Introduction

Hepatic osteodystrophy (HO) is the generic term defining the group of alterations in bone mineral metabolism found in patients with chronic liver disease***(Nakchbandi&van der Merwe,2009***).The term "hepatic osteodystrophy" covers both osteomalacia and osteoporosis ***(Heaf,1985)***.Osteoporosis is defined as a systemic disease of bones that leads to an increased risk of fracture***(Brian et al.,2009).***

In osteoporosis, the bone mineral density (BMD) is reduced, bone microarchitecture deteriorates, and the amount and variety of proteins in bone are altered.There is a disintegration of the bone matrix with normal ratio of mineral to matrix ***(Wilkin,1999***).

Osteoporosis is defined by the World Health Organization**(WHO)** as a bone mineral density of 2.5 standard deviations or more below the mean peak bone mass (average of young, healthy adults) as measured by dual-energy X-ray absorptiometry***(WHO,1994***).

The disease may be classified as primary type 1, primary type 2, or secondary***(Brian et al.,2009).*** The form of osteoporosis most common in women after menopause is referred to as primary type 1 or postmenopausal osteoporosis. Primary type 2 osteoporosis or senile osteoporosis occurs after age 75 and is seen in both females and males at a ratio of 2:1. Secondary osteoporosis may arise at any age and affect men and women equally. This form results from chronic

predisposing medical problems or disease, or prolonged use of medications such as glucocorticoids***(Wilkin,1999).***

Chronic liver disease (CLD) can be classified into diseases with primarily hepato-*cellular* damage and *cholestatic* diseases. Examples of hepato-cellular CLD are autoimmune chronic hepatitis (auCAH), chronic viral hepatitis B and C, and alcoholic liver disease.Cholestatic CLD includes primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) ***(Am,1993).***

In pre-transplant patients suffering from different liver disorders, the highest prevalence of metabolic bone disease was found in patients with PBC and PSC. Other studies, however, have reported similar prevalencerates for osteoporosis in patients with hepato-cellular CLD as in patients with cholestatic CLD, ranging from 9 to 53% ***(Keoghet al.,1999).***

In 1939 a 69 year old woman with long-standing intrahepatic obstructive jaundice and spinal osteoporosis with vertebral compressions was described ***(Loeper et al.,1939***). Since then it has been firmly established that chronic cholestasis, and also other forms of CLD, are associated with metabolic bone disease***(Wolfhagen et al.,2000).***

Over the last two decades, better histomorphometric techniques (including double-tetracycline labeling for diagnosing osteomalacia) have made it clear that the main bone abnormality in CLD, cholestatic or hepatocellular, is osteoporosis and that osteomalacia is very rare ***(Crosbie et al.,1999).***

The way in which liver failure affects osteoblasts and contributes to the development of osteoporosis is unclear. Many studies identified risk factorsinvolved in hepatic osteodystrophy as genetic predisposition, decrease of hepatic synthesis of substances involved in osteogenesis, as IGF-1, alteration of sexual hormones metabolism- hypogonadism, excessive alcohol consumption, iron and copper overload, defective fibronectin synthesis, decrease synthesis of osteoprotegerin, activation of proinflammatory cytokines, malnutrition, tubular renal acidosis, therapeutic imunosuppresion as well as antiviral treatments***(Motoi,2011).***

Toxic substances, such as aluminium and copper, which accumulate in liver failure might also affect bone metabolism. In haemochromatosis an increased iron burden might impair osteoblastic activity ***(Diamond et al.,1991).*** Bilirubin has been shown to inhibit osteoblast proliferation in vitro ***(Janeset al.,1995)***. Whether cholestasis per se is a risk factor for osteoporosis in CLD is uncertain.

Hyperparathyroidism, despite vitamin D replacement, has been described in PBC ***(Fonseca et al.,1987)***.Others have not found evidence of hyperparathyroidism in patients with CLD **(*Herlong et al.,1982).***

Treatment with corticosteroids and hypogonadism in men and women are reported by some as risk factors for osteoporosis in CLD ***(Olson et al.,1994).*** Others have not found treatment with corticosteroids to be associated with low BMD in CLD ***(Mitchison et al.,1992).*** Other general factors in patients with CLD such as alcohol consumption, low body

weight and physical inactivity have not been reported as independent risk factors for osteoporosis in CLD but can be assumed to be important***(Sanchez and Aranda-Michel, 2006).***

Consequently, a detailed bone mineral density (BMD) and bone metabolism evaluation should be performed in all patients with chronic liver disease in order to prevent fractures and chronic pain and improve quality of life***(Sanchez and Aranda-Michel,2006).***

Aim of the Work

The objective of this thesis was to describe BMD in patients with CLD and furthermore to study the prevalence,risk factors and types of osteoporosis in a cohort of patients with CLD.

Osteoporosis

Introduction

Osteoporosis is the condition in which a low bone mass and altered microarchitecture of the bone lead to increased risk of fracture. Worldwide, osteoporosis causes more than 8.9 million fractures annually, resulting in an osteoporotic fracture every 3 seconds***(Johnell and Kanis, 2006).***Meanwhile in Egypt calculations show that 53.9% of postmenopausal women have osteopenia while 28.4% have osteoporosis.21.9% of males aged 20-89 have osteoporosis***(Taha, 2011).***

Despite the adverse effects of osteoporosis, it is a condition that is often overlooked and undertreated, in large part because it is so often clinically silent before manifesting in the form of fracture. For example, a Gallup survey performed by the National Osteoporosis Foundation revealed that 86% of all women aged 45-75 years had never discussed osteoporosis with their physicians, and more than 80% were unaware that osteoporosis is directly responsible for disabling hip fractures***(National Osteoporosis Foundation, 1991).***So an underst-anding of the causes of osteoporosis is important for its prevention,diagnosis, and treatment***(Majumdar et al., 2009).***

Types:

Traditionally, osteoporosis has been classified into primary and secondary osteoporosis. Primary osteoporosis refers to osteoporotic conditions which are not related to other chronic illnesses and is usually associated with aging and

decreased gonadal function, such as decreased level of estrogen***(Howard, 2011)***.

Secondary osteoporosis is defined as bone loss, microarchitecural alterations, and fragility fractures due to an underlying disease or concurrent medication ***(Painteret al., 2006***)

Apart from the more well-known endocrine disorders, including Cushing's syndrome, hypogonadism, hyperthy-roidism, and hyperparathyroidism, the adverse effects of diabetes mellitus have just been acknowledged***(Hofbauer et al., 2010).***

In fact, patients with type 1 diabetes mellitus have a 12-fold higher risk of sustaining osteoporotic fractures, compared with non-diabetic controls ***(Nicodemus et al., 2001)***. In addition, chronic inflammation present in inflammatory bowel disease and rheumatoid arthritis cause osteoporosis, in part because of the pro-inflammatory cytokine milieu and immunosuppressive regimens***(Van et al., 2006).*** The emerging use of thiazolidinediones (TZDs)***(Schwartz & Sellmeyer, 2007),*** aromatase inhibitors (AIs)***(Eastellet al., 2006),*** androgen-deprivation therapy in men with prostate cancer***(Ebeling, 2008),*** and the growing field of bariatric surgery ***(Coates et al., 2004)***have emerged as novel and important etiologies of secondary osteoporosis.

Risk Factors

Since the clinical outcome of osteoporosis is bone fracture, attention is now increasingly focused on the identification of patients at high risk of fracture rather than the identification of people with osteoporosis as defined by BMD alone***(Siris and Delmas, 2008)***; ***(Tosteson et al., 2008).***

Although osteoporosis is defined in terms of BMD and microarchitectural deterioration of bone tissue, BMD is just one component of fracture risk. Accurate assessment of fracture risk should ideally take into account other proven risk factors that add information to that provided by BMD***(Leslie, 2008).***

Osteoporosis has been shown in studies to have a large genetic component. A parental history of fracture (particularly hip fracture) confers an increased risk of fracture that is independent of BMD ***(Kanis et al., 2004).***

The highest BMD that is reached by a fertile woman, along with other factors, can predict the occurrence of osteoporosis after menopause. Both osteopenia and osteoporosis in premenopausal women can be attributed to a low BMD during the growth period in childhood, adolescence and early adulthood or an excess loss of density after reaching peak BMD***(Londono et al., 2013).***

Other factors, including age, sedentary life, smoking, low weight, prolonged corticosteroid use, androgen deprivation therapy, dietary calcium intake, chronic lung disease, and prostate cancer***(Herrara et al., 2012).***

Physical inactivity:

Physical inactivity and a sedentary lifestyle as well as impaired neuromuscular function (e.g., reduced muscle strength, impaired gait and balance) are risk factors for developing fragility fractures***(Albrand et al., 2003).***

Muscle strength has been suggested as a predictor of BMD, indirectly indicating osteoporotic fracture risk resulting from the relationship between muscle attachment site integrity and the bone's ability to withstand the biomechanical forces involved in muscular pulling***(Zhou et al., 2013).*** Previous reports have demonstrated a relationship between hip abductor strength and femoral BMD, as well as isokinetic knee and elbow flexor and extensor strength with vertebral and femoral BMD***(Zhouetal.,2013).***Furthermore,advancedagesignificantlyd elays reaction times and prolonges movement speeds, although whether these losses in motor function result from physiological changes related to sedentary lifestyles of older individuals remains debatable***(Zhou et al., 2013).***

Cigarette smoking:

Cigarette smoking has deleterious effects on the musculo-skeletal system. The loss of bone mineral content and increased incidence of fractures are the best known negative consequences. The pathogenesis is complex, due to direct toxic effects on osteoblasts/osteoclasts activity of nicotine, and indirect actions on sex and adrenocortical hormones, vitamin D, intestinal calcium absorption, vessels and oxygen supply***(Abate et al., 2013).***

Age:

Risk for osteoporosis increases with age as bone mineral desity (BMD) declines. Senile osteoporosis is most common in persons aged 70 years or older. Secondary osteoporosis, however, can occur in persons of any age. Although bone loss in women begins slowly, it speeds up around the time of menopause, typically at about or after age 50 years. The frequency of postmenopausal osteoporosis is highest in women aged 50-70 years. Osteoporosis is estimated to affect 200 million women worldwide - approximately one-tenth of women aged 60, one-fifth of women aged 70, two-fifths of women aged 80 and two-thirds of women aged 90 ***(Kanis, 2007).***

It is well known that the underlying mechanisms of osteoporosis in older adults are different than those associated with estrogen deprivation. Age-related bone loss involves a gradual and progressive decline, which is also seen in men. Markedly increased bone resorption leads to the initial fall in bone mineral density. With increasing age, there is also a significant reduction in bone formation. This is mostly due to a shift from osteoblastogenesis to predominant adipogenesis in the bone marrow, which also has a lipotoxic effect that affects matrix formation and mineralization. We review new evidence on the pathophysiology of age-related bone loss with emphasis upon the mechanism of action of current osteoporosis treatments. New potential treatments are also considered, including therapeutic approaches to osteoporosis in the elderly that focus on the pathophysiology and potential reversal of adipogenic shift in bone***(Oddom et al., 2012)***.

In contrast to postmenopausal bone loss, which is associated with excessive osteoclast activity, the bone loss that accompanies aging is associated with a progressive decline in the supply of osteoblasts in proportion to the demand. This demand is ultimately determined by the frequency with which new multicellular units are created and new cycles of remodeling are initiated***(Oddom et al., 2012)***.

After the third decade of life, bone resorption exceeds bone formation and leads to osteopenia and, in severe situations, osteoporosis. Women lose 30-40% of their cortical bone and 50% of their trabecular bone over their lifetime, as opposed to men, who lose 15-20% of their cortical bone and 25-30% of trabecular bone***(Oddom et al., 2012)***.

- **Sex:**

Women are at a significantly higher risk for osteoporosis. According to the National Osteoporosis Foundation (NOF), of the estimated 10 million Americans who have osteoporosis, 80% are women***(National Osteoporosis Foundation, 2013).***

Men have a higher prevalence of secondary osteoporosis, with an estimated 45-60% of cases being a consequence of hypogonadism, alcoholism, or glucocorticoid excess***(Migliaccioet al., 2009).*** Only 35-40% of osteoporosis diagnosed in men is considered primary in nature. Overall, osteoporosis has a female-to-male ratio of 4:1***(National Osteoporosis Foundation, 2013).***

Fifty percent of all women and 25% of all men older than 50 years experience one or more osteoporosis-related fracture in their lifetime. Eighty percent of hip fractures occur in women.Women have a 2-fold increase in the number of fractures resulting from nontraumatic causes, as compared with men of the same age***(Smith and Wordsworth, 2006).***

- **Race:**

Osteoporosis can occur in persons of all races and ethnicities. In general, however, whites (especially of northern European descent) and Asians are at increased risk. In particular, non-Hispanic white women and Asian women are at higher risk for osteoporosis ***(Balfour, 2013).***

- **Calcium deficiency:**

The major mineral lost in bone loss is calcium, and calcium absorption is influenced by vitamin D. Therefore, individuals who consume calcium in low amounts and who are diagnosed with vitamin D deficiency also have an increased fracture risk ***(Gielen et al., 2011).***

Calcium, vitamin D, and PTH help maintain bone homeostasis. Insufficient dietary calcium or impaired intestinal absorption of calcium due to aging or disease can lead to secondary hyperparathyroidism. PTH is secreted in response to low serum calcium levels. It increases calcium resorption from bone, decreases renal calcium excretion, and increases renal production of 1,25-dihydroxyvitamin D (1,25[OH]2 D)-an active hormonal form of vitamin D that optimizes calcium and phosphorus absorption, inhibits PTH synthesis, and plays a minor role in bone resorption***(Bono and Einhorn, 2003).***

Vitamin D deficiency:

Recent research shows that low levels of free 25(OH) vitamin D result in bone loss ***(Al-oanzi et al., 2006).***

Vitamin D deficiency can result in secondary hyperparathyroidism via decreased intestinal calcium absorption. Interestingly, the effects of PTH and 1,25[OH]2 D on bone are mediated via binding to osteoblasts and stimulating the RANKL/RANK pathway. Osteoclasts do not have receptors for PTH or 1,25[OH]2D***(Bono and Einhorn, 2003).***

Glucocorticoids:

Glucocorticoid administration is the most common cause of secondary osteoporosis and the leading cause of nontraumatic osteonecrosis. In patients receiving long-term therapy, glucocorticoids induce fractures in 30 to 50% and osteonecrosis in 9 to 40%***(Robert, 2011).***

Histomorphometric studies in patients with glucocorticoid induced osteoporosis(GIO) consistently show reduced numbers of osteoblasts on cancellous bone and diminished wall width, a measure of the work performed by these cells ***(Weinstein, 2011).***The decreased osteoblasts are due to the direct effects of glucocorticoids to decrease the production of new osteoblast precursors and cause prematureapoptosis of the mature, matrix-secreting osteoblasts. Inadequate numbers of osteoblasts and incomplete erosion cavity repair during bone remodeling are the main cause of the

reduction in cancellous bone area, wall width, trabecular width and bone formation rate typically found in GIO***(Weinstein et al., 2010).***

- **Antidiabetic drugs:**

Antidiabetic drugs like thiazolidinedione also cause bone loss ***(Sardone et al., 2011).*** Many studies in humans as well as in animals have shown that bone loss is accelerated by thiazolidinedione**.**Rosiglitazone decreases bone quality by increasing porosity***(Grey,2009).*** In women and men, decreased bone mass in long bones, but not in the vertebrae, has been attributed to thiazolidinedione***(Chakreeyarat et al., 2010).***

There are a few studies that explain the mechanism by which these antidiabetic drugs cause bone loss, Glitazones reduce the biosynthesis of androgens, increase their binding to Sex hormone-binding globulin (*SHBG*), and attenuate androgen receptor activation, thus reducing the physiologic actions of testosterone, causing relative and absolute androgen deficiency ***(Carruthers et al., 2008).*** In addition to this, activation of peroxisome proliferator activated receptor gamma initiates an imbalance in the bone resorption and bone formation process, resulting in high bone loss***(Lecka-Czernik, 2010).*** Moreover, rosiglitazone induces apoptosis of osteoblasts which reduces bone formation ***(Soroceanu et al., 2004).***

Symptomsand Signs

Often, patients who have not experienced a fracture do not report symptoms that would alert the clinician to suspect a

diagnosis of osteoporosis; thus, this disease is a "silent thief" that generally does not become clinically apparent until a fracture occurs.But once bones have been weakened by osteoporosis, you may have signs and symptoms that include:

- Back pain, caused by a fractured or collapsed vertebra.
- Loss of height over time.
- A stooped posture.
- A bone fracture that occurs much more easily than expected***(Schnatz et al., 2011).***

Screening at-risk populations is, therefore, essential; unfortunately, many women are not receiving proper screening or treatment for osteoporosis, which, in turn, may result in improper management of this disease and its related complications***(Schnatz et al., 2011).***So, thorough history should be obtained to screen for and identify the presence of known risk factors for osteoporosis and osteoporotic fracture***(Geusens et al., 2008).***

- **Specifically, the history should focus on the following:**
  - Age (>50 years), sex (female), and race (white or Asian)***(Geusens et al., 2008)***; the US Preventive Services Task Force (USPSTF) recommendations include screening for osteoporosis in women aged 65 years or older and in younger women with a fracture risk that is the same or greater than that of a 65-year-