EVALUATION OF BONE RESORPTION IN MALE PATIENTS WITH BILHARZIAL PERIPORTAL HEPATIC FIBROSIS

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KEY WORDS: BONE RESORPTION, BILHARZIAL PERIPORTAL HEPATIC FIBROSIS.

ABSTRACT

Objective: To evaluate bone resorption and bone mineral metabolism in male patients suffering from bilharzial periportal hepatic fibrosis by assessment of liver function tests and factors that regulate bone resorption and formation and correlate these factors to bone mineral density assessing bone mineral metabolism.

Methodology: This study was carried out on 50 male patients suffering from bilharzial periportal hepatic fibrosis; their mean age was 38.6 ±8.14. Also 40 age matched healthy males were included in this study as a control group. Both patients and control groups were subjected to the following investigations (parathyroid hormone (PTH), testosterone, vitamin D3 (1-25 hydroxycholecalciferol), serum calcium and phosphorus, total alkaline phosphatase and liver function tests including (SGOT, SGPT, total protein, albumin, total and direct bilirubin) in addition to dual energy X-ray absorptiometry (DEXA) and abdominal ultrasonography.

Results: patients suffering from bilharzial periportal hepatic fibrosis showed highly significant reduction of serum testosterone and bone mineral density (BMD) in comparison to control group (p<0.001) and the testosterone is highly correlated with BMD (p<0.001) parathyroid hormone, vitamin D3, serum calcium and phosphorus showed non significant difference between both studied groups (p>0.05) and not correlated with BMD (p>0.05). However, liver function tests
were significantly higher in patients than control group (p<0.01).

**Conclusion:** Our results demonstrate that the liver is an important organ responsible for bone integrity and any chronic liver disease like bilharzial periportal liver fibrosis can directly affect the bone and causing osteoporosis which indicated by diminished BMD and this osteoporosis was accompanied with gonadal dysfunction indicated by reduced testosterone so it is called (Andropausal osteoporosis).

**INTRODUCTION**

Importance of bone loss due to liver diseases increased recently and became one of the most important causes of secondary osteoporosis due to improvement in the diagnostic and therapeutic tools of liver diseases that permit detection of fracture and osteoporosis in these patients.

Metabolic bone disease is common among patients with chronic liver diseases and the osteometabolic changes caused by liver disease are termed Hepatic osteodystrophy (William et al., 2003). The reported prevalence of osteoporosis among patients with chronic liver diseases ranges from 20 – 100 % depending on patients selection and diagnostic criteria (Bernstein et al., 2003).

There are many potential factors that either directly or indirectly alter the bone mass in chronic liver diseases include insulin growth factor-1 (IGF-1) deficiency, hypogonadism (estrogen and testosterone deficiency), hyperbilirubinemia, subnormal vitamin D level, vitamin D receptor genotype, excess tissue iron deposition, alcoholism, osteoprotegerin deficiency and immunosuppressive therapy preceding and following liver transplantation (Heathcote et al., 2000).

Bone remodeling is a surface phenomenon serves to maintain bone integrity and provides mechanisms by which calcium and phosphorus ions may be released from or conserved within the bone.

Bone remodeling consists of bone resorption by osteoclasts followed by bone formation by osteoblasts and it is regulated by complex interplay between mechanical factors such as stress and exercises stimulating mechanosensory bone cells (osteocytes) (Nijweide et al., 1996) and systemic hormones such as sex steroids (estrogen and testosterone), parathyroid hormone (PTH), thyroid hormone, growth hormones and vitamin D3 (1,25 cholecalciferol) (Lean et al., 1995) and locally produced factors such as
interleukins (IL-1α, IL-1β, IL-6, TNF-α, TNF-β and RANK-L), transforming growth factor-β (TGF-β), granulocyte/macrophage – colony stimulating factors (GM-CSF) and insulin growth factor-β (IGF-β) (Bonewald, 1996).

Most of these systemic hormones regulating bone resorption and bone formation are metabolized in the liver and can be affected by liver diseases e.g. (bilharzial liver fibrosis), so the liver diseases associated with changes of these systemic hormones may cause increased osteoclastic activity with decreased bone mass (osteoporosis).

Bilharzial periportal liver fibrosis is one of the most important chronic liver diseases and it occurs as a granulomatous reaction to eggs of 2 types of schistosomiasis (schistosoma mansoni and schistosoma japonicum). The liver develops fibrosis after 10-12 years of prolonged exposure to infection.

Histopathological examination of liver biopsy showed finger-sized bands of fibrosis (pipe-stem fibrosis) with nodules formation and scarring sufficient to cause deteriorated liver functions. The liver fibrosis encompases large portal tracts with replacement of portal veins by fibrous tissues and this leading to perisinoidal blockage, portal hypertension, splenomegaly and esophageal varices. The patients with bilharzial liver fibrosis commonly presented with hematemesis, enlarged liver and spleen, ascitis, hepatic coma, spider angioma, gynecomastia and osteoporosis.

Bilharzial liver fibrosis is commonly best diagnosed by abdominal ultrasonography which shows characteristic fibrous bands appear as dense echogenic areas surrounding the portal vein and its branches. This technique has more specificity and sensitivity than liver biopsy.

Aim of work:

This study is aimed to evaluate bone resorption and bone mineral metabolism in male patients suffering from bilharzial periportal hepatic fibrosis by assessment of liver functions tests (SGOT, SGPT, total protein, albumin, total and direct bilirubin) and factors that regulate bone resorption and formation (serum calcium and phosphorus, alkaline phosphatase, parathyroid hormone (PTH), vitamin D3 (1-25 dihydroxy Vit D2) and testosterone) and correlate these factors to bone mineral density assessing bone mineral metabolism.
PATIENTS AND METHODS

This study was carried out on 50 male patients suffering from bilharzial periportal liver fibrosis with age that ranged from 20 to 50 years (38.6 ± 8.14). The patients were chosen from the Tropical Medicine and Rheumatology Departments, Al-Hussein and Bab Al-Shaareya University Hospitals. The study also included 40 age matched healthy males as a control group.

All the patients included in this study were males to avoid effect of postmenopausal osteoporosis, with age not exceed 50 years to be far from development of senile osteoporosis, not complaining of any other systemic diseases affecting bone like (DM or thyroid diseases), not alcoholic or smoking, not receiving drugs affecting bone such as (steroids, heparin or anticonvulsants) and without renal troubles to eliminate the effect of renal osteodystrophy.

All the patients and control groups were subjected to careful history taking, general and musculoskeletal examination and to the following investigations:

From all patients and controls, 5 ml of venous blood was aspirated in a calcium free tube, incubated at 37 °C for 20 minutes, centrifuged and serum separated was divided into 2 parts, the first was used immediately for estimation of calcium, phosphorus, alkaline phosphatase and liver functions, while the second part was preserved at -70 °C for assay of parathyroid hormone (PTH), vitamin D3 (1-25 dihydroxy Vit D2) and testosterone.

- Calcium was estimated photometrically with methylthymol blue method (Gindler & King, 1972), phosphorus estimated photometrically using acid molybdate (Gamst & Try, 1980) and alkaline phosphatase estimated according to German clinical chemistry association (Rick, 1990).

- SGOT and SGPT determined with the kinetic method using commercial kit from biosystems SA Costa Brava 30 Barcelona Spain (Gella et al., 1985), albumin determined colorometrically using modified bromocresol green method (Domas, 1971), total protein with Buriet method (Cannon et al., 1974) and bilirubin by diazotized sulphanilic acid method (Jendrassik, 1938).

- Vitamin D3 was measured with radioimmunoassay based on polyclonal antibody specific for vitamin D3, the results counted on gamma counter and the values calculated directly from a calibrator curve (Hollis, 1986).
- Testosterone and parathyroid hormone estimated with chemiluminescence using commercial kits from diagnostic product corporation (DPC) USA, by a fully automated apparatus immulite 1, USA (Larry & Kricka, 1996)
- Abdominal ultrasonography for diagnosis of bilharzial periportal liver.

Fibrosis with Real Time Scanner
- Dual energy X-ray absorption (DEXA) using LUNAR DEXA device to measure bone mineral density (BMD) at wrist, lumber vertebrae and femoral neck. It utilizes an X-ray source that emits 2 photon beams of different energy and the BMD evaluation is based on measuring the differential absorption of energy from these 2 beams by tissues (Genant et al., 1996). The results of DEXA measurement of BMD includes 2 scores; T-score (represent the difference between the patient's value and that of normal subject aged 20 years) and Z-score (represent the difference between the patient's value and that of normal subject of the same age) (Christover et al., 2001).

RESULTS

This study was carried out on 50 male patients with bilharzial periportal liver fibrosis (BPLF) with mean age (38.6 ± 8.24) and disease duration not less than 15 years with mean duration (28.53 ± 15.20). The study also included 40 healthy subjects as a control group with mean age (38.8 ± 7.79). Statistical analysis showed no significant difference of age between both groups.

Table (1): Results of Liver Function Tests Measurement in patients with Bilharzial Liver Fibrosis and In Control Group.

<table>
<thead>
<tr>
<th>Liver function tests</th>
<th>Patients with BPLF group</th>
<th>Control group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGOT</td>
<td>75.76 ± 16.62</td>
<td>27.67 ± 5.85</td>
<td>p&lt; 0.01</td>
</tr>
<tr>
<td>SGPT</td>
<td>26.79 ± 20.23</td>
<td>15.64 ± 4.88</td>
<td>p&lt; 0.01</td>
</tr>
<tr>
<td>Total protein</td>
<td>6.1 ± 1.3</td>
<td>6.7 ± 0.3</td>
<td>p&gt; 0.05</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.05 ± 1.29</td>
<td>4.51 ± 0.89</td>
<td>p&lt; 0.05</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>2.80 ± 1.28</td>
<td>1.0 ± 0.18</td>
<td>p&lt; 0.01</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td>1.48 ± 0.79</td>
<td>0.2 ±0.41</td>
<td>p&lt; 0.01</td>
</tr>
</tbody>
</table>
Results of liver function tests measurement

Measurement of liver function tests in patients with bilharzial periportal liver fibrosis revealed increase of SGOT and SGPT enzymes levels and direct and total bilirubin levels in comparison to control group with statistical significant difference (p<0.01). The albumin level was decreased in patients with bilharzial periportal liver fibrosis (BPLF) in comparison to control group (p<0.05) and there was no significant difference of total protein level between both groups (p>0.01) as in (table1).

Results of bone remodeling regulating factors measurement

The results of serum calcium and phosphorus ions, alkaline phosphatase, parathyroid hormone, and vitamin D3 measurement in patients with bilharzial periportal liver fibrosis showed no significant difference in comparison to control group (p>0.05). The testosterone level in patients with bilharzial periportal liver fibrosis was decreased in comparison to control group (p<0.001) as in (table 2).

Table (2): Results of Bone Remodeling Regulating Factors Measurement in patients with Bilharzial Liver Fibrosis and In Control Group.

<table>
<thead>
<tr>
<th>Bone regulating factors</th>
<th>Patients with BPLF group</th>
<th>Control group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium</td>
<td>7.98 ± 1.15</td>
<td>8.24 ±1.06</td>
<td>p&gt; 0.05</td>
</tr>
<tr>
<td>Serum phosphorus</td>
<td>3.35 ± 0.42</td>
<td>3.45 ± 0.31</td>
<td>p&gt; 0.05</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>97.20 ± 19.65</td>
<td>94.13 ± 16.75</td>
<td>p&gt; 0.01</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>66.85 ± 12.49</td>
<td>64.30 ± 14.90</td>
<td>p&gt; 0.05</td>
</tr>
<tr>
<td>Vitamin D3</td>
<td>23.63 ± 6.01</td>
<td>29.14 ± 11.19</td>
<td>p&gt; 0.05</td>
</tr>
<tr>
<td>Testosterone</td>
<td>2.90 ± 1.8</td>
<td>5.45 ± 1.31</td>
<td>p&lt; 0.001</td>
</tr>
</tbody>
</table>

Results of bone mineral density (BMD) measurement

The results of BMD (T-score and Z-score) measurement in patients with bilharzial periportal liver fibrosis were decreased in comparison to control group (p< 0.001) as in (table 3).

Results of correlation of liver function tests with BMD

Our results showed that the liver enzymes (SGOT and SGPT) and total protein did not correlated with BMD (p>0.05). While the total and direct bilirubin correlated with BMD (p<0.01) and the albumin highly correlated with BMD (p<0.001) as in (table 4).
Table (3): Results of Bone Mineral Density Measurement in patients with Bilharzial Liver Fibrosis and In Control Group.

<table>
<thead>
<tr>
<th>Bone mineral density (BMD)</th>
<th>Patients with BPLF group</th>
<th>Control group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-score</td>
<td>-2.64 ± 0.83</td>
<td>0.90 ± 0.50</td>
<td>p&lt; 0.001</td>
</tr>
<tr>
<td>Z-score</td>
<td>-1.70 ± 0.97</td>
<td>0.80 ± 0.40</td>
<td>p&lt; 0.001</td>
</tr>
</tbody>
</table>

Table (4): Results of Correlation of Liver Function Tests with BMD.

<table>
<thead>
<tr>
<th>Liver function tests</th>
<th>BMD (T-score)</th>
<th>BMD (Z-score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGOT</td>
<td>r=0.503</td>
<td>p&gt; 0.05</td>
</tr>
<tr>
<td>SGPT</td>
<td>r=0.550</td>
<td>p&gt; 0.05</td>
</tr>
<tr>
<td>Total protein</td>
<td>r=0.368</td>
<td>p&gt; 0.05</td>
</tr>
<tr>
<td>Albumin</td>
<td>r=0.471</td>
<td>p&lt; 0.05</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>r=0.641</td>
<td>p&lt; 0.01</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td>r=0.610</td>
<td>p&lt; 0.01</td>
</tr>
</tbody>
</table>

Results of correlation of bone remodeling regulating factors with BMD

Our results showed that the testosterone was the only regulating factor correlated with BMD with high significant statistical data (p<0.001), but the other regulating factors did not show any correlation with BMD (P>0.05) as in (table 5).

Table (5): Results of Correlation of Bone Remodeling Regulating Factors with BMD.

<table>
<thead>
<tr>
<th>Bone regulating factors</th>
<th>BMD (T-score)</th>
<th>BMD (Z-score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium</td>
<td>r=0.184</td>
<td>p&gt; 0.05</td>
</tr>
<tr>
<td>Serum phosphorus</td>
<td>r=0.348</td>
<td>p&gt; 0.05</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>r=0.060</td>
<td>p&gt; 0.05</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>r=0.001</td>
<td>p&gt; 0.05</td>
</tr>
<tr>
<td>Vitamin D3</td>
<td>r=0.208</td>
<td>p&gt; 0.05</td>
</tr>
<tr>
<td>Testosterone</td>
<td>r=0.009</td>
<td>p&lt; 0.001</td>
</tr>
</tbody>
</table>
DISCUSSION

This work designated to study the effect of bilharzial periportal liver fibrosis on bone mineral density and to search for the possible pathogenesis in development of hepatic osteodystrophy through measurement of liver functions tests (SGOT, SGPT, total protein, albumin, total and direct bilirubin) and assessment of factors that regulate bone resorption and formation (serum calcium and phosphorus, alkaline phosphatase, parathyroid hormone (PTH), vitamin D3 (1-25 dihydroxy Vit D2) and testosterone) and correlate them to bone mineral density assessing bone mineral metabolism.

As regard to liver function tests, In our study the serum level of liver enzymes (SGOT and SGPT) increase in patients with BPLF in comparison to control group with statistical significant difference (P<0.01), but there is no direct correlation between liver enzymes and BMD. So the liver enzymes are helpful for follow up of hepatocellular activity and hepatopathology. This is also found by Bagur et al. (1998) who reported that elevated liver enzymes are not risk factors for development of osteoporosis and he consider the ascitis and esophageal varices are the clinical predictors for osteoporosis development in hepatic patients, while Angulo et al. (1998) stated that the liver enzymes are the mirror of hepatic pathophysiology and important indicator for osteoporosis development

Both total and direct bilirubin in our study are significantly increased in patients with BPLF than control individuals (p<0.01) and are directly correlated with BMD. So the bilirubin can be considered as an important investigation required for diagnosis and follow up of liver diseases and for prediction of osteoporosis development and this is agreed with Janes et al. (1995) who considered high level of direct bilirubin is a potent indicator for development of osteoporosis.

In our study the serum albumin decreased in patients group in comparison to healthy group (p<0.01) and correlated with BMD (p<0.001) so it is considered as one of important indicators of liver function assessment and development of hepatic osteoporosis. This is also reported by Kalef et al. (1996) who consider low level of serum albumin is example of inverse relationship between BMD and liver dysfunction.

As regard to serum calcium and phosphorus, our study showed that the serum levels of calcium and phosphorus are slightly decreased in patients group and did not show significant difference with control group (p>0.05) and these results agreed with Floreani et al. (2001) who stated that
serum levels of calcium and phosphorus did not change between hepatic patients and normal individuals.

The alkaline phosphatase remains within normal range in patients group and showed no significant difference with control group. But our results disagreed with Mehmet et al. (2001) who found increase in alkaline phosphatase level in hepatic patients, but he failed to get a positive correlation between alkaline phosphatase and BMD.

In our study, the serum level of parathyroid hormone (PTH) is slightly decreased and the vitamin D level is slightly increased in patients with bilharzial liver fibrosis (p>0.05) and we cannot obtain a direct correlation between them and BMD. Our results are in agreement with Long et al. (1998) who found that there is no histologic or radiologic evidence of excess parathyroid activity in patients with chronic liver diseases and osteoporosis. But, Gallego-Rojo et al. (2001) stated that elevation of PTH had been correlated with decrease of vitamin D and with severity of liver diseases.

Our study showed that there is significant reduction of testosterone level in patients with BPLF in comparison to control group (p<0.001) and there is direct correlation between testosterone level and BMD (either T-score or Z-score) so we can considered that low testosterone level is a very important cause for development of hepatic osteodystrophy because the testosterone hormone is the main androgenic sex steroid in bone building in males. Our results are in agreement with Floreani et al. (2001) and Guechot et al. (1994) who found that there is significant decrease of testosterone level in hepatic patients and this reduction correlated with BMD in these patients. While Ormarsdottir et al. (1999) found in his study that serum level of testosterone doesn't correlate with BMD

So the results of our study suggest that male hypogonadism is an important factor for development of osteoporosis in cases of bilharzial periportal hepatic fibrosis and suggest that decline of testosterone started in the liver as result of hepatic insult and this decrease of testosterone in male patients can be called andropause.

Measurement of bone mineral density in our study showed highly significant decrease of both T-score and Z-score (p< 0.001) in comparison to control group. Also we found that the BMD level ranged widely from osteopenia to sever osteoporosis and these results are in agreement with Gallego-Rojo et al. (2001) who described decrease bone density in 95% of patients with chronic liver diseases.
Conclusion:

We conclude that liver is one of the most important organ which is responsible for bone integrity and any chronic liver disease e.g. (bilharzial periportal liver fibrosis) can directly affect the bone and cause osteometabolic changes (hepatic osteodystrophy) So we recommend that any patient with osteoporosis must be checked out the liver by complete liver function as the liver may be the cause of osteoporosis.

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تقييم إصابة العظام بالتأكل في المرضى الذين مصابين بالتأكل الكبد
المصاحب للهبرهاسيا

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الهدف من البحث: يهدف هذا البحث إلى تقييم إصابة العظام بالتأكل في المرضى الذين مصابين بالتأكل الكبد
المصاحب للهبرهاسيا عن طريق قياس وظائف الكبد المختلفة و دراسة العوامل المنظمة لكل من عمليتي هدو و فسفر العظام و مقارنة هذه العوامل في قياس كثافة العظام.

الطريقة: أجري هذا البحث على 50 مريضاً من المرضى الذين مصابين بالتأكل الكبد
المصاحب للهبرهاسيا و تتراوح أعمارهم من 20-50 عاماً كما تم اختيار 40 شخصاً سليماً كمجموعة ضابطة و بعد تسجيل التاريخ المرضي و بعد الفحص الشامل تم إجراء الأبحاث الأتي:

قياس وظائف الكبد و تشمل (إنزيمات الكبد و الألبو تينوين و البيليروبين والبروتين الكلي) اختيار مستوى كل من الكالسيوم و الفوسفور و هرمون الباثروتون و هرمون الكورة

(التيستسترون) و فيتامين د بالدم.

عمل أشعة تلفزيونية للبطن و قياس كثافة العظام.

النتائج: وجد أن كثافة العظام تقل في المرضى الذين مصابين بالتأكل الكبد
المصاحب للهبرهاسيا عن الأشخاص الطبيعيين و أن إنزيمات الكبد تزيد في هؤلاء المرضى عن الأشخاص الطبيعيين ولكنها لا ترتبط بنقص كثافة العظام وأيضاً نسبة البيليروبين تزيد في المرضى الذين مصابين بالتأكل الكبد المصاحب للهبرهاسيا عن الأشخاص الطبيعيين ولكنها مرتبطة بنقص كثافة العظام بالنسبة للألبومين فإنه يقل في المرضى و يرتبط بنقص كثافة العظام.

أما العوامل المنظمة لعملية بناء و هدم العظام مثل الكالسيوم والفوسفور و هرمون
الباثروتون و فيتامين د بالدم فإنه اختفى في المرضى عن الأشخاص الطبيعيين ولكن بدون دلالات إحصائية كما أنها لا ترتبط بنقص كثافة العظام. أما هرمون الذكرة (التيستسترون) فإنه يقل في المرضى الذين مصابين بالتأكل الكبد المصاحب للهبرهاسيا عن الأشخاص الطبيعيين ويربط إحصائياً بنقص كثافة العظام.

الاستنتاج: يُستخلص من هذا البحث أن الكبد يلعب دوراً أساسياً في المحافظة على
سلامة العظام وأن أمراض الكبد المزمنة مثل التأكل الكبد المصاحب للهبرهاسيا يؤثر تأثيراً
مباشر على العظام و يتسبب في حدوث هشاشة العظام وذاه يجب أن يتم فحص الكبد جيداً وعمل
قياس لوظائف الكبد في المرضى المصابين بقضايا العظام.