Osteoporosis in patients with chronic liver disease: An unfamiliar late complication

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Abstract
Hepatic osteodystrophy is a frequent late complication in chronic liver diseases in which patients usually present bone mineral density reduction, osteopenia, osteoporosis and fractures. Strategies to decrease incidence, avoid comorbidity and improve patient quality of life have yet to be implemented in clinical practice. Hepatic osteodystrophy’s pathophysiology is poorly understood. There is controversy about the use of screening tests especially regarding which patients are eligible, at what moment of the disease and with what frequency. Risk factors which are dependent on liver disease and other risk factors which are not liver disease dependent have been identified, all of which affect the natural history of hepatic osteodystrophy and all of which must be taken into account for screening, checkups and treatment. Recommendations for treatment are widely discussed but focus mainly on reduction of risk factors, antiresorptive drugs, calcium supplements and vitamin D.

Key words
Hepatic osteodystrophy, osteoporosis, chronic liver disease, bone mineral density, fractures.

INTRODUCTION
Liver cirrhosis, especially at reaches chronic levels, creates a series of changes in the organism. The term hepatic osteodystrophy usually refers to osteomalacia and osteoporosis in the presence of chronic liver disease (1). A stronger association has been found between cirrhosis and osteoporosis than between cirrhosis and osteomalacia. While osteomalacia is found infrequently among cirrhosis patients (5), 12 to 55% of these patients have been found to have osteoporosis in different studies (2-4): 50% of hepatitis C virus patients, 10% of hepatitis B virus patients and, 30% of patients with alcoholic liver disease and autoimmune disease. Osteomalacia is usually reported to be related to cholestatic diseases such as primary biliary cirrhosis (PBC) and sclerosing cholangitis (6).

Although the pathophysiology of osteoporosis in cirrhotic patients is not completely understood, it primarily affects the trabecular bone and is characterized by diminished bone mineral density (BMD), poor functioning of osteoblasts, increased osteoclastic cell activity and low levels of osteocalcin (6). It is known that osteoporosis is directly related to the type, severity and progression of liver disease.

Cirrhotic patients present lower levels of 25-hydroxyvitamin D and 1,25 dihydroxyvitamin D. They also have diminished bone mineral density, most frequently in the spine.

The diagnosis of osteoporosis in cirrhotic patients requires high clinical expertise because there are no symptoms during the initial stages.

PREVALENCE OF OSTEOPOROSIS IN PATIENTS WITH CHRONIC LIVER DISEASE

The prevalence of osteoporosis in chronic liver diseases is summarized in Table 1 (5), which summarizes results from studies performed mainly on patients with chronic cirrhosis.
Table 1. Prevalence of osteoporosis and fractures in patients with liver disease.

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Cases</th>
<th>Age (Med/Ran)</th>
<th>Fem %</th>
<th>Postmenop %</th>
<th>Osteoporosis</th>
<th>Osteopenia</th>
<th>Other Fractures</th>
<th>Liver Disease Etiology %</th>
<th>Other EHA</th>
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<tr>
<td><strong>Primary biliary cirrhosis</strong></td>
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<tr>
<td>Guañabens et al. (13)</td>
<td>38</td>
<td>51 (37-62)</td>
<td>100</td>
<td>63</td>
<td>DPA</td>
<td>45</td>
<td>13 NR</td>
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<td>55 (34-81)</td>
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<td>68</td>
<td>DPA</td>
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<td></td>
<td>24</td>
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<td>54 ± 1.1</td>
<td>100</td>
<td>79</td>
<td>DXA</td>
<td>21</td>
<td>10 10 13</td>
<td>100</td>
<td>100</td>
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<td>176</td>
<td>53 (29-72)</td>
<td>83</td>
<td>45</td>
<td>DXA</td>
<td>20</td>
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<tr>
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<td>63</td>
<td>DXA</td>
<td>31</td>
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<tr>
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<td>53 (21-81)</td>
<td>100</td>
<td>70</td>
<td>DXA</td>
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<td>54 ± 0,8</td>
<td>100</td>
<td>69</td>
<td>DXA</td>
<td>31</td>
<td>14 11 14</td>
<td>100</td>
<td>100</td>
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<tr>
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<td>53 ± 0,7</td>
<td>86</td>
<td>76</td>
<td>DXA</td>
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<td>22 NR</td>
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<td>185</td>
<td>56 (28-79)</td>
<td>100</td>
<td>82</td>
<td>DXA</td>
<td>32</td>
<td>11 12 21</td>
<td>100</td>
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<td><strong>Mixed liver disease</strong></td>
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<td>115</td>
<td>50 (20-74)</td>
<td>37</td>
<td>30*</td>
<td>QCT</td>
<td>16**</td>
<td>16 17 28</td>
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<td>133</td>
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<td>26</td>
<td>24 26 36</td>
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<td>7 ND</td>
<td>12 73</td>
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<td>50 (32-60)</td>
<td>32</td>
<td>74</td>
<td>DXA</td>
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<td>24 65 11 100</td>
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<td>46</td>
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<td>16 22 35 11 3 13 100</td>
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<td>243</td>
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<td>47</td>
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<td>19 30 29 7 2</td>
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<td>Carey et al. (26)</td>
<td>207</td>
<td>51 (32-68)</td>
<td>37</td>
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<td>14 10 24</td>
<td>67 33</td>
<td>0 100</td>
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<tr>
<td>Sokhi et al. (27)</td>
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<td>54 ± 1,3</td>
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<td>DXA</td>
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</tbody>
</table>

HMC: Hemochromatosis. CH: Chronic hepatitis. ALD: Advanced liver disease.

**Osteoporosis Z-score < 2.0.

From: Guañabens N, Parés A. Liver and Bone. Archives of Biochemistry and Biophysics [serial on the Internet] 2010; 503
cholestatic diseases, primary biliary cirrhosis and a study of patients with varied liver diseases.

Four diagnostic categories (9) have been established based on the percentages of osteopenia and osteoporosis reported by the European Foundation for Osteoporosis and Bone Disease, the National Osteoporosis Foundation in the United States and by the World Health Organization WHO (7, 8).

- Normal (T score): mineral bone density (MBD) less than 1 standard deviation (SD) below the T score.
- Low bone mass or osteopenia: MBD greater than 1 but less than 2.5 SD below the T score.
- Osteoporosis: MBD greater than 2.5 SD.
- Severe or established osteoporosis: MBD greater than 2.5 SD and 1 or more vertebral compression fractures.

It is important to mention that there are different densitometric criteria used for osteoporosis in different studies. Consequently Table 1 defines osteoporosis postmenopausal women as T scores greater than 2.5, but defines it as Z scores greater than 2 for men who are less than 50 years old and for premenopausal women.

A series of 185 female Spanish patients with chronic cholestasis in which the lumbar spine was affected more than the femoral neck found that up to 37% of the patients had osteoporosis (10).

A study performed by Joe George and colleagues in India in 2009 found decreased BMD in 68% of the patients diagnosed with cirrhosis. These patients were divided into groups according to etiology: 72% of the group with hepatitis B had decreased BMD, as did 100% of the group with hepatitis C and 56.7% of the alcoholic cirrhosis group. The study also showed that the loss of BMD was the same for all classifications according to the Child score (11). The impact was greater and more severe in the trabecular bone (lumbar spine) than in the cortical bones (femoral neck). The mean of densitometric measurements was -2.28 ± 1.1 in the spine, 1.27 ± 0.74 in the hips, -1.3 ± 0.8 for the trochanter; and 0.75 ± 0.86 in the femoral neck (12).

Similarly, in a large series of patients at the Mayo Clinic, Menon et al. found that up to 20% of patients with primary biliary cirrhosis had osteoporosis (16). Although osteoporosis has been proven to be more frequent among women with PBC than among healthy women (10, 16, 19), there is a still debate on whether osteoporosis is a specific complication of PBC or is simply related to postmenopausal age among women (17, 18).

The data are not yet conclusive (4, 20) for non-cholestatic disorders such as hemochromatosis (25 to 34%) (23, 30) or for disorders which are more frequent causes of chronic liver diseases such as viruses and alcohol ingestion.

Contradictory results have been obtained regarding the relation of chronic viral hepatitis and its treatment with ribavirin and interferon and osteodystrophy. There have been studies that show no significant relation (31) while others show prevalences of nearly 100% (12). Non-conclusive evidence has been found regarding the relation between antiretroviral therapy for hepatitis and the development of unprecedented osteopenia (6, 32-37).

Alcohol consumption leads to abnormal liver function, is directly related to decreased BMD, and doubles risk of fractures. High risk levels of alcohol consumption can be defined by the following criteria (38):

- Men: 280 g/week (40g/day) of pure alcohol
- Women: 168 g/week (24g/day) of pure alcohol
- 80 grams/day, at least once a month, whether or not the weekly limit is exceeded
- Any consumption by pregnant women and minors or by people with pathologies for which alcohol consumption is discouraged or whose treatments are incompatible with alcohol consumption.

Various studies have shown that a high percentage of patients with chronic alcoholism have a significantly decreased BMD. Up to 29% have osteoporosis regardless of liver involvement (39-43).

It has been shown that after two or more years of abstinence there is significant bone mass improvement and the reduction of fracture risk (41).

24-38% of patients with chronic liver disease have osteoporosis according to the densitometric criteria reported in Table 1 (5). Guichelaar et al. conducted a study of 360 patients with advanced cholestatic disease (PBC and primary sclerosing cholangitis) and found that 38% had osteoporosis, 39% osteopenia and 23% had normal bone mass.

Other series show percentages from 12% to 55% in patients varying in age, etiologies, degree of liver disease, nutritional state and hypogonadism (1-4).

Many patients with terminal liver disease are transplant candidates (44). Transplantation has been associated with osteoporosis and increased risk of fractures, especially lumbar fractures, for several decades (1, 5). Osteoporosis and fractures occur primarily in the first few months following transplants, a period that is characterized by significant weight loss due to factors such as administration of immunosuppressants and glucocorticoids (reviewed below). It has been proven that BMD decreases by about 6% three months after transplantation. After adequate monitoring, lumbar BMD reaches reference values two years after surgery. However, femoral BMD may take up to 5 years to reach reference values.
Transplantation is an additional cause of osteoporosis and fractures, particularly during the first months after surgery, a period associated with a high rate of bone mass loss (5, 10, 45).

PREVALENCE OF FRACURES AMONG PATIENTS WITH CHRONIC LIVER DISEASE

Fracture prevalence among patients with chronic liver disease ranges from 7% to 35% in the studies shown in Table 1 (4, 5, 16, 19). A recent study by Parés and Guanábens of 170 patients with primary biliary cirrhosis showed an 11.2% prevalence of vertebral fractures, 12.2% for non-vertebral fractures and 20.8% for general fractures (10). Although prevalence of fractures among patients with alcoholic disease has hardly been evaluated, one study found that fractures were present in 36% of 76 men with alcoholic cirrhosis (22). In effect, this study has elated alcohol consumption to fractures. The appearance of osteoporotic fractures was evaluated in a meta-analysis of patients who did not consume alcohol and those who drank more than two glasses a day. That study found that the latter group had a greater risk of hip fractures and diminished BMD (46). Vertebral fractures are frequent among terminal cirrhosis patients and among transplant patients, especially during the first 6 to 12 months (22, 24, 41) when incidences range from 22% to 65% (16). The highest fracture rates are found in immunosuppressed patients with cholestatic diseases (5).

PATHOPHYSIOLOGY OF HEPATIC OSTEODYSTROPHY

The skeletal system is one of the main systems of the organism. Its active cellular components and bone matrix have several key functions, the most important of which is protection and support of the soft tissues (e.g. the cardiovascular system), support for the muscular system allowing for body movement, provision of a reservoir of ions such as calcium and phosphorous, as an active deposit of bone marrow which plays a leading role in hematopoiesis (47) (Figure 1).

Bone regulation maintenance depends on bone density and bone quality. The latter is understood as architecture, bone renewal, accumulation of injuries, and mineralization.

Any rupture in the balance of bone regulation can lead to fragility and increased risk of fracture. Support for this conclusion is to be found in the statistics which indicate that the probability of a 50 year old person developing a hip fracture is 14% for women and 5% to 6% for men (48) while the probability that postmenopausal women will develop some degree of vertebral deformity is 25% (49).

Osteoporosis in patients with chronic liver disease: An unfamiliar late complication

Osteoporosis is defined as “a systemic skeletal disease, characterized by low bone mass and deterioration of the bone tissue’s microarchitecture which increases bone fragility and consequently increases risk of bone fractures” (48). This definition has also been adopted by the WHO. Its clinical significance lies in the fractures which are its consequences and in the ensuing morbidity and mortality which can result (52).

The etiology of osteoporosis in patients with chronic liver disease has yet to be clarified. Various authors have proposed that many factors can intervene in the formation of liver osteodystrophy. Among them are nutritional state, active alcoholism, physical exercise, toxins such as tobacco, diseases such as diabetes, bone fractures in adults and the severity of liver disease. Nutritional state can be evaluated by skinfold measurement and the severity of cirrhosis can be evaluated with the Child-Pugh classification (11). The other the variables are determined by the patient’s clinical history (53).

The table 2 presents risk factors for the development of osteoporosis which are independent of bone mineral density (1).

Other recently described factors that have become important are (54) rheumatoid arthritis which it may appear in an autoimmune context such as autoimmune hepatitis and Type 2 diabetes mellitus which is common in patients with fatty liver disease associated with metabolic syndrome.
Figure 1. Pathophysiology of hepatic osteodystrophy. Continuous arrows represent established routes, discontinuous lines represent routes that have insufficient evidence. Osteoclast precursors are activated by pro-inflammatory cytokines like TNF α, whose levels increase in patients with viral hepatitis and alcoholic liver disease. Colony stimulating factor 1 (Csf1) binds to its receptor c-fms to induce osteoclastogenesis. An increase in Csf1 levels has been identified in patients with cholestatic liver disease which might be induced by inflammation of this organ. IL-17 is a cytokine produced by a subset of T lymphocytes (Th 17 cells). Their numbers increase in patients with alcohol related liver disease which may induce bone loss. RA NKL is a key regulator for osteoclast functioning. It binds to its RA NKL receptor to induce osteoclastogenesis. OPG is a decoy receptor that inhibits RA NKL-RA NKL-OPG axis may or may not have an important role in bone loss associated with chronic liver disease. Vitamin D, PTH, IGF-I and oncofetal fibronectin affect the formation of osteoblasts. The oncofetal fibronectin produced by activated star cells suppresses osteoblasts and bone formation in patients with primary biliary cirrhosis. Intermittent HPTH 1-34 secretion stimulates osteoblasts into functioning but has not been studied in patients with liver disease (50). Modified from: Nakchbandi A, Schalk W. Current Understanding of Osteoporosis Associated with Liver Disease 2009; 6(11): 660-70. Review.
Bone densitometry is a precise procedure for establishing a diagnosis for osteoporosis (58). Patients with chronic liver disease should be evaluated for osteoporosis and osteopenia, especially those with the following risk factors: chronic alcohol consumption, smoking, early menopause, body mass index (BMI) < 19 kg/m², male hypogonadism, secondary amenorrhea for more than 6 months, hemochromatosis, family history of fractures and osteoporosis, and glucocorticoid treatment of 5 mg/day for more than 3 months (5).

However, there is controversy about what is the right moment to perform bone densitometry. Some authors believe that it should be performed when a patient has had previous fractures, exposure to glucocorticoids and prior to a liver transplant. In addition, BMD evaluation seems appropriate for primary biliary cirrhosis, chronic cholestasis, cirrhosis, some individuals with risks for fractures mentioned above and for those who have received a transplant (19).

Another topic of discussion that arises frequently when defining BMD measurements is that it should be performed every year or two in patients with chronic cholestasis with risk factors, patients who have been treated with glucocorticoids and liver transplants. Measurements every three years should be performed on patients with normal test results and those with low risk of developing osteoporosis (5).

The American Gastroenterological Association guidelines suggest that bone mineral density should be measured in all patients diagnosed with primary biliary cirrhosis and patients with bilirubin three times the upper limit. A study performed at the Mayo Clinic found that 26% of patients with primary sclerosing cholangitis require liver transplants and also met the criteria for osteoporosis. For this reason this group of patients received periodic mineralization tests (1, 3).

Screening tests must be performed to prevent fractures and their recurrence (59) because they are associated with declining quality of life. Lumbar and femoral bone densitometry, lumbar and dorsal x-rays are recommended to rule out vertebral fractures. Measurement of serum calcium, parathyroid hormone, phosphorous and vitamin D is also recommended. Perform of renal function tests and PTH measurements in patients with chronic cirrhosis complications such as type-2 hepatorenal syndrome are also important since this condition could worsen bone mineralization.

Measurement of biochemical markers for bone turnover such as alkaline phosphatase, serum osteocalcin, type-I serum peptide (formation), N-telopeptide, C-telopeptide, Deoxypyridinoline (resorption) can be useful for monitoring individual reactions to treatment for osteoporosis (60). However, there is little information on how this is modified by chronic liver disease given that the degree of hepatic fibrosis can interfere with the markers’ levels (59, 61). Bone biopsies are only indicated when mineralization disorders are suspected, and these disorders are rare in liver diseases (62).

**PREVENTION AND TREATMENT**

Most important among measures for prevention of BMD loss and development osteoporosis is decreasing risk factors such as alcohol, body mass index and smoking. Physical exercise is also recommended for patients who do not have other contraindicating pathologies.

A study of 75 cirrhotic men performed in the Basurto Hospital in Bilbao, Spain found that 82.3% of the parti-
Participants showed bone loss in the lumbar spine and 17.7% in the necks of both femurs. The body fat percentage was 28.92% in non-osteopenic patients and 27.69% in osteopenic patients. The body fat percentage was also slightly lower for the group with osteopenia (9). Even though this study concluded that fat percentages and nutritional states were unrelated to bone mass loss, other sources support the relation between poor nutritional state and BMD.

It is important for patients to receive 1,000mg to 1,500mg daily calcium supplements and either 260mg of hydroxyvitamin D for two weeks or 800U of oral vitamin D3 daily (5000 U/week). When it is possible to perform periodic tests it is even desirable to set doses at levels required to maintain normal levels (5). Since studies have not yet been performed to establish vitamin D supplement and calcium dosages for patients with chronic liver diseases, a simple scheme could be 800 UI of vitamin D and 1 gram of calcium per day.

A study of 25 patients with alcoholic cirrhosis and low serum vitamin D levels found that administering hydroxyvitamin D3 raised BMD above initial levels. Another study of 76 patients with cirrhosis showed that the use of 1 alpha 25 hydroxyvitamin D3 resulted in brief increases of BMD in the lumbar spine though no data was obtained on whether the supplement really diminishes risk of fracture. Patients with poor absorption may require higher doses (63, 64).

Hormone replacement has been poorly studied in patients with chronic liver diseases since it is considered that high levels of ethinylestradiol may worsen the initial condition especially in women whose hepatic fibrosis is in advanced stages. Nevertheless, several studies have shown that hormone replacement can be used safely in this group of patients. If possible, hormones should be administered subdermally since this minimizes the impact on the diseased liver. The recommended dosage is 50mcg/day, and the duration of treatment should be between 5 and 10 years, even though there are guidelines yet that recommend specific treatment time. Even though the relation between BMD and hormone replacement has not been thoroughly studied, the data which does exist shows increments in bone mineralization. Similarly, even though testosterone replacement has been proven to be beneficial for BMD in male patients with hypogonadism, it has not been studied in patients with chronic liver diseases (5, 59, 61). The percentage of cirrhotic patients with hypogonadism is unknown but believed to be high, especially in the late stages of the disease. It is known that high levels of testosterone can increase the risk of hepatocellular carcinoma which is why the risk-benefit trade-off of replacement therapy should be evaluated for each patient. As with estrogen, the preferred method of administration is subdermal.

Bisphosphonates, widely used in osteoporosis treatment, have had favorable results for BMD and in decreasing vertebral and non-vertebral fracture risk. There are no studies comparing the effectiveness of different bisphosphonates. 10 to 70 mg doses of alendronate may be used weekly, but it must be noted that it can cause esophageal ulcerations which is why it must be used with precaution on patients with portal hypertension that might develop esophageal varices. This complication has not been reported with Risedronate. Cyclic etidronate has been used safely for several years without complications. The use of bisphosphonates has become important in preventive treatment of osteoporosis in patients who receive glucocorticoids for underlying diseases including autoimmune hepatitis and primary biliary cirrhosis and following transplants. This treatment has resulted in BMD improvement in all of these types of patients. Zoledronic acid, a powerful bisphosphonate, significantly decreases acute bone loss following transplants. It is administered 7 days after transplantation and then at the end of the first, third, sixth and ninth months after transplantation (1, 65).

Bisphosphonates must be taken 2 hours before breakfast, and immediate consumption of other medicines or supplements such as calcium which bond with and inactivate bisphosphonates must be avoided. The use of low or pulsatile doses of pulsatile parathyroid hormone (PTH) contributes to bone formation and remodeling, although it has not been studied in patients with chronic liver disease (5, 59, 61).

Calcitonin has been used in postmenopausal women with osteoporosis to prevent vertebral fractures and increase mineralization, but its results have not been entirely satisfactory. Calcitonin administered intramuscularly or subdermally has yet to be evaluated in patients with chronic liver diseases. For this reason its use is not recommended and is limited to a last option when antiresorptive drugs do not have any effect or are counter indicated. The recommendations of the American Gastroenterological Association about osteoporosis in patients with liver disorders supports the treatments mentioned above (64).

CONCLUSIONS

• Hepatic osteodystrophy is a rarely used term in daily clinical practice. It refers to the presence of osteopenia or osteoporosis in patients affected by chronic liver diseases. Prevalence lies somewhere between 12% and 55% according to various studies. Prevalence is related to the type, evolution and severity of these diseases.

• It was found that the prevalence of osteoporosis among patients with hepatotropic virus infection is up to 100% to 56.7% among patients with alcoholic cirrhosis.
Bone densitometry is the diagnostic and monitoring procedure of choice for hepatic osteodystrophy. It should be performed every 1 or 2 years for patients with fracture risks and every 3 years if the initial test results are normal or show low risks.

- Lumbar and dorsal x rays are suggested to rule out vertebral fractures. Measurements of serum calcium, parathyroid hormone, phosphorus and vitamin D are also recommended.

- Measurement of bone turnover biomarkers is not standard but may be used according to the opinion of the treating physician.

- All patients require education regarding lifestyle changes.

- All patients should receive 1 gram to 1.2 gram doses of elemental Calcium and 400-800 IU of vitamin D daily. Vitamin D deficiency may be corrected by increasing serum levels of 25 hydroxyvitamin D to between 25ng/mL and 30ng/mL.

- Hormone replacement (sub dermal administration is preferred) in women younger than 45 y/o with hypogonadism or menopause prevents the development of osteoporosis.

- The use of testosterone is recommended for men with hypogonadism.

- Bisphosphonates should be considered for patients with osteoporosis, vertebral fracture or for patients who must continue using corticosteroids after three months of treatment. They are approved by the Food and Drug Administration (FDA) for treating and preventing fractures, so they may be used safely for patients with chronic liver diseases (special precaution must be taken with patients who have portal hypertension).

- The use of parathormone is FDA approved even though its efficiency has yet to be evaluated in patients with hepatic dystrophy.

REFERENCES


