Guidelines on the management of osteoporosis associated with chronic liver disease

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1.0 BACKGROUND AND SCOPE OF GUIDELINES

An important complication of chronic liver disease is osteodystrophy which includes osteoporosis and the much rarer osteomalacia. Both conditions are associated with significant morbidity through fractures resulting in pain, deformity, and immobility. There is also a further significant increase in the risk of fractures following liver transplantation for end stage chronic liver disease.

Osteoporosis is defined as a "progressive systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" (World Health Organisation, 1994). Common fractures are vertebral compression fractures, fractures of the distal radius, and proximal femur.

Although guidelines on the prevention and management of osteoporosis, and specifically corticosteroid induced osteoporosis and osteoporosis in men, have recently been published, there is no consensus on how to manage osteoporosis in patients with chronic liver disease.[1–3]

The scope of these guidelines is to review the assessment and diagnosis of osteoporosis, the therapeutic agents available, and the way in which they can be used in patients with chronic liver disease to prevent osteoporosis with the aim of reducing fracture rate. A number of research priorities have also been identified.

2.0 FORMULATION OF GUIDELINES

2.1 Grading of recommendations and evidence level in patients with chronic liver disease

The guidelines developed are based on systematic review of the published literature. As not all recommendations are based on randomised controlled trials, the recommendations have been scored according to the following criteria.

Grade A: based on meta-analysis or at least one randomised controlled trial.

Grade B: based on at least one well designed but not necessarily controlled study including case control and comparative studies.

Grade C: based on expert reports or opinions.

2.2 Process of guideline formation

A systematic review of the literature was undertaken and draft guidelines prepared. The guidelines were then reviewed in a consensus workshop following which a final draft was prepared. The consensus workshop was supported by the British Association for the Study of the Liver and the British Liver Trust.

3.0 DEFINITION OF CHRONIC LIVER DISEASE

For the purpose of these guidelines, chronic liver disease is defined as cirrhosis (clinically suspected or histologically proved) or the presence of severe cholestatic liver disease. Severe cholestatic liver disease is defined as the presence of a serum bilirubin level more than three times the upper limit of normal for more than six months.

4.0 OSTEOPOROSIS AND BONE MINERAL DENSITY

4.1 Definition and diagnosis of osteoporosis

The definition of osteoporosis is centred on measurement of bone mineral density (BMD) and identifies the majority of patients who will sustain a fracture in the future. It is defined in women as a BMD in the hip and/or spine that is 2.5 standard deviations (SDs) or more below the young adult mean value (T score less than −2.5). A similar cut off may be used in men although the evidence to support this is less secure than in women. Osteopenia is defined as a T score between −1 and −2.5. Although a T score is used to define osteoporosis (World Health Organisation, 1994) BMD can also be compared with age matched controls. A z score of −2 defines a BMD 2 SDs below the mean value of age matched controls.

4.2 Relationship between BMD and fracture risk

Prospective studies have shown that the risk of fracture increases progressively with decreasing BMD, the risk of fracture increasing two to threefold for each SD decrease in BMD.[4] BMD has a high specificity for fracture but a low sensitivity and so has not been advocated for population screening.

4.3 Measurement of bone mineral density

Bone density can be measured at a number of skeletal sites, including the lumbar spine and femoral neck, using dual energy *x* ray absorptiometry (DXA). Lumbar spine measurements are unreliable in the elderly due to the presence of osteophytes, extraskeletal calcification, and vertebral and/or spinal deformity. Ultrasound measurements of the os calcis have been shown to predict fracture risk in postmenopausal women but diagnostic thresholds have not been established and so this cannot yet be recommended in clinical practice.

5.0 CLINICAL RISK FACTORS FOR OSTEOPOROSIS

Bone mass increases through childhood reaching a peak in the third decade and then after 40 years declines in both sexes but more rapidly in women, accelerating after the menopause. Peak bone mass is determined by genetic factors, hormonal status, diet, and exercise, and men have a higher peak bone mass than women. Thus irrespective of other factors, the incidence of osteoporosis increases in the elderly as age related bone loss is a normal phenomenon.

The risk of fracture is determined not only by bone density but also by trabecular architecture, skeletal geometry, bone

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Abbreviations: BMD, bone mineral density; DXA, dual energy *x* ray absorptiometry; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; HRT, hormone replacement therapy; SHBG, sex hormone binding globulin; LH, luteinising hormone; FSH, follicle stimulating hormone.

turnover, and non-skeletal risk factors such as postural instability and the propensity for falls.

Risk factors for osteoporosis and subsequent fracture, irrespective of the presence of chronic liver disease, include low body mass index (<19 kg/m^2), alcohol excess, prolonged corticosteroid therapy (prednisolone 5 mg/day for more than three months), physical inactivity, previous fragility fracture, *early* maternal hip fracture (<60 years), hypogonadism, and premature menopause (age <45 years).

When assessing the risk of osteoporosis in individuals with liver disease it is important to realise that these patients often have a low body mass index, may drink excessive amounts of alcohol, and may be receiving corticosteroids. Certain liver diseases such as primary biliary cirrhosis occur predominately in postmenopausal women and cirrhosis is more prevalent with increasing age.

6.0 BIOCHEMICAL MARKERS OF BONE DISEASE
There is an association between bone turnover and fracture risk, independent of BMD.

Biochemical markers of bone turnover can be divided into two groups: markers of resorption and markers of formation. The principal markers of bone formation are the procollagen propeptides of type 1 collagen, osteocalcin, and the bone isoenzyme of alkaline phosphatase. The latter is less useful in chronic liver disease as it is difficult to measure accurately in the presence of high values of liver alkaline phosphatase.

The most widely used markers of bone resorption are: urinary excretion of deoxypyridinoline, pyridinoline, and type 1 collagen cross linked N-telopeptide. These are usually expressed in relation to urinary creatinine. Urine hydroxyproline is a poor marker and now rarely used.

These serum bone markers may prove useful in assessing response to treatment in the future in individuals without chronic liver disease. However, as the levels are affected by the extent of hepatic fibrosis and none of these markers has been studied in patients with chronic liver disease, they cannot yet be recommended as a means of assessing bone loss and the risk of fracture in cirrhotic patients.

7.0 PATHOGENESIS OF BONE LOSS IN CHRONIC LIVER DISEASE
7.1 Osteoporosis
Bone loss occurs as a result of increased bone turnover and/or remodelling imbalance. The latter may be due to reduced formation or increased resorption or a combination of the two. Some studies have shown increased bone resorption, even in the absence of osteoporosis, in the presence of chronic liver disease whereas most others have shown decreased bone formation.[5] [6]

7.2 Osteomalacia
Osteomalacia can also lead to low BMD. The classical biochemical changes are hypocalcaemia, hypophosphataemia, increased parathyroid hormone, and elevated bone alkaline phosphatase although serum calcium and phosphate are often normal. Hepatic osteomalacia, as defined by strict histomorphometric criteria, is rare.[7] [8] In a recent study of 60 patients awaiting liver transplantation none had evidence of osteomalacia on bone biopsy (J E Compston, personal communication).

7.3 Vitamin D deficiency/insufficiency
Vitamin D is obtained from endogenous skin synthesis which involves exposure to sunlight, leading to the production of cholecalciferol (vitamin D$_3$). Ergocalciferol (vitamin D$_2$) and vitamin D$_3$ are also acquired from natural and fortified food. Vitamin D undergoes 25 hydroxylation in the liver which is only impaired in the presence of severe chronic liver disease.

Vitamin D insufficiency is associated with secondary hyperparathyroidism, increased bone turnover, and accelerated bone loss. As vitamin D deficiency becomes more severe, impaired bone mineralisation leads to accumulation of osteoid which is a feature of osteomalacia.

Many studies have shown low serum levels of 25-hydroxyvitamin D in patients with chronic liver disease[9] [10] and levels fall with disease progression in cirrhosis.[11] Although malabsorption of 25-hydroxyvitamin D has been demonstrated in patients with chronic liver disease, this does not completely account for the low vitamin D levels seen in these patients. It is likely that both reduced exposure to UV light and dietary insufficiency account for vitamin D deficiency in the majority of cases. There is also impaired cutaneous synthesis of vitamin D in the presence of jaundice.

8.0 PREVALENCE OF OSTEOPOROSIS AND FRACTURE
There are no prospective studies addressing the fracture rate in patients with chronic liver disease and no good observational studies. Many studies have investigated the prevalence of osteoporosis, as defined by BMD measurements. However, in these studies different methodologies and different sites were used to assess BMD. The definition of osteoporosis also differed between studies and patients were selected using different criteria.

Patients with chronic liver disease also have other risk factors for osteoporosis related to their disease, such as hypogonadism, vitamin D insufficiency, excess alcohol consumption, corticosteroid use, and low body mass index. The proportion of patients with these risk factors also varies between studies. Table 1 summarises the studies that have assessed the prevalence of osteoporosis and fractures in various patient groups with liver disease.

Vertebral fracture is the most commonly described fracture in patients with chronic liver disease, as relatively few survive to the age at which hip fracture occurs most commonly (peak incidence around 80 years).

8.1 Cirrhosis
Osteoporosis and fractures are more common in cirrhotics than in the normal population in the absence of confounding risk factors such as female sex, cholestasis, and excess alcohol. In a study of male cirrhotics with a viral aetiology, half of the 32 patients were osteoporotic, defined as a T score of less than -2.5 at the lumbar spine or femoral neck. The mean z score at the lumbar spine was -1.27 (1.6) g/cm^2, indicating the wide interindividual variation in bone density even among this relatively homogeneous population of cirrhotics.[6]

In another study of 74 males with hepatitis B or C cirrhosis, osteoporosis in the lumbar spine, defined as a z score of less than -2, was seen in 20% and fractures in 6.7%, mean BMD being significantly lower than in healthy controls.[12] The prevalence of osteoporosis is related to the severity of liver disease in cirrhosis.[6] [13]

In a study of 58 cirrhotic patients referred for liver transplantation, 43% had osteoporosis, defined by at least one vertebral fracture and/or a lumbar spine BMD more than 2 SDs below the mean value for normal subjects of the same age (z score <-2.0). Alcoholics and those with more severe liver disease—that is, Child Pugh class C patients—had the lowest BMD.[13]

8.2 Cholestatic liver disease
A high prevalence of osteoporosis has also been reported in individuals with cholestatic liver disease.

8.2.1 Primary biliary cirrhosis
Many studies have evaluated BMD in patients with primary biliary cirrhosis (PBC).[14–21] It is not clear whether osteoporosis occurs in early stage PBC where there is cholestasis without

Table 1 Prevalence of osteoporosis and fractures in chronic liver disease

Disease type	n	Cirrhotic (%)	Type of assessment	Osteoporosis	Fracture	Reference
Alcoholics	17		BMD-LS	23%		Feitelberg 1987[31]
ALD	10		BMD-LS	0%		Laitinen 1993[36]
PBC	33		Iliac crest biopsy	0%		Mitchison 1988[22]
PBC	55	45	BMD-LS			Van-Berkum 1990[14]
PBC	20		Iliac crest biopsy	35%		Guanabens 1990[18]
PBC	210		BMD-LS	13%**		Eastell 1991[16]
PBC	88		BMD-LS	35%*		Lindor 1995[15]
PSC	81	23	BMD-LS	17%	3%	Angulo 1998[23]
Viral	74	100	BMD-LS	20%**	7%	Chen 1996[12]
Viral	32	100	BMD-LS	53%**		Gallego-Rojo 1998[6]
Mixed	115	52	BMD-LS	16%**	12–18%	Diamond 1989[27]
Mixed	133		BMD-LS	26%**		Bonkovsky 1990[25]
Mixed	58	100	BMD-LS	43%**		Monegal 1997[13]
Mixed	32	53	BMD-LS	28%		Sinigaglia 1997[28]

Osteoporosis is defined as T score <-2.5 except for: *defined as fracture threshold below 0.85 g/cm²;
**defined as z score <-2.
ALD, alcoholic liver disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; BMD-LS, bone mineral density in lumbar spine.

significant hepatic fibrosis. However, reduction in BMD is related to the severity of liver disease.[14–16]

Not all patients with PBC will develop osteoporosis and the rate of bone loss varies between patients. In 25 patients with PBC and low BMD (z score <-2), spinal BMD fell by 3.5% over a six month period[17] whereas in another study, 210 women with PBC with a range of bone densities, mean rate of bone loss was 2%/year.[16] In a study of 36 PBC patients who were not osteoporotic (defined as lumbar spine BMD >0.800 g/cm²) at the start of a three year follow up, 11 subsequently became osteoporotic and had a higher annual bone loss than the other 25 patients.[19] In contrast, in a retrospective study of 225 patients with PBC, following on from an earlier study,[22] of the 46% with late stage disease (stage 3/4) who had repeated BMD measurements, only one patient developed osteoporosis (defined as a z score <-2) during a mean follow up of 10 years (D Jones, personal communication). In contrast with osteoporosis, osteomalacia is rarely seen in PBC.[20]

Other factors that have been associated with osteoporosis in PBC include disease duration and degree of cholestasis, the latter reflecting the stage of liver disease. In a small study of 20 PBC patients, seven (35%) of whom were osteoporotic, osteoporosis was associated with longer duration of disease, intestinal calcium malabsorption, and postmenopausal state.[18]

Although studies have suggested that cholestasis itself is a risk factor for osteoporosis, this may just be a reflection of the coexistence of cirrhosis with severe cholestasis as ursodeoxycholic acid, which improves cholestasis, has no effect on BMD. In a study of 88 female PBC patients, 50 treated with ursodeoxycholic and 38 controls, there was no overall change in BMD in either group over a three year period.[15]

8.2.2 Primary sclerosing cholangitis

Individuals with primary sclerosing cholangitis (PSC) have multiple risk factors for osteoporosis. Patients may be cirrhotic as well as cholestatic and may also have been taking corticosteroids for many years for coexistent inflammatory bowel disease.

In a study of 81 patients with PSC followed up for five years, overall BMD of the lumbar spine was lower than age and sex matched controls.[23] Those patient who had fractures were older, had a longer duration of inflammatory bowel disease, and more advanced liver disease. The incidence of osteoporosis (defined as a T score <-2.5) increased with worsening liver disease and 40% were osteoporotic at the time of liver transplantation and so at increased risk of post transplant fracture.

8.3 Non-cholestatic non-cirrhotic liver disease

The prevalence of osteoporosis in non-cirrhotic patients who are not cholestatic or hypogonadal is unknown. Studies that have included such patients suggest that cirrhosis is the major independent risk factor for osteoporosis and fracture.

In a study of 115 patients with chronic liver disease, of whom 20% were cholestatic, 36% alcoholic, 52% cirrhotic, and 18% on more than 7.5 mg/day of prednisolone, 29% were found to have osteoporosis, defined as a z score of less than -2. Mean age of the patients was 49 years (range 20–70). Between 12% and 18% had spinal fractures, and peripheral fractures were more common among alcoholics. Both fractures and osteoporosis were more common in cirrhotics than non-cirrhotics and hypogonadal patients. Multiple regression analysis showed age, cirrhosis, and hypogonadism to be predictive of osteoporosis in the lumbar spine. Hypogonadism, low BMD, and severity of liver disease were predictive of spinal fracture.[24]

In a further study of 133 individuals with chronic liver disease, 24% alcoholic and 36% cirrhotic, the prevalence of lumbar spine osteoporosis varied between 16% and 50% (defined as a z score of less than -2). The highest rates were observed in cirrhotics and PSC patients. In a group of 19 non-cirrhotic patients with chronic active hepatitis, 21% were osteoporotic but 50% of the group were taking corticosteroids.[25]

8.4 Haemochromatosis

In two small studies, haemochromatosis was associated with low BMD.[26 27] In one study those patients who were hypogonadal had a lower BMD than eugonadal haemochromatotic patients.[26] In a further study of 32 patients (90% male and 55% cirrhotic), osteoporosis, defined as a lumbar spine T score of less than -2.5, was observed in 28%, with higher iron loads rather than cirrhosis being associated with osteoporosis.[28]

8.5 Alcohol

Alcohol is an independent risk factor for osteoporosis, alcoholism being associated with a 2.8-fold increase in the risk of hip fractures. In men, excess alcohol, irrespective of cirrhosis or low testosterone levels, is a risk for osteoporotic fractures.[29–36] In a study of 76 men drinking more than 27 units/day for more than 24 years, only 22% of whom had abnormal hepatic histology, lumbar spine BMD was lower than in age matched controls. Thirty per cent had vertebral compression fractures although only 4% were symptomatic.[34] In a further study of 58 male non-cirrhotic drinkers, osteopenia was seen in 23% drinking >10 units/day and cumulative

Table 2 Interventional studies to prevent and treat osteoporosis in patients with liver disease

Source	Intervention	Duration	Type of study	Subjects	Size (n)	Outcome
Bisphosphonates						
Wolfhagen et al[37]	T=cyclical etidronate 400 mg and calcium 500 mg/day; C=calcium 500 mg/day. All on prednisolone	1 y	Randomised placebo controlled	PBC stage III/IV; Childs Pugh A	12; C=6, T=6	BMD (L2–4): T=+0.4% (p=0.001), C=−3%; BMD (FN): no change, no change in incident fractures. Cyclical etidronate prevents bone loss associated with steroid treatment in PBC
Guanabens et al[38]	T1=cyclical etidronate 400 mg; T2=sodium fluoride 50 mg/day. All received calcium 1–1.5 g/day in addition to diet and vitamin D 226 µg every 2 weeks orally	2 y	Randomised	PBC (all F); age 57 (1.3) y; 19% previous fracture	32; T1=16, T2=16	BMD: T1=+0.53% LS, no change FN; T2=no change in LS; 5.89% at FN. Vertebral fracture: T1=0/16, T2=2/16. Cyclical etidronate more effective in preventing bone loss in PBC than sodium fluoride
Pares et al[39]	T1=alendronate 10 mg/day; T2=cyclical etidronate 400 mg. All received calcium 1–1.5 g and vitamin D 266 µg orally	1 y	Randomised		26; T1=13, T2=13	BMD (L2–4): T1=+4.8% (p=0.001), T2=+0.587 (NS); BMD (FN): T1=+3.44% (p=0.01), T2=+1.69% (NS). Veretebral fracture nil. Non-vertebral fracture: T1=2/12, T2=1/13. Alendronate increases bone mass in PBC and has greater effect than etidronate
Vitamin D						
Matloff et al[40]	T1=25-hydroxy vitamin D 20–120 µg/day. All calcium to 1 g/day	1 y	Non-controlled open, non-randomised	PBC (all female). All bone disease	10	Bone mineral content (photon absorpt) decreased in 8/8 patients. 25-hydroxyvitamin D ineffective in reversing bone loss in PBC
Herlong et al[41]	T1=25-hydroxyvitamin D 100 µg/day	1 y	Not controlled open, non-randomised	PBC (all F). Low vitamin D in 11/15 corrected by treatment. Age 48 (33–66 y). Postmenopause 5/15	15	Bone density (photon beam radius): decrease (0.82 g/cm v 0.77 g/cm; p=0.029). Despite correction of vitamin D deficiency, progression of osteoporosis seen in PBC
Eastell et al[16]	All calcium 1.3 g/day and vitamin D2 1.25 mg/week if 25 hydroxyvitamin D low	2 y median (0.5–6 y)	Longitudinal	PBC (all F); 38% postmenopausal. Controls aged matched normal women. BMD 7% lower in PBC than controls	105	BMD lumbar spine (dual photon absorptiometry): bone loss 2%/y v 1%/y in controls. Progressive bone loss despite calcium and vitamin D but no PBC controls
Oestrogens						
Crippin et al[42]	T1=oestrogens, T2=calcium	Up to 8 y	Retrospective analysis	PBC (stage 1–1V); 50.3 (10.2) y; 59% postmenopause; 37% BMD <fracture threshold	203; T1=16, T2=187	BMD (dual photon absorption): T1=+0.014 (n=16) v −0.03 (n=91) with no oestrogens; T2=no difference in 8 y FU in those receiving calcium (47% patients) or not. 16.1% (9/56) vitamin D deficient given vitamin D. 8/9 no change or fall in BMD over 1 y. Oestrogen replacement in postmenopausal women with PBC improves spine BMD. Calcium and vitamin D, even if deficient, do not improve BMD
Olsson et al[43]	T1=oestrogen/progesterone, C=nil	2 y	Non-randomised controlled	PBC (all F); 9/10 osteoporosis; 1/10 osteopenia	10	Increase BMD in HRT group.
Calcium						
Epstein et al[44]	T1=calcium gluconate 40 mmol, T2=hydroxyapatite 8 g, C= nil. All received vitamin D 100 000 IU monthly im	14 months	Randomised controlled	PBC (all F); postmenopausal	53; T1=17, T2=15, C= 21	Metacarpal cortical thickness: T1=+1.5%, T2=+6.1%, C=−5.5%. Calcium prevented bone thinning, hydroxyapatite increased cortical bone thickenening
Calcitonin						
Camisasca et al[17]	T1=calcitonin 40 IU alt days sc for 6 months, C=calcitonin 1 IU ×2 weekly alternate months. All received vitamin D 10 000 IU im monthly. Calcium 1 g started after 6/12 drug free observation period	21 months	Randomised controlled crossover study	PBC (all F); severe osteopenia; BMD <2 SD below age matched. Excluded patients vertebral fractures. Mean age 65 y; 60% cirrhotic; 76% postmenopausal	25	BMD (dual photon absorption), observation period 6/12, BMD −3.5%: T=+4.3%; C +4.9%; crossover after 3/12 washout, T=−2.7%, C=−4.9%. No vertebral fractures seen. No difference in BMD between control and calcitonin but calcium had transient benefit
Floreani et al[19]	T1=1,25 OH vitamin D 0.5 µg twice daily for 5/7 and calcium 1.5 g 1/12 and calcitonin 40 IU ×3 weekly repeated every 3 months, C=nil	3 y	Non-randomised controlled	PBC (all F) stratified by BMD. T1=<0.800 g/cm, T2=>0.800 g/cm	59; T1=23, C=36	BMD (dual photon absorption): increase in T1 in follow up (p<0.05). After 11/12, 11 patients in C group BMD <0.800 g/cm and treated group. Calcitonin, vitamin D, and calcium associated with increase in BMD in PBC with low bone density
Calcitriol						
Shiomi et al[45]	T1=1 alpha 25 OH vitamin D3 0.5 µg bd, C=nil	12–57 months	Randomised controlled	Cirrhosis, mean age 62 y	76; T1=38, C=38	BMD L2–4 (DEXA): males: T1=+1.1%, C=−0.4% mean/y; females: T1=−0.5%, C=−2.3%. Median values significant only: males: T=+0.6%, C=−1.4% (p=0.013); females: T=−0.5%, C=−1.5% (p=0.011). Calcitriol can prevent bone loss in cirrhosis

C, control group; T, treatment group; FN, femoral neck; LS, lumbar spine; PBC, primary biliary cirrhosis; im, intramuscularly; sc, subcutaneously.

Table 3 Agents shown to be effective in the prevention of osteoporotic fracture in postmenopausal women. There are no studies assessing antifracture efficiacy of interventions in chronic liver disease

	Spine	Non-vertebral	Hip
Alendronate	A	A	A
Calcitonin	A*	B	B
Calcitriol	A*	A*	NA
Calcium	A	B	B
Calcium and vitamin D	NA	A	A
Cyclical etidronate	A	B	B
HRT	A	A	B
Raloxifene	A	ND	ND
Risedronate	A	A	A
Vitamin D	NA	B	B

HRT, hormone replacement therapy; NA, not assessed; ND, not demonstrated; * data inconsistent.
Grade A, meta-analysis or randomised controlled trial or at least one randomised controlled trial.
Grade B, from at least one well designed controlled study without randomisation, from at least one other well designed quasi-experimental study, or from well designed non-experimental descriptive studies, for example, comparative studies, correlation studies, case controlled studies.
Grade C, from expert committee reports/opinions/or clinical experience of authorities.
The tables come from the Royal College of Physician/Bone and Tooth Society updated guidelines on the "Management of osteoporosis".

Table 4 Agents shown to be effective in the prevention/reduction of postmenopausal bone loss

	Grade of evidence
Alendronate	A
Calcitonin	A*
Calcitriol	A*
Calcium	A
Cessation of smoking	B
Cyclical etidronate	A
HRT	A
Physical exercise	A
Raloxifene	A
Reduced alcohol consumption	C
Risedronate	A
Tibolone	A
Vitamin D and calcium	A

HRT, hormone replacement therapy; *data inconsistent.
Grade A, meta-analysis or randomised controlled trial or at least one randomised controlled trial.
Grade B, from at least one well designed controlled study without randomisation, from at least one other well designed quasi-experimental study, or from well designed non-experimental descriptive studies, for example, comparative studies, correlation studies, case controlled studies.
Grade C, from expert committee reports/opinions/or clinical experience of authorities.
The table comes from the Royal College of Physician/Bone and Tooth Society updated guidelines on the "Management of osteoporosis".

alcohol intake was inversely related to BMD.[35] In women, excess alcohol in the absence of hypogonadism and cirrhosis is not associated with osteoporosis.[36]

9.0 MANAGEMENT
9.1 Introduction
There are only a few small randomised controlled trials examining the role of intervention in preventing osteoporosis and reducing subsequent fractures in chronic liver disease. Most of the studies are 1–3 year intervention studies in patients with PBC, not all of whom were cirrhotic. None of the studies was adequately powered to assess reduction in fracture rate as an end point (table 2).

Agents shown to be useful in preventing or reducing bone loss in healthy non-osteoporotic postmenopausal women include calcium, cyclical etidronate, alendronate, risedronate, hormone replacement therapy (HRT) (including tibolone), raloxifene, calcitonin, and combined vitamin D/calcium and calcitriol. Some of these agents have also been shown to be effective in the prevention of osteoporotic fractures (tables 3, 4).

The role of these agents in managing osteoporosis in patients with chronic liver disease is discussed below. Table 2 summarises intervention studies and their outcomes in patients with chronic liver disease. Figure 1 shows a summary of the strategy for the management of osteoporosis in chronic liver disease.

9.2 Calcium and vitamin D
In elderly women living in sheltered accommodation, combined calcium and vitamin D supplementation reduces the risk of hip and other non-vertebral fractures.

The role of calcium and vitamin D in preventing osteoporosis and fracture in chronic liver disease is unclear. In a cross sectional study of 55 patients with PBC who were all taking adequate dietary calcium and vitamin D or who had been supplemented if deficient, mean BMD was 8% lower than in age and sex matched controls.[14] In another small retrospective study in PBC, vitamin D_3 and calcium supplementation did not lead to a significant increase in BMD over baseline in the treated group.[42] In the absence of larger studies on the effect of

vitamin D supplementation on BMD it seems reasonable to recommend correction of vitamin D insufficiency with an oral daily dose of 800 IU of *vitamin D_3* and 1 g of calcium.

Osteomalacia has been shown to respond to treatment with oral or parenteral vitamin D or oral alfacalcidol.[46] The role of high dose vitamin D in preventing osteoporosis and fractures is unclear and the efficiency of vitamin D absorption in the setting of chronic liver disease has been poorly studied. However, in one non-randomised controlled study in alcoholic cirrhotics with low BMD and low serum levels of 25 hydroxy-vitamin D, oral supplementation with 50 000 IU of vitamin D_2 or 20–50 μg of 25-OH vitamin D did increase BMD over baseline values in the treated group.[10]

9.3 Hormone replacement therapy
HRT is given as sequential combination therapy, continuous combination therapy, or oestrogens alone in women who have had a hysterectomy. In patients with chronic liver disease HRT can be given safely.[47 48] It should be given, where possible, via the transdermal route as physiological blood oestrogen levels can be achieved without exposing the liver to high levels of conjugated oestrogens. Transdermal oestradiol should be used at a dose of 50 μg/day, equivalent to 2 mg daily of oral oestradiol. Unopposed oestrogens can be given to patients who have had a hysterectomy. Sequential or continuous combination therapy of oestrogens followed by progestogen should be given to women who have a uterus as this protects against endometrial hyperplasia. In women who cannot tolerate monthly bleeding, continuous combination therapy can be given providing that the patient has been free of bleeding for a year and is aged over 51 years.

In general, in those women in whom it is indicated, the recommended duration of HRT is 5–10 years. However, the risk of osteoporosis in chronic liver disease continues beyond 10 years and the optimal duration of therapy has not been defined. The decision to continue HRT beyond 10 years has to be made on an individual basis in view of the increased risk of breast carcinoma after 5–10 years of therapy.

In individuals with secondary amenorrhoea, for example patients with autoimmune chronic active hepatitis, hypogonadism can be treated using the oral contraceptive pill or
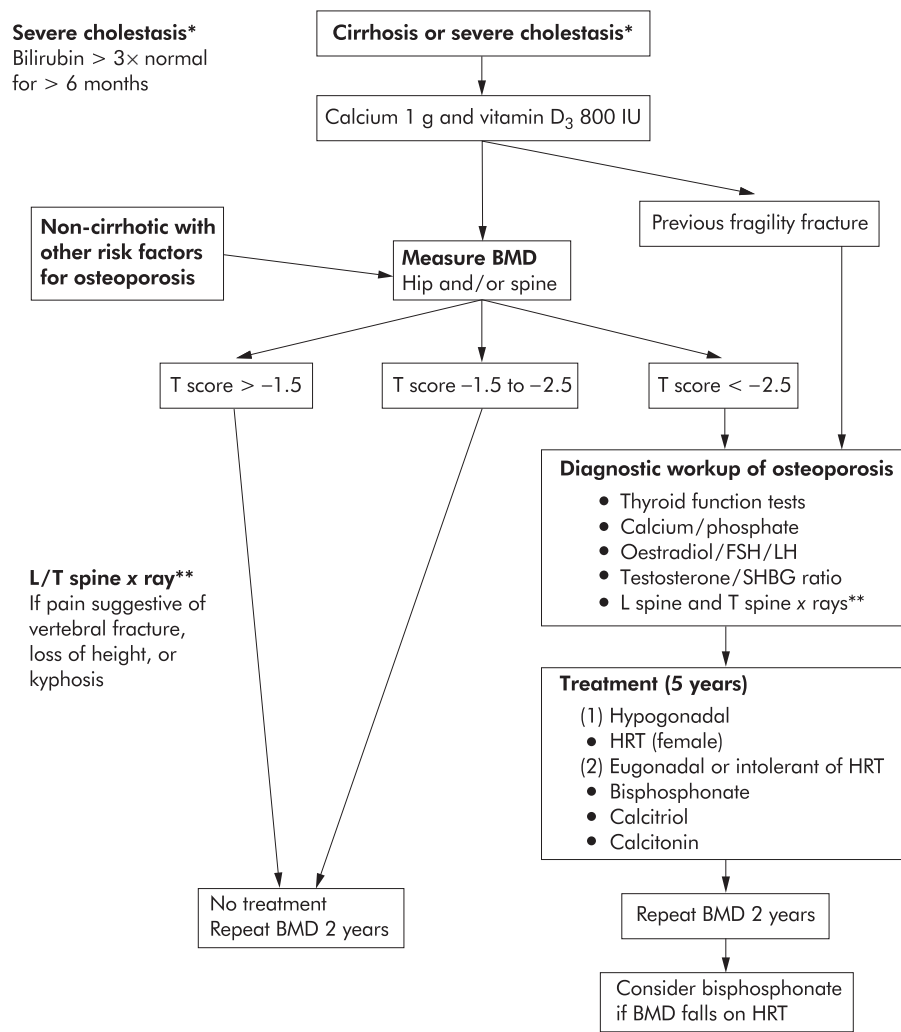
Figure 1 Summary of the strategy for prevention and treatment of osteoporosis in chronic liver disease. BMD, bone mineral density measured by dual energy x ray absorptiometry; HRT, hormone replacement therapy; SHBG, sex hormone binding globulin; FH, follicle stimulating hormone; LH, luteinising hormone.

combination HRT. The former contains ethinyl oestradiol which is less degradable than oestradiol and so may be more hepatotoxic.

HRT in postmenopausal women without chronic liver disease has been shown to increase BMD in the lumbar spine and other sites.[49] Observational studies, which may overestimate the benefits of HRT, show that oestrogens also lower the rate of veterbral and non-vertebral fractures in osteoporotic postmenopausal women.[50] There are also a few small prospective studies showing that HRT reduces vertebral and non-vertebral fracture.[51–54]

Few studies have examined the effect of HRT on BMD and fracture rates in postmenopausal or hypogonadal women with chronic liver disease. In a small retrospective study of 16 postmenopausal patients with PBC, oestrogen replacement resulted in a significant increase in BMD compared with untreated patients at one year and there was no evidence of worsening cholestasis.[42] Long term controlled studies are needed to assess the effect of HRT on BMD and fracture rates in hypogonadal women with chronic liver disease.

9.4 Testosterone
Testosterone replacement in hypogonadal men without chronic liver disease leads to increases in BMD.[55] The role of testosterone in eugonadal men is still under evaluation. In a small study of 23 men with fractures, testosterone given for six months resulted in an increase in spinal BMD.[56] In a trial of testosterone in patients with corticosteroid induced osteoporosis, some of whom were hypogonadal, there was also a significant increase in spinal BMD.[57]

There are no studies of the effects of testosterone replacement in patients with chronic liver disease on BMD and the subsequent fracture risk. Although hypogonadism is reported in male cirrhotics with chronic liver disease and male patients with end stage liver disease being assessed for liver transplantation, the overall prevalence is unknown.[12 13 58]

In patients with chronic liver disease an increase in testosterone binding globulin levels may occur and total serum testosterone levels may overestimate free testosterone. Total testosterone should therefore be expressed in relation to testosterone sex hormone binding globulin (SHBG) levels *if free testosterone levels cannot be measured.*

One concern about restoring testosterone levels to normal in cirrhotics is that this might increase the risk of hepatocellular carcinoma. Cirrhotics have relatively high oestrogen levels and male sex is a major risk factor for hepatocellular carcinoma. As the relative risk of inducing hepatocellular carcinoma in relation to testosterone levels is not known, the potential risk/benefit must be discussed with individuals before starting replacement therapy. Transdermal testosterone is the preferred route of administration in cirrhotic patients as it leads to stable testosterone concentrations within the normal range, therefore avoiding exposure of the liver to the high levels seen with oral preparations, depot injections, or implants.

9.5 Bisphosphonates
Bisphosphonates include oral alendronate, cyclical etidronate, and risedronate. In postmenopausal women with osteoporosis without liver disease, bisphosphonates increase BMD and

decrease the incidence of veretebral and non-vertebral fractures.[59] There are no comparative studies comparing the different preparations. Oral alendronate, which can be given as a daily dose of 10 mg or as a 70 mg dose weekly, may cause oesophageal ulceration and so should be avoided in patients with cirrhosis who may have portal hypertension and oesophageal varices because of the potential to precipitate a variceal haemorrhage. No adverse effects on the oesophageal mucosa have been reported with risedronate in clinical trials although post marketing data are not yet available.[60]

Cyclical etidronate has been given safely for up to seven years. However, there is some theoretical concern about the use of long term bisphosphonates as although they increase BMD they may also increase bone mineralisation with potential adverse effects on bone strength.

Bisphosphonates are also effective in preventing corticosteroid induced osteoporosis in patients with PBC. In a randomised placebo controlled trial of 12 patients with late stage PBC who were given 10 mg of prednisolone for >1 year and who had normal z scores at baseline, cyclical etidronate prevented the fall of 3 SD in BMD which was seen in untreated patients.[37] There are no long term studies of bisphosphonates in preventing fractures in individuals with chronic liver disease.

Bisphosphonates should be taken on an empty stomach in the morning, 0.5–2 hours before consumption of food and other drugs, and at a different time to calcium supplements as calcium binds and inactivates bisphosphonates.

9.6 Calcitonin
Calcitonin prevents bone loss in postmenopausal women with osteoporosis and some randomised controlled trials have shown a decrease in vertebral fracture rate. Calcitonin given with calcium for six months in a randomised controlled crossover study in women with PBC with a z score of −2 did not affect the rate of bone loss compared with a control group treated with calcium alone.[17] However, calcitonin has to be given either subcutaneously or intramuscularly, which has limited its use. An intranasal preparation is likely to be available in the near future.

9.7 Anabolic steroids
These drugs can cause abnormal liver biochemistry and should be avoided in patients with chronic liver disease

9.8 Combination therapies
The role of combination therapy in managing postmenopausal osteoporosis is a current area of interest. In a small non-randomised controlled study of patients with PBC, whose lumbar spine BMD was less than 0.8 g/cm^2, three years of treatment with 0.5 μg daily of calcitriol (1,25 dihydroxyvitamin D), 1.5 g of calcium, and 40 Medical Research Council units of carbocalcitonin, given subcutaneously three times a week, resulted in an improvement in bone density in the treated group compared with baseline values.[19]

10.0 MANAGEMENT OF THE INDIVIDUAL PATIENT
10.1 Patients at risk of osteoporosis
The following are strong risk factors for osteoporosis, even in the absence of chronic liver disease as defined below, and the presence of one or more of these risk factors *in any individual with liver disease* is an indication for bone density measurement and consideration of therapy to prevent subsequent fracture:

- oral prednisolone 5 mg or equivalent for three months;
- hypogonadism (premature menopause (age <45 years), prolonged secondary amenorrhoea >6 months, primary hypogonadism);
- height loss >4 cm;
- *x* ray evidence of osteopenia;

- history of early maternal hip fracture (<60 years); and
- low body mass index (<19 kg/m^2).

The presence of a fragility fracture denotes severe osteoporosis and patients should be offered treatment without the need for BMD measurement

Patients with chronic liver disease, as defined below, should also have BMD performed. BMD measurement is not indicated routinely in other patients with liver disease as there is no evidence at present that osteoporosis is more prevalent in patients who are non-cirrhotic and not cholestatic but further controlled studies are needed.

Guidelines for the management of corticosteroid induced osteoporosis have recently been published.[2]

10.2 Definition of chronic liver disease
Chronic liver disease is defined as cirrhosis, clinically or histologically proved, or severe cholestasis (bilirubin more than three times the upper limit of normal for more than six months).

10.3 General measures for all patients with chronic liver disease
(1) Lifestyle measures (recommendation grade C)
- Reduction in alcohol intake if excessive.
- Regular weight bearing exercise.
- Stop smoking.

(2) Dietary (recommendation grade C)
- Ensure adequate nutrition as low body mass index is an independent risk factor.
- Supplementation with calcium (1 g/day)+vitamin D$_3$ (800 U/day).

There is no risk of hypercalcaemia except in patients with sarcoidosis where calcium levels should be monitored.

10.4 Diagnostic workup if osteoporotic (T score <−2.5 or fragility fracture) (recommendation grade C)
(1) BMD (DXA) lumbar spine and femoral neck
- The T score refers to the lumbar spine or femoral neck: if normal, repeat in two years; if osteopenic (T −1 to −2.5) repeat in two years; and if osteoporotic (T <−2.5) consider treatment.

(2) Lumbar and thoracic spine *x* rays (lateral and anteriorposterior)
- This is indicated if there is a clinical suspicion of spinal fracture (kyphosis, height loss, or back pain), as this is an indication for treatment, irrespective of bone density.

The prevalence of asymptomatic vertebral fractures in patients with chronic liver disease is unknown and needs further study. However, in one study of 37 patients with chronic liver disease undergoing assessment for liver transplantation, 35% were found to have one or more prevalent vertebral fractures.[61]

10.5 Additional assessment in patients with osteoporosis (recommendation grade C)
10.51 Thyroid function tests
10.52 Bone function tests
These include corrected serum calcium and serum phosphate. In a few patients, 800 IU vitamin D may be insufficient. If calcium remains below the normal range with supplementation, further investigation including 25-OH vitamin D and parathyroid hormone levels are needed. As serum calcium may be normal in vitamin D deficiency, consider checking 25-hydroxyvitamin D level after 3–6 months of supplementation.

10.53 Serum oestradiol and LH/FSH
These should be assessed if there is menstrual irregularity or other evidence of hypogonadism in premenopausal women. In hypogonadism, low oestradiol levels are accompanied by

elevated luteinising hormone (LH) and follicle stimulating hormone (FSH) levels.

10.54 Serum testosterone/SHBG/LH/FSH
Free testosterone is a better index of gonadal status than total testosterone but cannot be measured by all laboratories. If total testosterone is being measured it is important to express it as a ratio of SHBG to total testosterone as SHBG is often high in alcoholics. A ratio of total testosterone/SHBG (free testosterone index) <0.3 indicates hypogonadism. Serum for testosterone levels should be taken in the morning because of the significant diurnal variation in levels.

10.55 Serum 25-OH vitamin D
This is indicated in patients who are at high risk of vitamin D deficiency—that is, housebound individuals or coexistent malabsorption—or if hypocalcaemic (see bone function tests above). It should also be measured in patients with chronic cholestasis at baseline and to monitor adequacy of vitamin D supplementation, particularly in the presence of coexistent fat malabsorption.

10.6 Therapeutic interventions
The optimum duration of therapy has not been established. The current recommendation is that treatment should be given for a minimum of five years and bone density repeated after two years and at the end of treatment.

(1) Treat hypogonadism (recommendation grade C)
- Hypogonadism is defined in 10.5 above. In women, oestrogen replacement, with progesterone, should be offered to premenopausal women. Transdermal HRT for premenopausal or postmenopausal women (oestrogen only if no uterus otherwise combined/sequential or combined/continuous HRT) can be given. The oral contraceptive pill can be given to premenopausal women who also need contraception.
- For men, transdermal testosterone can be given to hypogonadal men (only after discussion of the theoretical risks of hepatocellular carcinoma).

(2) Unable to take HRT/testosterone or eugonadal (recommendation grade C)
- The bisphosphonates include didronel PMO, alendronate (this should be used with caution because of oesophageal side effects), and risedronate. Bisphosphonates should be considered in all patients who have had a fragility fracture or have a T score <−2.5. They can be used either initially with HRT or if further bone loss occurs despite HRT.

(3) Calcitriol and calcitonin
- These agents should be considered in those with osteoporosis who are either intolerant of HRT and bisphosphonates or whose BMD worsens despite either use of bisphosphonates or treatment of hypogonadism.

10.7 Monitoring and follow up (recommendation grade C)
If therapy has commenced, bone density should be repeated in two years and again at the end of treatment. If no therapy has been instituted, repeat bone density in two years.

11.0 FUTURE AREAS OF RESEARCH
There are no large randomised controlled trials of interventions in patients with chronic liver disease and osteoporosis and the guidelines are consequently largely based on expert opinion (level C). The development of these guidelines has highlighted the need for clinical research in several areas. Current research requirements include:

(1) a prospective study of the prevalence of fractures in patients with chronic liver disease;

(2) a study of the prevalence of osteoporosis in patients with all stages of PBC compared with sex and age matched controls;

(3) a prospective study of the prevalence of hypogonadism in males with cirrhosis with and without osteoporosis;

(4) assessment of the safety of restoring testosterone levels to the normal range in patients with cirrhosis; and

(5) a two year placebo controlled randomised trial of the effects of intervention (a bisphosphonate proven to have anti-fracture efficacy in postmenopausal women or HRT) on BMD in patients with cirrhosis.

12.0 APPENDIX
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