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Hepatic Osteodystrophy: Pathophysiology, diagnosis and management

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Abstract: *Hepatic osteodystrophy is commonly observed in patients with the chronic liver disease with disease severity related to more bony loss. Liver transplantation and immunosuppressive therapy further aggravate the bony loss in patients of chronic liver disease. Hepatic osteodystrophy may constitute either osteopenia or osteoporosis. Osteopenia is diagnosed when bone mineral density (BMD) is 1- 2.5 standard deviation below the reference value. Osteoporosis is diagnosed when the bone mineral content is greater than two standard deviations below the control mean value, matched for age and sex. Various techniques are used to measure the BMD which helps in early identification of bone loss in chronic liver disease. Management options include nutrition therapy, hormone replacement, and various drugs.*

Keywords: *Hepatic Osteodystrophy, bone mineral density Osteoporosis*

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I. Introduction

Hepatic Osteodystrophy is a disease of multifactorial origin associated with the chronic liver disease. The reported prevalence of hepatic osteodystrophy ranges from 13-70% based upon bone mineral density (BMD) measurements[1,2]. Disturbances in the endocrine calcium-parathyroid hormone (PTH) –Vitamin D axis seems to play a role in the pathogenesis of hepatic osteodystrophy.

Patients with cirrhosis may ultimately require liver transplantation, and immunosuppressive therapy, which further leads to more bony loss[3]. Recognition of patients at risk may help to prevent bone loss before the development of fractures. The rate of fractures ranging from 17%-60% has been seen in the first year after liver transplantation[4]. There are many methods which help in measuring the bone mineral density and assessing for hepatic osteodystrophy. Dual Energy X-ray Absorptiometry (DEXA) is the gold standard to measure bone mass because it is accurate and can measure multiple skeletal sites[5].

II. Research Methodology

Electronic databases of Google Scholar and MEDLINE (PubMed) search engines were searched for relevant studies and reviews published from all time since the inception of the database. The keywords used were "Hepatic osteodystrophy" "pathophysiology" "diagnosis" "management" "treatment." Also, the reference list of relevant recently published articles and reviews were also screened. Titles, abstracts, and full-texts of peer-reviewed articles about related topics published were included for the study. Only articles published in English were included.

III. Pathophysiology Of Hepatic Osteodystrophy

The liver has a critical role in Vitamin D metabolism by hydroxylation and consequently the formation of biologically active metabolites[6]. Low serum 25-hydroxy Vitamin D concentrations have been reported in patients with a variety of hepatic disorders such as primary biliary cirrhosis (PBC), alcoholic liver disease (ALD) and chronic liver disease. These low circulating serum 25- hydroxy Vitamin D levels are due to impaired metabolism, low dietary intake, impaired cutaneous synthesis, and malabsorption of Vitamin D[7]. Disorders of Vitamin D metabolism in turn cause disturbances in calcium homeostasis which leads to osteomalacia, possibly sometimes complicated by secondary hyperparathyroidism, osteoporosis, and periosteal new bone formation[8].

Although diet was believed to be the primary source of Vitamin D in man, it has been shown that endogenous skin synthesis is quantitatively the most important source of Vitamin D. Cholecalciferol (Vitamin D3) is produced from the 7-dehydrocholesterol in the skin in the presence of ultraviolet light[9].

Early evidence for impaired hepatic production of 25(0H)D in liver disease has been observed by Hepner et al. who showed an impaired 25(0H)D response to Vitamin D in 21 patients with alcoholic cirrhosis; however, in 3 patients with primary biliary cirrhosis, a normal response was seen[10].

Vitamin D absorption is bile acid-dependent and thus reduced in chronic cholestatic liver disease. Several authors[11-13] had reported vitamin D malabsorption in patients of biliary steatorrhoea. Vitamin D insufficiency, in turn, causes decreased calcium absorption and reduced bone mineral density[14]. Diamond et al. reported a significant correlation between Vitamin D and bone mineral density in patients with the chronic liver disease. Subnormal serum concentrations of 25-hydroxy Vitamin D among patients with the chronic cholestatic liver disease have also been reported[15]. Moreover, recent clinical trials that evaluated treatment with Vitamin D or 25-hydroxyvitamin D, was unable to reverse or halt the progression of osteoporosis as assessed by the histomorphometry, bone mineral density, and fracture incidence[16].

Hepatic osteodystrophy may constitute either osteopenia or osteoporosis.

1) **Osteopenia**

Osteopenia is recognized as a complication of the chronic liver disease. Diagnosis depends upon bone density measurements (BMD). When T-score is between 1- 2.5 standard deviation below the reference value it is called as osteopenia. Osteopenia is a risk factor for the development of fractures, which may be a source of morbidity and contribute to mortality in patients already debilitated by chronic liver disease. Herbert et al. demonstrated a prevalence (13% to 39%) of osteopenia in a group of 133 patients with chronic liver disease[17].

2) **Osteoporosis**

Osteoporosis is a heterogeneous skeletal disorder characterized by bone loss,42 which may cause chronic pain, fractures, inability to participate in normal daily activities.59 Fractures, particularly of the vertebrae, hip, and forearm are seen[18].

Osteoporosis is diagnosed when the bone mineral content at clinically relevant skeletal sites is greater than two standard deviations below the control mean value, matched for age and sex. Early diagnosis requires measurement of bone mineral content at selected sites of clinical interest, particularly vertebral bone and femoral neck[19].

Osteoporosis may include either:

a) Trabecular Osteoporosis

Severe back pain, vertebral crush fractures, and kyphosis are reported in patients with chronic cholestatic liver disease[19].

b) Cortical osteoporosis

The first quantitative study of cortical osteoporosis in chronic liver disease was published by Paterson and Losowsky, who carried out metacarpal thickness measurements in 38 patients with the chronic liver disease[20]. A study by Stellon et al. [21] using metacarpal morphometry, single absorptiometry of the radius and measurements of mean cortical thickness in iliac crest biopsies found evidence of cortical osteoporosis in 28% of 36 unselected patients with the chronic cholestatic liver disease, a figure similar to that reported by Epstein et al.[22] using metacarpal morphometry alone.

Cholestatic liver disease

Conditions like primary biliary cirrhosis, primary sclerosing cholangitis have an incidence of hepatic osteodystrophy ranging from 10%-68%. Cholestasis results in an intraluminal deficiency of bile salts in the small bowel which are essential for absorption of Vitamin D. This result in decreased calcium absorption and results in the development of hepatic osteodystrophy. Low to normal levels of Vitamin D have been seen in patients of primary biliary cirrhosis (PBC) and primary sclerosing cholangitis(PSC). Oral Vitamin D is poorly absorbed in patients with the cholestatic liver disease. Excellent post liver transplant survival of the patients with end-stage PBC and PSC has been complicated by a high incidence of atraumatic fractures. Therefore, the mechanism, recognition, and management of low bone mass in chronic cholestatic liver disease have assumed new clinical importance[23].

Non-cholestatic liver disease.

A study by Cristina et al. consisting of 150 cirrhotic patients included alcoholics 57(38%), HBsAg positive41(27%) and Anti HCV positive.42(34%) in the study. DEXA scan was used for measuring bone mineral density. Fifty-seven patients (38%) with cirrhosis had osteoporosis (T score>-2.5) or osteopenia (T score between-1.5 and -2.5)[24].

Patients with cirrhosis having alcohol etiology are more prone to develop osteoporosis[25].

In a study by Diamond et al. Prevalence rates of spinal and forearm fractures were twice as high among patients with the chronic liver disease than in control subjects[15].

Bone loss following liver transplantation

Increased resorption and inadequate new bone formation are the major contributors to additional bone loss following liver transplantation. Bone loss is reported in the first few months following liver transplantation. Serial bone density measurements performed after liver transplant show that greatest bone loss occurs in the first three to six months.BMD increases by the end of the first year which reaches the levels close to preoperative values and increases above baseline values at two years[26].

Major risk factors for the development of decreased BMD post-transplant included pre-existing bone loss compounded by the additional bone loss due to immunosuppression, e.g., steroids use. Vitamin D also plays a role following liver transplantation[26].

IV. Techniques For Measuring BMD

1 **Radiography**: This is usually done on metacarpal, calcaneum femoral neck, and vertebral bodies. The significant disadvantage is that radiographic exposure is more in this modality. Approximately more than 30% bone loss must be there to be appreciated on plain radiographs[27].

2 **Neutron activation analysis**: In this technique neutrons from an accelerator bombard a small fraction of total calcium of the body, changing it into radioactive isotope. By counting its activity total calcium content of the body is estimated. However, it does not reflect the state of trabecular bone and does not correlate well with spinal bone density measurement. Another disadvantage is its large radiation dose[28].

3 **Single energy photon absorptiometry**: It requires a gamma camera, a detector that measures the beam attenuation through bone and expresses the result in bone mineral per sq cm scanned. It is useful in a population study. A significant limitation of this technique is that it reflects the status of peripheral long bones and measures primarily the cortex[29].

4 **Dual-energy photon absorptiometry**: Here radioisotopes emit photons at two different energy levels. The chief advantage of Dual-energy photon absorptiometry is that the gamma ray energy of the source is higher and it has a normal path length. This technique yields integral of all mineral within the scan path including the vertebral bodies, end plates, and posterior elements. A significant disadvantage is that vertebral compression fractures with callus formation articular facet hypertrophy, and marginal osteophytosis are also included in the integral measurement[30].

5 **Dual-energy x-ray absorptiometry (DEXA)**: The principle behind DEXA is the measurement of transmission through the body with x-rays of high and low photon energies. The main advantage is the ability to measure the bone mineral density in the spine and femur, the two most common sites of osteoporotic fractures. Other benefits include low radiation dose, short scan time, high-resolution images and excellent precision. Disadvantages are similar to those of dual energy photon absorptiometry[31].

6 **Quantitative computed tomography**: It uses a mineral calibration phantom, that is placed in the CT scanner with the patient and provides correction for machine drift. Quantitative readings are obtained from the regular site. These readings are then averaged and used to calculate the mineral density[32].

V. Management Of Hepatic Osteodystrophy

General Measures: Potentially reversible factors that may affect bone loss should be eliminated whenever possible. Alcohol cessation, regular weight-bearing exercise is integral to the maintenance of skeletal integrity by maintaining both muscle and bone mass. Exercise in combination with adequate dietary intake of calcium delays the progression of bone loss in postmenopausal women. It may prevent bone loss in liver disease patients. For patients with the advanced liver disease, physical therapy with a focus on strengthening of the back muscles may be of benefit[33].

Nutritional Therapy: Early calcium supplementation is essential because of its bone-protective effects. A study of osteoporotic women with PBC revealed an independent positive effect of oral calcium on bone mineral density. However, early trials of administration of vitamin D in osteoporotic patients with the cholestatic liver disease was unable to delay the progression of osteoporosis as assessed by the bone mineral density and fracture incidence[34].

Hormone Replacement: A gradual decline in serum testosterone and free testosterone levels occurs with advancing age. The presence of chronic liver disease accelerates this decline. It is well documented that hormone replacement therapy during menopause prevents postmenopausal bone loss and reduces the incidence of fractures. Concern regarding the cholestatic potential of estrogen because of a decrease in bile flow and the lack of sizeable randomized trial data have limited the use of estrogen replacement among women with the chronic liver disease[35].

Bisphosphonates: Bisphosphonates attach to the surface of the bone and thereby prevent osteoclast-mediated resorption. Etidronate is one of the first bisphosphonates available for oral use. Pamidronate is a second generation parenteral bisphosphonate. It is more potent than etidronate and may be administered every 3 to 6 months as a single infusion. Alendronate and risedronate, oral amino-bisphosphonates, have been shown to

increase vertebral bone mineral density and reduce the incidence of vertebral fractures in women of postmenopausal age group when ingested daily. Bisphosphonates are also useful for preventing bone loss caused by corticosteroid treatment. Cyclical administration of etidronate has been shown to prevent corticosteroid-induced bone loss in at least two randomized trials. Ulcerative esophagitis with daily oral bisphosphonate administration has hindered its routine use in patients of esophageal varices and advanced liver disease because of concerns of precipitating esophageal variceal bleeding[36].

Sodium fluoride: Sodium fluoride stimulates osteoblast proliferation and increases bone formation. Fluoride use may improve bone mineral density in corticosteroid-induced osteoporosis. However, excessive exposure to fluoride may result in reduced bone strength and quality with an increased potential for fractures[37].

Future Therapeutic Options: Liver disease-specific therapies, including ursodeoxycholicacid and interferon, have independent effects on bone metabolism. Ursodeoxycholic acid has been shown to increase calcium absorption in PBC patients. Interferon inhibits the formation of osteoclast-like cells in vitro and has been shown to reduce the urinary excretion of collagen degradation products (markers of bone resorption) in patients with hepatitis C. Cytokines such as transforming growth factor β and growth hormones including IGF-1, have anabolic effects on bone in vitro and in vivo and may have a future role in the treatment of hepatic osteodystrophy[38,39].

VI. Therapeutic Implications

Without adequate screening, osteometabolic disease silently progresses leading to fractures which is a significant source of morbidity and mortality in these patients. Bone density assessment by DEXA scan is safe and easily accessible to most individuals. Patients with the chronic liver disease need screening for bone mineral density measurements

Alcohol cessation, regular weight-bearing exercise is integral to the maintenance of skeletal integrity by maintaining both muscle and bone mass[25]. Exercise in combination with adequate dietary intake of calcium has been shown to be useful for delaying the progression of bone loss. Early calcium supplementation is essential because of its bone-protective effects[34].

Bisphosphonates prevent osteoclast-mediated resorption and have been shown to increase vertebral bone mineral density and reduce the incidence of vertebral fractures[36]. Liver cirrhosis is a direct risk factor for the development of bone loss and development of hepatic osteodystrophy[36]. Early recognition of hepatic osteodystrophy may prevent the development of bone complications, i.e., trauma and fractures in these patients.

References

[1]. Chinnaratha MA, Chaudhary S, Doogue M, McCormick RJ, Woodman RJ, Wigg AJ. Prevalence of hepatic osteodystrophy and vitamin D deficiency in cirrhosis. Internal medicine journal. 2015 Dec;45(12):1230-5.

[2]. Tsuneoka K, Tameda Y, Takase K, Nakano T. Osteodystrophy in patients with chronic hepatitis and liver cirrhosis. Journal of gastroenterology. 1996 Oct 1;31(5):669-78.

[3]. Epstein S. Post-transplantation bone disease: The role of immunosuppressive agents and the skeleton. Journal of Bone and Mineral Research. 1996 Jan;11(1):1-7.

[4]. Leidig-Bruckner G, Hosch S, Dodidou P, Ritschel D, Conradt C, Klose C, Otto G, Lange R, Theilmann L, Zimmerman R, Pritsch M. Frequency and predictors of osteoporotic fractures after cardiac or liver transplantation: a follow-up study. The Lancet. 2001 Feb 3;357(9253):342-7.

[5]. Watts NB. Fundamentals and pitfalls of bone densitometry using dual-energy X-ray absorptiometry (DXA). Osteoporosis international. 2004 Nov 1;15(11):847-54.

[6]. Arteh J, Narra S, Nair S. Prevalence of vitamin D deficiency in chronic liver disease. Digestive diseases and sciences. 2010 Sep 1;55(9):2624-8.

[7]. Mawer EB, Klass HJ, Warnes TW, Berry JL. Metabolism of vitamin D in patients with primary biliary cirrhosis and alcoholic liver disease. Clinical Science. 1985 Nov 1;69(5):561-70.

[8]. Parfitt AM. The actions of parathyroid hormone on bone: Relation to bone remodeling and turnover, calcium homeostasis, and metabolic bone disease: Part IV of IV parts: The state of the bones in uremic hyperparathyroidism—The mechanisms of skeletal resistance to PTH in renal failure and pseudohypoparathyroidism and the role of PTH in osteoporosis, osteopetrosis, and osteofluorosis. Metabolism. 1976 Oct 1;25(10):1157-88.

[9]. Reichrath J. Vitamin D and the skin: an ancient friend, revisited. Experimental dermatology. 2007 Jul;16(7):618-25.

[10]. Hepner GW, Roginsky M, Moo HF. Abnormal vitamin D metabolism in patients with cirrhosis. The American journal of digestive diseases. 1976 Jul 1;21(7):527-32.

[11]. Leevy CM, Thompson A, Baker H. Vitamins and liver injury. The American journal of clinical nutrition. 1970 Apr 1;23(4):493-8.

[12]. Danielsson Å, Lorentzon R, Larsson SE. Intestinal absorption and 25-hydroxylation of vitamin D in patients with primary biliary cirrhosis. Scandinavian journal of gastroenterology. 1982 Apr 1;17(3):349-55.

[13]. Sitrin MD, Bengoa JM. Intestinal absorption of cholecalciferol and 25-hydroxycholecalciferol in chronic cholestatic liver disease. The American journal of clinical nutrition. 1987 Dec 1;46(6):1011-5.

[14]. Heaney RP, Dowell MS, Hale CA, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. Journal of the American college of nutrition. 2003 Apr 1;22(2):142-6.

[15]. Diamond TH, Stiel D, Lunzer M, Wilkinson M, Roche J, Posen S. Osteoporosis and skeletal fractures in chronic liver disease. Gut. 1990 Jan 1;31(1):82-7.

[16]. McCaughan GW, Feller RB. Osteoporosis in chronic liver disease: pathogenesis, risk factors, and management. Digestive Diseases. 1994;12(4):223-31.

[17]. 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 Aug 1;12(2):273-80.
[18]. Crosbie OM, Freaney R, McKenna MJ, Hegarty JE. Bone density, vitamin D status, and disordered bone remodeling in end-stage chronic liver disease. Calcified tissue international. 1999 Apr 1;64(4):295-300.
[19]. Compston JE. Hepatic osteodystrophy: vitamin D metabolism in patients with liver disease. Gut. 1986 Sep;27(9):1073.
[20]. Paterson CR, Losowsky MS. The bones in chronic liver disease. Scandinavian journal of gastroenterology. 1967 Nov 1;2(4):293-300.
[21]. Stellon AJ, Davies A, Compston J, Williams R. Osteoporosis in chronic cholestatic liver disease. QJM: An International Journal of Medicine. 1985 Nov 1;57(2):783-90.
[22]. Epstein 0, Kato Y, Dick R, Sherlock S. The prevalence and pattern of cortical bone thinning in chronic cholestatic and parenchymal liver diseases. In: 16th Meeting of the European Association for the Study of the Liver Lisbon: 1981, p. 44.
[23]. Conditions like primary biliary cirrhosis, primary sclerosing cholangitis have an incidence of hepatic osteodystrophy ranging from 10%-68%
[24]. Cijevschi C, Mihai C, Zbranca E, Gogalniceanu P. Osteoporosis in liver cirrhosis. Rom J Gastroenterol. 2005 Dec;14(4):337-41.
[25]. Spencer H, Rubio N, Rubio E, Indreika M, Seitam A. Chronic alcoholism. Frequently overlooked cause of osteoporosis in men. The American journal of medicine. 1986 Mar 1;80(3):393-7.
[26]. Torres A, Lorenzo V, Salido E. Calcium metabolism and skeletal problems after transplantation. Journal of the American Society of Nephrology. 2002 Feb 1;13(2):551-8.
[27]. Ito Y, Hasegawa Y, Toda K, Nakahara S. Pathogenesis and diagnosis of delayed vertebral collapse resulting from osteoporotic spinal fracture. The Spine Journal. 2002 Mar 1;2(2):101-6.
[28]. Nelp WB, Palmer HE, Murano R, Pailthorp K, Hinn GM, Rich C, Williams JL, Rudd TG, Denney JD. Measurement of total body calcium (bone mass) in vivo with the use of total body neutron activation analysis. The Journal of laboratory and clinical medicine. 1970 Jul 1;76(1):151-62.
[29]. Cullum ID, Ell PJ, Ryder JP. X-ray dual-photon absorptiometry: a new method for the measurement of bone density. The British journal of radiology. 1989 Jul;62(739):587-92.
[30]. Mazess RB, Barden HS, Bisek JP, Hanson J. Dual-energy x-ray absorptiometry for total-body and regional bone-mineral and soft-tissue composition. The American journal of clinical nutrition. 1990 Jun 1;51(6):1106-12.
[31]. Svendsen OL, Haarbo J, Hassager C, Christiansen C. Accuracy of measurements of body composition by dual-energy x-ray absorptiometry in vivo. The American Journal of Clinical Nutrition. 1993 May 1;57(5):605-8.
[32]. Engelke K, Adams JE, Armbrecht G, Augat P, Bogado CE, Bouxsein ML, Felsenberg D, Ito M, Prevrhal S, Hans DB, Lewiecki EM. Clinical use of quantitative computed tomography and peripheral quantitative computed tomography in the management of osteoporosis in adults: the 2007 ISCD Official Positions. Journal of clinical densitometry. 2008 Jan 1;11(1):123-62.
[33]. Collier JD, Ninkovic M, Compston JE. Guidelines on the management of osteoporosis associated with chronic liver disease. Gut. 2002 Feb 1;50(suppl 1):i1-9.
[34]. Plauth M, Merli M, Kondrup J, Weimann A, Ferenci P, Müller MJ. ESPEN guidelines for nutrition in liver disease and transplantation. Clinical nutrition. 1997 Apr 1;16(2):43-55.
[35]. Olsson R, Mattsson LÅ, Obrant K, Mellström D. Estrogen-progestogen therapy for low bone mineral density in primary biliary cirrhosis. Liver. 1999 Jun;19(3):188-92.
[36]. Shaw NJ, Bishop NJ. Bisphosphonate treatment of bone disease. Archives of Disease in Childhood. 2005 May 1;90(5):494-9.
[37]. Pak CY, Sakhaee K, Adams-Huet B, Piziak V, Peterson RD, Poindexter JR. Treatment of postmenopausal osteoporosis with slow-release sodium fluoride: final report of a randomized controlled trial. Annals of internal medicine. 1995 Sep 15;123(6):401-8.
[38]. Guañabens N, Parés A. Osteoporosis in chronic liver disease. Liver International. 2018 May;38(5):776-85.
[39]. Zakharia K, Tabibian A, Lindor KD, Tabibian JH. Complications, symptoms, quality of life and pregnancy in cholestatic liver disease. Liver International. 2018 Mar;38(3):399-411.

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