatic diseases. Most therapy studies of sufficient size are in populations of postmenopausal women or corticosteroid-treated patients who do not have gastrointestinal or hepatic disease. Studies are required that assess interventions directed at bone health in these patients specifically and use fracture prevention as end points. Although there is much enthusiasm to address bone disease in hepatic diseases, there is a pressing need for prospectively conducted research to define the magnitude of the problem and the interventions required.

WILLIAM D. LESLIE

University of Manitoba

Winnipeg, Manitoba, Canada

CHARLES N. BERNSTEIN

University of Manitoba

Winnipeg, Manitoba, Canada

MERYL S. LEBOFF

Brigham and Women's Hospital

Harvard Medical School

Boston, Massachusetts, USA

References

- Bernstein CN, Leslie WD, LeBoff MS. AGA technical review on osteoporosis in gastrointestinal diseases. *Gastroenterology* 2003;124:795–841.
- Fuleihan GE, Testa MA, Angell JE, Porrino N, LeBoff MS. Reproducibility of DXA absorptiometry: a model for bone loss estimates. *J Bone Miner Res* 1995;10:1004–1014.
- Smith CB, Smith DA. Relations between age, mineral density and mechanical properties of human femoral compacta. *Acta Orthop Scand* 1976;47:496–502.
- Courtney AC, Wachtel EF, Myers ER, Hayes WC. Age-related reductions in the strength of the femur tested in a fall-loading configuration. *J Bone Joint Surg Am* 1995;77:387–395.
- Miller PD, Zapalowski C, Kulak CA, Bilezikian JP. Bone densitometry: the best way to detect osteoporosis and to monitor therapy. *J Clin Endocrinol Metab* 1999;84:1867–1871.
- Report of a WHO Study Group. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. *World Health Organ Tech Rep Ser* 1994;843:1–129.
- Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 1996;312:1254–1259.
- Hans D, Dargent-Molina P, Schott AM, Sebert JL, Cormier C, Kotzki PO, Delmas PD, Pouilles JM, Breart G, Meunier PJ. Ultrasonographic heel measurements to predict hip fracture in elderly women: the EPIDOS prospective study. *Lancet* 1996;348:511–514.
- Bauer DC, Gluer CC, Cauley JA, Vogt TM, Ensrud KE, Genant HK, Black DM. Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women. A prospective study. Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 1997;157:629–634.
- Looker AC, Bauer DC, Chesnut CH III, Gundberg CM, Hochberg MC, Klee G, Kleerekoper M, Watts NB, Bell NH. Clinical use of biochemical markers of bone remodeling: current status and future directions. *Osteoporos Int* 2000;11:467–480.
- Bauer DC, Sklarin PM, Stone KL, Black DM, Nevitt MC, Ensrud KE, Arnaud CD, Genant HK, Garnero P, Delmas PD, Lawaetz H, Cummings SR. Biochemical markers of bone turnover and prediction of hip bone loss in older women: the study of osteoporotic fractures. *J Bone Miner Res* 1999;14:1404–1410.
- Melton LJ III, Khosla S, Atkinson EJ, O'Fallon WM, Riggs BL. Relationship of bone turnover to bone density and fractures. *J Bone Miner Res* 1997;12:1083–1091.
- Chesnut CH III, Bell NH, Clark GS, Drinkwater BL, English SC, Johnson CC Jr, Notelovitz M, Rosen C, Cain DF, Flessland KA, Mallinak NJ. Hormone replacement therapy in postmenopausal women: urinary N-telopeptide of type I collagen monitors therapeutic effect and predicts response of bone mineral density. *Am J Med* 1997;102:29–37.
- Greenspan SL, Parker RA, Ferguson L, Rosen HN, Maitland-Ramsey L, Karpf DB. Early changes in biochemical markers of bone turnover predict the long-term response to alendronate therapy in representative elderly women: a randomized clinical trial. *J Bone Miner Res* 1998;13:1431–1438.
- Greenspan SL, Rosen HN, Parker RA. Early changes in serum N-telopeptide and C-telopeptide cross-linked collagen type 1 predict long-term response to alendronate therapy in elderly women. *J Clin Endocrinol Metab* 2000;85:3537–3540.
- Sackett DHR, Guyatt G, Tugwell P. *Clinical epidemiology: a basic science for clinical medicine*. 2nd ed. Boston: Little, Brown, 1991.
- Heathcote EJ. Management of primary biliary cirrhosis. The American Association for the Study of Liver Diseases practice guidelines. *Hepatology* 2000;31:1005–1013.
- Floreani A, Chiamonte M, Giannini S, Malvasi L, Lodetti MG, Castrignano R, Giacomini A, D'Angelo A, Naccarato R. Longitudinal study on osteodystrophy in primary biliary cirrhosis (PBC) and a pilot study on calcitonin treatment. *J Hepatol* 1991;12:217–223.
- Janes CH, Dickson ER, Okazaki R, Bonde S, McDonagh AF, Riggs BL. Role of hyperbilirubinemia in the impairment of osteoblast proliferation associated with cholestatic jaundice. *J Clin Invest* 1995;95:2581–2586.
- Diamond TH, Stiel D, Lunzer M, McDowall D, Eckstein RP, Posen S. Hepatic osteodystrophy. Static and dynamic bone histomorphometry and serum bone Gla-protein in 80 patients with chronic liver disease. *Gastroenterology* 1989;96:213–221.
- Cemborain A, Castilla-Cortazar I, Garcia M, Quiroga J, Muguierza B, Picardi A, Santidrian S, Prieto J. Osteopenia in rats with liver cirrhosis: beneficial effects of IGF-I treatment. *J Hepatol* 1998;28:122–131.
- Gallego-Rojo FJ, Gonzalez-Calvin JL, Munoz-Torres M, Mundi JL, Fernandez-Perez R, Rodrigo-Moreno D. Bone mineral density, serum insulin-like growth factor I, and bone turnover markers in viral cirrhosis. *Hepatology* 1998;28:695–699.
- Masaki K, Shiomi S, Kuroki T, Tanaka T, Monna T, Ochi H. Longitudinal changes of bone mineral content with age in patients with cirrhosis of the liver. *J Gastroenterol* 1998;33:236–240.
- Shiomi S, Masaki K, Habu D, Takeda T, Nishiguchi S, Kuroki T, Tanaka T, Ochi H. Calcitriol for bone disease in patients with cirrhosis of the liver. *J Gastroenterol Hepatol* 1999;14:547–552.

25. Guanabens N, Pares A, Marinoso L, Brancos MA, Piera C, Serrano S, Rivera F, Rodes J. Factors influencing the development of metabolic bone disease in primary biliary cirrhosis. *Am J Gastroenterol* 1990;85:1356–1362.
26. Cabré E, Gassull MA. Nutritional and metabolic issues in cirrhosis and liver transplantation. *Curr Opin Clin Nutr Metab Care* 2000;3:345–354.
27. Idilman R, de Maria N, Uzunalimoglu O, van Thiel DH. Hepatic osteodystrophy: a review. *Hepatogastroenterology* 1997;44:574–581.
28. Angulo P, Jorgensen RA, Keach JC, Dickson ER, Smith C, Lindor KD. Oral budesonide in the treatment of patients with primary biliary cirrhosis with a suboptimal response to ursodeoxycholic acid. *Hepatology* 2000;31:318–323.
29. Angulo P, Batts KP, Jorgensen RA, LaRusso NA, Lindor KD. Oral budesonide in the treatment of primary sclerosing cholangitis. *Am J Gastroenterol* 2000;95:2333–2337.
30. Leuschner M, Maier KP, Schlichting J, Strahl S, Herrmann G, Dahm HH, Ackermann H, Happ J, Leuschner U. Oral budesonide and ursodeoxycholic acid for treatment of primary biliary cirrhosis: results of a prospective double-blind trial. *Gastroenterology* 1999;117:918–925.
31. Guanabens N, Pares A, Navasa M, Martinez de Osaba MJ, Hernandez ME, Munoz J, Rodes J. Cyclosporin A increases the biochemical markers of bone remodeling in primary biliary cirrhosis. *J Hepatol* 1994;21:24–28.
32. Kurihara N, Roodman GD. Interferons-alpha and -gamma inhibit interleukin-1 beta-stimulated osteoclast-like cell formation in long-term human marrow cultures. *J Interferon Res* 1990;10:541–547.
33. Solis-Herruzo JA, Castellano G, Fernandez I, Munoz R, Hawkins F. Decreased bone mineral density after therapy with alpha interferon in combination with ribavirin for chronic hepatitis C. *J Hepatol* 2000;33:812–817.
34. Trombetti A, Giostra E, Mentha G, Negro F, Rizzoli R. Lack of evidence for ribavirin-induced bone loss. *Hepatology* 2002;36:255–257.
35. Compston JE. Hepatic osteodystrophy: vitamin D metabolism in patients with liver disease. *Gut* 1986;27:1073–1090.
36. Mitchison HC, Malcolm AJ, Bassendine MF, James OF. Metabolic bone disease in primary biliary cirrhosis at presentation. *Gastroenterology* 1988;94:463–470.
37. Cuthbert JA, Pak CY, Zerwekh JE, Glass KD, Combes B. Bone disease in primary biliary cirrhosis: increased bone resorption and turnover in the absence of osteoporosis or osteomalacia. *Hepatology* 1984;4:1–8.
38. Hodgson SF, Dickson ER, Eastell R, Eriksen EF, Bryant SC, Riggs BL. Rates of cancellous bone remodeling and turnover in osteopenia associated with primary biliary cirrhosis. *Bone* 1993;14:819–827.
39. Bagur A, Mautalen C, Findor J, Sorda J, Somoza J. Risk factors for the development of vertebral and total skeleton osteoporosis in patients with primary biliary cirrhosis. *Calcif Tissue Int* 1998;63:385–390.
40. Pereira SP, Bray GP, Pitt PI, Li FM, Moniz C, Williams R. Non-invasive assessment of bone density in primary biliary cirrhosis. *Eur J Gastroenterol Hepatol* 1999;11:323–328.
41. Shih MS, Anderson C. Does “hepatic osteodystrophy” differ from peri- and postmenopausal osteoporosis? A histomorphometric study. *Calcif Tissue Int* 1987;41:187–191.
42. Hay JE, Lindor KD, Wiesner RH, Dickson ER, Krom RA, LaRusso NF. The metabolic bone disease of primary sclerosing cholangitis. *Hepatology* 1991;14:257–261.
43. Dickey W, McMillan SA, Callender ME. High prevalence of celiac sprue among patients with primary biliary cirrhosis. *J Clin Gastroenterol* 1997;25:328–329.
44. Kingham JG, Parker DR. The association between primary biliary cirrhosis and coeliac disease: a study of relative prevalences. *Gut* 1998;42:120–122.
45. Sorensen HT, Thulstrup AM, Blomqvist P, Norgaard B, Fonager K, Ekbohm A. Risk of primary biliary liver cirrhosis in patients with coeliac disease: Danish and Swedish cohort data. *Gut* 1999;44:736–738.
46. Floreani A, Betterle C, Baragiotta A, Martini S, Venturi C, Basso D, Pittoni M, Chiarelli S, Sategna Guidetti C. Prevalence of coeliac disease in primary biliary cirrhosis and of antimitochondrial antibodies in adult coeliac disease patients in Italy. *Dig Liver Dis* 2002;34:258–261.
47. Volta U, De Franceschi L, Molinaro N, Cassani F, Muratori L, Lenzi M, Bianchi FB, Czaja AJ. Frequency and significance of anti-gliadin and anti-endomysial antibodies in autoimmune hepatitis. *Dig Dis Sci* 1998;43:2190–2195.
48. Volta U, Rodrigo L, Granito A, Petrolini N, Muratori P, Muratori L, Linares A, Veronesi L, Fuentes D, Zauli D, Bianchi FB. Celiac disease in autoimmune cholestatic liver disorders. *Am J Gastroenterol* 2002;97:2609–2613.
49. Sjoberg K, Lindgren S, Eriksson S. Frequent occurrence of non-specific gliadin antibodies in chronic liver disease. Endomysial but not gliadin antibodies predict coeliac disease in patients with chronic liver disease. *Scand J Gastroenterol* 1997;32:1162–1167.
50. Chatzicostas C, Roussomoustakaki M, Drygiannakis D, Niniraki M, Tzardi M, Koulentaki M, Dimoulis P, Mouzas I, Kouroumalis E. Primary biliary cirrhosis and autoimmune cholangitis are not associated with coeliac disease in Crete. *BMC Gastroenterol* 2002;2:5.
51. Habior A, Lewartowska A, Orlowska J, Zych W, Sankowska M, Bauer A, Butruk E. Association of coeliac disease with primary biliary cirrhosis in Poland. *Eur J Gastroenterol Hepatol* 2003;15:159–164.
52. Stewart TL, Ralston SH. Role of genetic factors in the pathogenesis of osteoporosis. *J Endocrinol* 2000;166:235–245.
53. Halmos B, Szalay F, Cserniczky T, Nemesanszky E, Lakatos P, Barlage S, Schmitz G, Romics L, Csaszar A. Association of primary biliary cirrhosis with vitamin D receptor Bsm1 genotype polymorphism in a Hungarian population. *Dig Dis Sci* 2000;45:1091–1095.
54. Springer JE, Cole DE, Rubin LA, Cauch-Dudek K, Harewood L, Evrovski J, Peltekova VD, Heathcote EJ. Vitamin D-receptor genotypes as independent genetic predictors of decreased bone mineral density in primary biliary cirrhosis. *Gastroenterology* 2000;118:145–151.
55. Pares A, Guanabens N, Alvarez L, de Osaba MJ, Oriola J, Pons F, Caballeria L, Monegal A, Salvador G, Jo J, Peris P, Rivera F, Ballesta AM, Rodes J. Collagen type I alpha1 and vitamin D receptor gene polymorphisms and bone mass in primary biliary cirrhosis. *Hepatology* 2001;33:554–560.
56. Corazza GR, Trevisani F, Di Stefano M, De Notariis S, Veneto G, Cecchetti L, Minguzzi L, Gasbarrini G, Bernardi M. Early increase of bone resorption in patients with liver cirrhosis secondary to viral hepatitis. *Dig Dis Sci* 2000;45:1392–1399.
57. Tsuneoka K, Tameda Y, Takase K, Nakano T. Osteodystrophy in patients with chronic hepatitis and liver cirrhosis. *J Gastroenterol* 1996;31:669–678.
58. Chen CC, Wang SS, Jeng FS, Lee SD. Metabolic bone disease of liver cirrhosis: is it parallel to the clinical severity of cirrhosis? *J Gastroenterol Hepatol* 1996;11:417–421.
59. Resch H, Pietschmann P, Krexner E, Woloszczuk W, Willvonseder R. Peripheral bone mineral content in patients with fatty liver and hepatic cirrhosis. *Scand J Gastroenterol* 1990;25:412–416.
60. Chappard D, Plantard B, Petitjean M, Alexandre C, Riffat G. Alcoholic cirrhosis and osteoporosis in men: a light and scan-

- ning electron microscopy study. *J Stud Alcohol* 1991;52:269–274.
61. Stellan AJ, Davies A, Compston J, Williams R. Osteoporosis in chronic cholestatic liver disease. *Q J Med* 1985;57:783–790.
 62. Crilly RG, Anderson C, Hogan D, Delaquerriere-Richardson L. Bone histomorphometry, bone mass, and related parameters in alcoholic males. *Calcif Tissue Int* 1988;43:269–276.
 63. Mobarhan SA, Russell RM, Recker RR, Posner DB, Iber FL, Miller P. Metabolic bone disease in alcoholic cirrhosis: a comparison of the effect of vitamin D₂, 25-hydroxyvitamin D, or supportive treatment. *Hepatology* 1984;4:266–273.
 64. Diamond T, Stiel D, Lunzer M, Wilkinson M, Posen S. Ethanol reduces bone formation and may cause osteoporosis. *Am J Med* 1989;86:282–288.
 65. Nyquist F, Ljunghall S, Berglund M, Obrant K. Biochemical markers of bone metabolism after short and long time ethanol withdrawal in alcoholics. *Bone* 1996;19:51–54.
 66. Diamond T, Stiel D, Posen S. Osteoporosis in hemochromatosis: iron excess, gonadal deficiency, or other factors? *Ann Intern Med* 1989;110:430–436.
 67. Sinigaglia L, Fargion S, Fracanzani AL, Binelli L, Battafarano N, Varenna M, Piperno A, Fiorelli G. Bone and joint involvement in genetic hemochromatosis: role of cirrhosis and iron overload. *J Rheumatol* 1997;24:1809–1813.
 68. Bengoa JM, Sitrin MD, Meredith S, Kelly SE, Shah N, Baker AL, Rosenberg IH. Intestinal calcium absorption and vitamin D status in chronic cholestatic liver disease. *Hepatology* 1984;4:261–265.
 69. Long RG, Varghese Z, Meinhard EA, Skinner RK, Wills MR, Sherlock S. Parenteral 1,25-dihydroxycholecalciferol in hepatic osteomalacia. *Br Med J* 1978;1:75–77.
 70. Compston JE, Thompson RP. Intestinal absorption of 25-hydroxyvitamin D and osteomalacia in primary biliary cirrhosis. *Lancet* 1977;1:721–724.
 71. Davies M, Mawer EB, Klass HJ, Lumb GA, Berry JL, Warnes TW. Vitamin D deficiency, osteomalacia, and primary biliary cirrhosis. Response to orally administered vitamin D₃. *Dig Dis Sci* 1983;28:145–153.
 72. Compston JE, Ayers AB, Horton LW, Tighe JR, Creamer B. Osteomalacia after small-intestinal resection. *Lancet* 1978;1:9–12.
 73. Arnaud SB. 25-Hydroxyvitamin D₃ treatment of bone disease in primary biliary cirrhosis. *Gastroenterology* 1982;83:137–140.
 74. Hay JE. Bone disease in cholestatic liver disease. *Gastroenterology* 1995;108:276–283.
 75. Jung RT, Davie M, Siklos P, Chalmers TM, Hunter JO, Lawson DE. Vitamin D metabolism in acute and chronic cholestasis. *Gut* 1979;20:840–847.
 76. Krawitt EL, Grundman MJ, Mawer EB. Absorption, hydroxylation, and excretion of vitamin D₃ in primary biliary cirrhosis. *Lancet* 1977;2:1246–1249.
 77. Long RG, Skinner RK, Wills MR, Sherlock S. Formation of vitamin D metabolites from 3H- and 14C-radiolabelled vitamin D₃ in chronic liver diseases. *Clin Chim Acta* 1978;85:311–317.
 78. Issenman RM, Atkinson SA, Radoja C, Fraher L. Longitudinal assessment of growth, mineral metabolism, and bone mass in pediatric Crohn's disease. *J Pediatr Gastroenterol Nutr* 1993;17:401–406.
 79. Dibble JB, Sheridan P, Hampshire R, Hardy GJ, Losowsky MS. Osteomalacia, vitamin D deficiency and cholestasis in chronic liver disease. *Q J Med* 1982;51:89–103.
 80. Diamond T, Stiel D, Mason R, Lissner D, Bikle D, Wilson S, Posen S. Serum vitamin D metabolites are not responsible for low turnover osteoporosis in chronic liver disease. *J Clin Endocrinol Metab* 1989;69:1234–1239.
 81. Bonkovsky HL, Hawkins M, Steinberg K, Hersh T, Galambos JT, Henderson JM, Millikan WJ, Galloway JR. Prevalence and prediction of osteopenia in chronic liver disease. *Hepatology* 1990;12:273–280.
 82. Herlong HF, Recker RR, Maddrey WC. Bone disease in primary biliary cirrhosis: histologic features and response to 25-hydroxyvitamin D. *Gastroenterology* 1982;83:103–108.
 83. Pietschmann P, Resch H, Muller C, Woloszczuk W, Willvonseder R. Decreased serum osteocalcin levels in patients with liver cirrhosis. *Bone Miner* 1990;8:103–108.
 84. Ormarsdóttir S, Ljunggren O, Mallmin H, Brahm H, Loof L. Low body mass index and use of corticosteroids, but not cholestasis, are risk factors for osteoporosis in patients with chronic liver disease. *J Hepatol* 1999;31:84–90.
 85. Shiomi S, Kuroki T, Masaki K, Takeda T, Nishiguchi S, Nakajima S, Seki S, Kobayashi K, Okamura T, Ochi H. Osteopenia in primary biliary cirrhosis and cirrhosis of the liver in women, evaluated by dual-energy X-ray absorptiometry. *J Gastroenterol* 1994;29:605–609.
 86. Van Berkum FN, Beukers R, Birkenhager JC, Kooij PP, Schalm SW, Pols HA. Bone mass in women with primary biliary cirrhosis: the relation with histological stage and use of glucocorticoids. *Gastroenterology* 1990;99:1134–1139.
 87. Diamond T, Stiel D, Lunzer M, Wilkinson M, Roche J, Posen S. Osteoporosis and skeletal fractures in chronic liver disease. *Gut* 1990;31:82–87.
 88. Conte D, Caraceni MP, Duriez J, Mandelli C, Corghi E, Cesana M, Ortolani S, Bianchi PA. Bone involvement in primary hemochromatosis and alcoholic cirrhosis. *Am J Gastroenterol* 1989;84:1231–1234.
 89. Heathcote J. Treatment of primary biliary cirrhosis. *J Gastroenterol Hepatol* 1996;11:605–609.
 90. Eastell R, Dickson ER, Hodgson SF, Wiesner RH, Porayko MK, Wahner HW, Cedel SL, Riggs BL, Krom RA. Rates of vertebral bone loss before and after liver transplantation in women with primary biliary cirrhosis. *Hepatology* 1991;14:296–300.
 91. Lindor KD, Janes CH, Crippin JS, Jorgensen RA, Dickson ER. Bone disease in primary biliary cirrhosis: does ursodeoxycholic acid make a difference? *Hepatology* 1995;21:389–392.
 92. Kalef-Ezra JA, Merkouropoulos MH, Challa A, Hatzikonstantinou J, Karantanas AH, Tsianos EV. Amount and composition of bone minerals in chronic liver disease. *Dig Dis Sci* 1996;41:1008–1013.
 93. Olsson R, Johansson C, Lindstedt G, Mellstrom D. Risk factors for bone loss in chronic active hepatitis and primary biliary cirrhosis. *Scand J Gastroenterol* 1994;29:753–756.
 94. Angulo P, Therneau TM, Jorgensen A, DeSotel CK, Egan KS, Dickson ER, Hay JE, Lindor KD. Bone disease in patients with primary sclerosing cholangitis: prevalence, severity and prediction of progression. *J Hepatol* 1998;29:729–735.
 95. Crippin JS, Jorgensen RA, Dickson ER, Lindor KD. Hepatic osteodystrophy in primary biliary cirrhosis: effects of medical treatment. *Am J Gastroenterol* 1994;89:47–50.
 96. Shiomi S, Masaki K, Habu D, Takeda T, Nishiguchi S, Kuroki T, Ochi H. Calcitriol for bone loss in patients with primary biliary cirrhosis. *J Gastroenterol* 1999;34:241–245.
 97. Lindor KD, Jorgensen RA, Tiegs RD, Khosla S, Dickson ER. Etidronate for osteoporosis in primary biliary cirrhosis: a randomized trial. *J Hepatol* 2000;33:878–882.
 98. Stellan AJ, Davies A, Compston J, Williams R. Bone loss in autoimmune chronic active hepatitis on maintenance corticosteroid therapy. *Gastroenterology* 1985;89:1078–1083.
 99. Riggio O, Andreoli A, Diana F, Fiore P, Meddi P, Lionetti R, Montagnese F, Merli M, Capocaccia L, De Lorenzo A. Whole body and regional body composition analysis by dual-energy X-ray absorptiometry in cirrhotic patients. *Eur J Clin Nutr* 1997;51:810–814.
 100. Guanabens N, Pares A, del Rio L, Roca M, Gomez R, Munoz J,

- Rodes J. Sodium fluoride prevents bone loss in primary biliary cirrhosis. *J Hepatol* 1992;15:345-349.
101. Wolfhagen FH, van Buuren HR, den Ouden JW, Hop WC, van Leeuwen JP, Schalm SW, Pols HA. Cyclical etidronate in the prevention of bone loss in corticosteroid-treated primary biliary cirrhosis. A prospective, controlled pilot study. *J Hepatol* 1997; 26:325-330.
 102. Cheung AM. Post-liver transplantation osteoporosis. *J Hepatol* 2001;34:337-338.
 103. Park KM, Hay JE, Lee SG, Lee YJ, Wiesner RH, Porayko MK, Krom RA. Bone loss after orthotopic liver transplantation: FK 506 versus cyclosporine. *Transplant Proc* 1996;28:1738-1740.
 104. Movsowitz C, Epstein S, Fallon M, Ismail F, Thomas S. Cyclosporin-A in vivo produces severe osteopenia in the rat: effect of dose and duration of administration. *Endocrinology* 1988;123: 2571-2577.
 105. Schlosberg M, Movsowitz C, Epstein S, Ismail F, Fallon MD, Thomas S. The effect of cyclosporin A administration and its withdrawal on bone mineral metabolism in the rat. *Endocrinology* 1989;124:2179-2184.
 106. Cvetkovic M, Mann GN, Romero DF, Liang XG, Ma Y, Jee WS, Epstein S. The deleterious effects of long-term cyclosporine A, cyclosporine G, and FK506 on bone mineral metabolism in vivo. *Transplantation* 1994;57:1231-1237.
 107. Reich D, Rothstein K, Manzarbeitia C, Munoz S. Common medical diseases after liver transplantation. *Semin Gastrointest Dis* 1998;9:110-125.
 108. Neuhaus R, Kubo A, Lohmann R, Rayes N, Hierholzer J, Neuhaus P. Calcitriol in prevention and therapy of osteoporosis after liver transplantation. *Transplant Proc* 1999;31:472-473.
 109. McDonald JA, Dunstan CR, Dilworth P, Sherbon K, Sheil AG, Evans RA, McCaughan GW. Bone loss after liver transplantation. *Hepatology* 1991;14:613-619.
 110. Vedi S, Greer S, Skingle SJ, Garrahan NJ, Ninkovic M, Alexander GA, Compston JE. Mechanism of bone loss after liver transplantation: a histomorphometric analysis. *J Bone Miner Res* 1999; 14:281-287.
 111. Crosbie OM, Freaney R, McKenna MJ, Hegarty JE. Bone density, vitamin D status, and disordered bone remodeling in end-stage chronic liver disease. *Calcif Tissue Int* 1999;64:295-300.
 112. Feller RB, McDonald JA, Sherbon KJ, McCaughan GW. Evidence of continuing bone recovery at a mean of 7 years after liver transplantation. *Liver Transpl Surg* 1999;5:407-413.
 113. Trautwein C, Possienke M, Schlitt HJ, Boker KHW, Horn R, Raab R, Manns MP, Brabant G. Bone density and metabolism in patients with viral hepatitis and cholestatic liver diseases before and after liver transplantation. *Am J Gastroenterol* 2000; 95:2343-2351.
 114. Compston JE, Greer S, Skingle SJ, Stirling DM, Price C, Friend PJ, Alexander G. Early increase in plasma parathyroid hormone levels following liver transplantation. *J Hepatol* 1996;25:715-718.
 115. Arnold JC, Hauser D, Ziegler R, Kommerell B, Otto G, Theilmann L, Wuster C. Bone disease after liver transplantation. *Transplant Proc* 1992;24:2709-2710.
 116. Crosbie OM, Freaney R, McKenna MJ, Curry MP, Hegarty JE. Predicting bone loss following orthotopic liver transplantation. *Gut* 1999;44:430-434.
 117. Hay JE. Bone disease in liver transplant recipients. *Gastroenterol Clin North Am* 1993;22:337-349.
 118. Hockerstedt K, Isoniemi H, Risteli J, Risteli L. A simple method for predicting bone fractures in PBC patients after liver transplantation. *Transpl Int* 1994;7(Suppl 1):S121-S122.
 119. Guardiola J, Xiol X, Sallie R, Nolla JM, Roig-Escofet D, Jaurieta E, Casais L. Influence of the vitamin D receptor gene polymorphism on bone loss in men after liver transplantation. *Ann Intern Med* 1999;131:752-755.
 120. Cordier P, Decruynaere C, Devogelaer JP. Bone mineral density in posttransplantation patients: Effects of physical activity. *Transplant Proc* 2000;32:411-414.
 121. Keogh JB, Tsalamandris C, Sewell RB, Jones RM, Angus PW, Nyulasi IB, Seeman E. Bone loss at the proximal femur and reduced lean mass following liver transplantation: a longitudinal study. *Nutrition* 1999;15:661-664.
 122. Floreani A, Fries W, Luisetto G, Burra P, Fagioli S, Boccagni P, Della Rovere GR, Plebani M, Piccoli A, Naccarato R. Bone metabolism in orthotopic liver transplantation: a prospective study. *Liver Transpl Surg* 1998;4:311-319.
 123. Hamburg SM, Piers DA, van den Berg AP, Slooff MJH, Haagsma EB. Bone mineral density in the long term after liver transplantation. *Osteoporos Int* 2000;11:600-606.
 124. Meys E, Fontanges E, Fourcade N, Thomasson A, Pouyet M, Delmas PD. Bone loss after orthotopic liver transplantation. *Am J Med* 1994;97:445-450.
 125. Valero MA, Loinaz C, Larrodera L, Leon M, Moreno E, Hawkins F. Calcitonin and bisphosphonates treatment in bone loss after liver transplantation. *Calcif Tissue Int* 1995;57:15-19.
 126. Monegal A, Navasa M, Guanabens N, Peris P, Pons F, Martinez de Osaba MJ, Rimola A, Rodes J, Munoz-Gomez J. Osteoporosis and bone mineral metabolism disorders in cirrhotic patients referred for orthotopic liver transplantation. *Calcif Tissue Int* 1997;60:148-154.
 127. Lopez MB, Gonzalez P, Hawkins F, Valero MA, Leon M, Loinaz C, Garcia I, Gomez R, Moreno Gonzalez E. Effect of liver transplantation and immunosuppressive treatment on bone mineral density. *Transplant Proc* 1992;24:3044-3046.
 128. Hussaini SH, Oldroyd B, Stewart SP, Roman F, Smith MA, Pollard S, Lodge P, O'Grady JG, Losowsky MS. Regional bone mineral density after orthotopic liver transplantation. *Eur J Gastroenterol Hepatol* 1999;11:157-163.
 129. Giannini S, Nobile M, Ciuffreda M, Iemmolo RM, Dalle CL, Minicuci N, Casagrande F, Destro C, Gerunda GE, Sartori L, Crepaldi G. Long-term persistence of low bone density in orthotopic liver transplantation. *Osteoporos Int* 2000;11:417-424.
 130. Reeves HL, Francis RM, Manas DM, Hudson M, Day CP. Intravenous bisphosphonate prevents symptomatic osteoporotic vertebral collapse in patients after liver transplantation. *Liver Transpl Surg* 1998;4:404-409.
 131. Porayko MK, Wiesner RH, Hay JE, Krom RA, Dickson ER, Beaver S, Schwerman L. Bone disease in liver transplant recipients: incidence, timing, and risk factors. *Transplant Proc* 1991;23: 1462-1465.
 132. Hawkins FG, Leon M, Lopez MB, Valero MA, Larrodera L, Garcia-Garcia I, Loinaz C, Moreno Gonzalez E. Bone loss and turnover in patients with liver transplantation. *Hepatogastroenterology* 1994;41:158-161.
 133. Hay JE, Malinchoc M, Dickson ER. A controlled trial of calcitonin therapy for the prevention of post-liver transplantation atraumatic fractures in patients with primary biliary cirrhosis and primary sclerosing cholangitis. *J Hepatol* 2001;34:292-298.
 134. Abdelhadi M, Eriksson SA, Ljusk ES, Ericzon BG, Nordenstrom J. Bone mineral status in end-stage liver disease and the effect of liver transplantation. *Scand J Gastroenterol* 1995;30:1210-1215.
 135. Sambrook PN, Kelly PJ, Fontana D, Nguyen T, Keogh A, Macdonald P, Spratt P, Freund J, Eisman JA. Mechanisms of rapid bone loss following cardiac transplantation. *Osteoporos Int* 1994;4:273-276.
 136. Riemens SC, Oostdijk A, van Doormaal JJ, Hijn CJ, Drent G, Piers DA, Groen EW, Meerman L, Slooff MJ, Haagsma EB. Bone loss after liver transplantation is not prevented by cyclical etidronate, calcium and alphacalcidol. The Liver Transplant Group, Groningen. *Osteoporos Int* 1996;6:213-218.
 137. Navasa M, Monegal A, Guanabens N, Peris P, Rimola A, Munoz-

- Gomez J, Visa J, Rodes J. Bone fractures in liver transplant patients. *Br J Rheumatol* 1994;33:52-55.
138. Navasa M, Forns X, Sanchez V, Andreu H, Marcos V, Borrás JM, Rimola A, Grande L, Garcia-Valdecasas JC, Granados A, Rodes J. Quality of life, major medical complications and hospital service utilization in patients with primary biliary cirrhosis after liver transplantation. *J Hepatol* 1996;25:129-134.
 139. Ramsey-Goldman R, Dunn JE, Dunlop DD, Stuart FP, Abecassis MM, Kaufman DB, Langman CB, Salinger MH, Sprague SM. Increased risk of fracture in patients receiving solid organ transplants. *J Bone Miner Res* 1999;14:456-463.
 140. Ninkovic M, Skingle SJ, Bearcroft PWP, Bishop N, Alexander GJM, Compston JE. Incidence of vertebral fractures in the first three months after orthotopic liver transplantation. *Eur J Gastroenterol Hepatol* 2000;12:931-935.
 141. Leidig-Bruckner G, Hosch S, Dodidou P, Ritschel D, Conrad C, Klose C, Otto G, Lange R, Theilmann L, Zimmerman R, Pritsch M, Ziegler R. Frequency and predictors of osteoporotic fractures after cardiac or liver transplantation: a follow-up study. *Lancet* 2001;357:342-347.
 142. Rust C, Rau H, Gerbes AL, Pape GR, Haller M, Kramling H, Schildberg FW, Paumgartner G, Beuers U. Liver transplantation in primary biliary cirrhosis: risk assessment and 11-year follow-up. *Digestion* 2000;62:38-43.
 143. Lindenthal B, Leuschner MS, Ackermann H, Happ J, Leuschner UF. Is primary biliary cirrhosis (PBC) in itself a risk factor for osteoporosis? *Hepatology* 2000;32:23.
 144. Haagsma EB, Thijn CJ, Post JG, Slooff MJ, Gips CH. Bone disease after orthotopic liver transplantation. *J Hepatol* 1988;6:94-100.
 145. Sheiner PA, Magliocca JF, Bodian CA, Kim-Schluger L, Altaca G, Guarrera JV, Emre S, Fishbein TM, Guy SR, Schwartz ME, Miller CM. Long-term medical complications in patients surviving > or = 5 years after liver transplant. *Transplantation* 2000;69:781-789.
 146. Camisasca M, Crosignani A, Battezzati PM, Albisetti W, Grandinetti G, Pietrogrande L, Biffi A, Zuin M, Podda M. Parenteral calcitonin for metabolic bone disease associated with primary biliary cirrhosis. *Hepatology* 1994;20:633-637.
 147. Rosen H. Primary biliary cirrhosis and bone disease. *Hepatology* 1995;21:253-255.
 148. Reed JS, Meredith SC, Nemchausky BA, Rosenberg IH, Boyer JL. Bone disease in primary biliary cirrhosis: reversal of osteomalacia with oral 25-hydroxyvitamin D. *Gastroenterology* 1980;78:512-517.
 149. Rouillard S, Lane NE. Hepatic osteodystrophy. *Hepatology* 2001;33:301-307.
 150. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. *Arthritis Rheum* 2001;44:1496-1503.
 151. Haden ST, Fuleihan GE, Angell JE, Cotran NM, LeBoff MS. Calcidiol and PTH levels in women attending an osteoporosis program. *Calcif Tissue Int* 1999;64:275-279.
 152. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. *Lancet* 1998;351:805-806.
 153. Mart G, Gomez R, Jodar E, Loinaz C, Moreno E, Hawkins E. Long-term follow-up of bone mass after orthotopic liver transplantation: effect of steroid withdrawal from the immunosuppressive regimen. *Osteoporos Int* 2002;13:147-150.
 154. Isoniemi H, Appelberg J, Nilsson CG, Makela P, Risteli J, Hockerstedt K. Transdermal oestrogen therapy protects postmenopausal liver transplant women from osteoporosis. A 2-year follow-up study. *J Hepatol* 2001;34:299-305.
 155. Floreani A, Mega A, Tizian L, Burra P, Boccagni P, Baldo V, Faggioli S, Naccarato R, Luisetto G. Bone metabolism and gonad function in male patients undergoing liver transplantation: a two-year longitudinal study. *Osteoporos Int* 2001;12:749-754.
 156. Ninkovic M, Love S, Tom BD, Bearcroft PW, Alexander GJ, Compston JE. Lack of effect of intravenous pamidronate on fracture incidence and bone mineral density after orthotopic liver transplantation. *J Hepatol* 2002;37:93-100.
 157. Vedi S, Ninkovic M, Garrahan NJ, Alexander GJ, Compston JE. Effects of a single infusion of pamidronate prior to liver transplantation: a bone histomorphometric study. *Transpl Int* 2002;15:290-295.
 158. Rodino MA, Shane E. Osteoporosis after organ transplantation. *Am J Med* 1998;104:459-469.
 159. Bernstein CN, Blanchard JF, Leslie W, Wajda A, Yu BN. The incidence of fracture among patients with inflammatory bowel disease — a population-based cohort study. *Ann Intern Med* 2000;133:795-799.

Address requests for reprints to: Chair, Clinical Practice Committee, AGA National Office, c/o Membership Department, 4930 Del Ray Avenue, Bethesda, Maryland 20814. Fax: (301) 654-5920.

Supported by the American Gastroenterological Association. C.N.B. is supported in part by a Research Scientist Award from the Crohn's and Colitis Foundation of Canada and an Investigator Award from the Canadian Institutes of Health Research.

The Clinical Practice Committee acknowledges the following individuals whose critiques of this review paper provided valuable guidance to the authors: Francis A. Farraye, M.D., M.Sc., Richard M. Green, M.D., Rajender K. Reddy, M.D., and Hillary Steinhart, M.D. The authors thank Jacqueline Cantin for assistance in the preparation of the manuscript.