ALTERED RANKL/OPG SYSTEM IN 
HEPATIC OSTEODYSTROPHY

HANAN AL-SAADANY, HANAN SOLIMAN *, FERAL AL-CALLA *, GAMAL KASEM*, HALA NAGY**, HEBA MORAD** AND AMAL AL-BENDARY**

Rheumatology & Rehabilitation, Tropical Medicine*and Clinical Pathology** Departments, Tanta University Faculty of Medicine

KEY WORDS: HEPATIC OSTEODYSTROPHY, RANKL, OPG, BMD, INR, Ca.

ABSTRACT

Hypothesis: The coexistence of liver disease and metabolic bone disease has been recognized for many years and is now the subject of increasing attention. Hepatic Osteodystrophy was established in patients with cholestatic liver disease, but new research suggests that it is prevalent in patients with other chronic liver diseases. Its etiology is complex and multifactorial. Receptor activator of nuclear factor Kb ligand (RANKL) plays a role in the differentiation and activation of bone resorbing osteoclasts by binding to its high affinity receptor (RANK) located on the surface of osteoclasts. This effect is counterbalanced by osteoprotegren (OPG), which acts as a decoy receptor competing with RANKL for RANK.

Objective: To evaluate bone mineral density (BMD) and OPG/RANKL system in cirrhotic patients with backache.

Methodology: This study included 50 subjects suffering from backache, divided into 4 groups as follows: Group I: 10 subjects with normal BMD, Group II: 10 patients with pathological BMD but otherwise healthy considered as control, Group III: 15 patients with cirrhosis and normal BMD, Group IV: 15 patients with cirrhosis and pathological BMD. All patients underwent clinical examination, routine liver function tests, alkaline phosphatase, total calcium, serum OPG, serum RANKL, added to BMD.

Results: The lowest BMD values are estimated at the lumber spine, femoral neck, and lastly lower end of radius. There was a significant decrease in OPG in osteopenic/osteoporotic non cirrhotic patients compared to control group,
while it is significantly higher than control in both osteopenic/osteoporotic and patients with normal BMD of cirrhotic groups. RANKL was significantly higher in non cirrhotic patients with pathological BMD compared to control group, but lower than control in cirrhotic groups both with normal and pathological BMD, with significant difference in cirrhotic with pathological BMD and non significant in those with normal BMD compared to controls. Serum OPG was negatively correlated to serum calcium, albumin, and International Normalized Ratio (INR), but positively correlated to bone alkaline phosphatase, and AST in cirrhotic patients of both groups.

**Conclusion:** In cirrhotic patients, low BMD has tendency to affect axial bone early, which is similar to postmenopausal osteoporosis. On the contrary, higher OPG and lower RANKL levels are opposite to postmenopausal osteoporosis. This difference indicates that: OPG/RANKL system is activated in a different way in cirrhosis, suggesting a role for OPG/RANKL system in pathogenesis of hepatic osteodystrophy.

**INTRODUCTION**

Hepatic osteodystrophy is defined as metabolic bone disease associated with chronic liver disease (CLD). Conceptually it can be divided into osteomalacic disorder and osteopenic/osteoporotic disorders. Osteopenia accounts for the majority of cases in CLD whereas osteomalacia is rare in absence of advanced liver disease and malabsorption *(Diamond et al., 1989)*. Osteoporosis is defined as a progressive systemic skeletal disease characterized by bone mass and micro architectural deterioration with subsequent increase in bone fragility and susceptibility to fractures. The commonest fractures are compression vertebral fractures, fractures of distal radius and proximal femur *(WHO Study Group, 1994)*.

Traditionally; osteodystrophy was evaluated through bone biopsies or X ray. However, the first is too invasive and the second is not reliable. The development of dual energy x ray absorptiometry (DEXA) has facilitated the accuracy of BMD determination with low doses of radiation *(Melton et al., 1990)*.

The WHO has defined osteopenia as a BMD between-1 and -2.5 standard deviation (SD) and osteoporosis as BMD < -2.5 SD the mean peak
value in young adults (T score). Another BMD parameter is to compare the mean peak value to that of normal subjects of the same age, sex, and ethnic group (Z score). A Z score below -2 SD corresponds to a value in the lowest 25 percentile of the reference range, a value at which the risk of fracture is approximately doubled (WHO Study Group, 1994).

Hepatic osteodystrophy had a prevalence ranged between 20% and 100% depending upon selection criteria. It can result in spontaneous or low-trauma fracture with significant impact on morbidity, quality of life and even survival (Rouillard & Lane 2001). However, correlation between liver dysfunction as assessed by Child–Pugh score and the incidence of osteodystrophies is poor (Tsuneoka et al., 1996).

Standard therapies for osteoporosis, given to post-menopausal women with chronic liver disease are much less effective than if they were given to non hepatic women. An incomplete understanding of the pathogenesis of hepatic osteodystrophy has hampered the development of effective therapy for this troublesome complication (Floreani et al., 1997). The pathogenesis of hepatic osteodystrophy is thought to comprise multiple factors including the genetic background, nutritional deficiency, low vitamin D, Ca deficiency, low insulin-like growth factor I, and excessive alcohol intake (Leslie et al., 2003).

Hepatic osteodystrophy could be due to decrease bone formation or increased bone resorption. The most widely used markers of bone resorption are: urinary excretion of deoxypyridinoline, pyridinoline, and type 1 collagen cross linked N-telopeptide. These are usually expressed in relation to urinary creatinine. However, as their levels are affected by the extent of hepatic fibrosis, they cannot be recommended as a means of assessing bone loss and the risk of fracture in cirrhotic patients (Collier et al., 2002).

Van der Merwe et al., (2000) hypothesized that cytokines, through suppression of bone formation or increased bone resorption, are important in the osteodystrophy associated with both parenchymal and cholestatic liver disease. They suggest cytokine activation to be the final common pathway leading to the osteodystrophy of both parenchymal and cholestatic liver diseases.

RANKL- a member of TNF family - is a 317-aminoacid ligand in the form of type II transmembrane protein as well as a soluble molecule. RANKL gene expression by marrow stromal cells and osteoblasts is most abundant in the skeleton and lymphoid tissues (Yasuda et al., 1998) and plays a role in the differentiation and activation of bone resoring
osteoclasts by binding to its high affinity receptor (RANK) located on the surface of osteoclasts (Hsu et al., 1999).

This effect is counterbalanced by OPG, which acts as a decoy receptor competing with RANKL for RANK. The biological effect of OPG is the inhibition of both the terminal stages of osteoclastogenesis (differentiation from osteoclast precursors) and activity of mature osteoclasts (Simonet et al., 1997 and Known et al., 1998).

High mRNA levels of OPG and moderate levels of RANKL have been detected in liver tissue and low serum RANKL and high OPG levels have been reported in primary biliary cirrhosis (Szalay et al., 2003) and Wilson’s disease (Hegedu set al., 2002), but little is known about this system in post-hepatitis cirrhosis. If OPG/RANKL system was involved in hepatic osteodystrophy, it would be possible to add new measures to standard therapy of osteoporosis in cirrhotic patients.

Aim of Work:

This study aimed at evaluation of OPG/RANKL system in cirrhotic patients.

**PATIENTS AND METHODS**

To address this issue we screened cirrhotic patients suffering from backache for bone mineral density (BMD). Exclusion criteria were: body mass index <19, corticosteroids (5 mg/day more than 3 months), hormonal therapy, alcohol intake, serum bilirubin >3mg%, hypogonadism, early menopause (<45 years), as these are risk factors for osteoporosis regardless liver condition (Collier et al., 2002) The first 15 patients with normal BMD were included (male/female 6/9, age ranged from 45 to 62), then 15 age and sex matched cirrhotic patients with low BMD were included (male/female 6/9, age ranged from 44 to 64), unmatched cases were excluded from the study. For comparison, 20 patients with backache but otherwise healthy were included as control group 10 of them with normal BMD (male/female 4/6, age ranged from 47 to 63), and 10 with low BMD (male/female 4/6, age ranged from 48 to 65). They were grouped as follow:

**Group I:** 10 subjects with normal BMD

**Group II:** 10 patients with pathological BMD but otherwise healthy

**Group III:** 15 patients with cirrhosis and normal BMD

**Group IV:** 15 patients with cirrhosis and pathological BMD
The 4 groups were age and sex matched. All female patients included were post menopausal. At the time of the study, no patient had symptomatic fractures. All patients underwent clinical examination, BMD examination, routine liver function tests, alkaline phosphatase, total calcium, serum OPG and RANKL measurements.

Nine millilitres of blood were collected into sterile tube, centrifuged at 1200 g for 15 min at 4°C. Serum separated was aliquoted into 1 ml portions and stored at -80°C until assayed. Levels of OPG and RANKL in serum specimens were determined by commercially available specific ELISAs according to manufacturers’ protocols (DuoSet Development System, human OPG, R&D Systems; RANKL ELISA, Biomedica GmbH, Vienna, Austria). Absorption was determined with an ELISA reader at 450 nm.

Alkaline phosphatase was measured in serum before and after heating to 45°C for 15 mints. The subtraction of them equals bone alkaline phosphatase as it is heat labile.

The total Ca level was corrected according to albumin level raising total Ca 0.8mg/dL for each 1gm decrease in serum albumin below 4 gm/dL (Fedman & Wolfson, 1990).

BMD was assessed with a HOLOGIC QD 4500A X-ray bone densitometer (DEXA) for PA lumbar spine between L2 and L4, femoral neck with an antero-posterior projection and lower end radius. The procedures proposed by the manufacture BMD was expressed as gram/square centimeter, T- and Z-scores were determined for each patient according to the WHO Study Group Recommendations and supplied as computerized report. For the Definition of Osteoporosis and Osteopenia, a T-score between -1 and -2.5 classified as osteopenia and below -2.5 classified as osteoporosis [WHO Study Group].

**Statistical analysis:**

The collected data were organized, tabulated, and statistically analyzed using SBSS soft wear statistical computer package Ver 12. For quantitative data mean & SD were calculated, differences between means were analyzed using ANOVA test. Pearson's correlation was used to test associations between two quantitative values, and confidence interval of 95% was adopted for significance in all used tests, where (p≤0.05) is considered significant.
RESULTS

Table (1): Comparison of BMD in all studied groups.

<table>
<thead>
<tr>
<th>T score</th>
<th>At lumbar spine</th>
<th>At femoral neck</th>
<th>At lower end radius</th>
</tr>
</thead>
<tbody>
<tr>
<td>groups</td>
<td>G I</td>
<td>G II</td>
<td>G III</td>
</tr>
<tr>
<td>mean</td>
<td>0.34</td>
<td>-1.69</td>
<td>-0.87</td>
</tr>
<tr>
<td>SD</td>
<td>0.33</td>
<td>0.98</td>
<td>0.94</td>
</tr>
<tr>
<td>F</td>
<td>26.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>q</td>
<td>11.05*</td>
<td>2.739</td>
<td>3.43*</td>
</tr>
<tr>
<td>q1</td>
<td>9.37*</td>
<td>1.325</td>
<td></td>
</tr>
<tr>
<td>q2</td>
<td>11.95*</td>
<td></td>
<td>21.79*</td>
</tr>
</tbody>
</table>

q = Control versus other groups.
q1 = Control with pathological BMD versus cirrhosis with or without normal BMD.
q2 = Cirrhosis with normal BMD versus cirrhosis with pathological BMD.
* = Significant (p< 0.05).

Table (2): Comparison of serum OPG, RANKL in all studied groups.

<table>
<thead>
<tr>
<th>Control with normal BMD</th>
<th>Control with pathological BMD</th>
<th>Cirrhosis with normal BMD</th>
<th>Cirrhosis with pathological BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPG (Pmol/L)</td>
<td>RANKL (Pmol/L)</td>
<td>OPG (Pmol/L)</td>
<td>RANKL (Pmol/L)</td>
</tr>
<tr>
<td>Mean</td>
<td>1.15</td>
<td>1.4</td>
<td>0.49</td>
</tr>
<tr>
<td>SD</td>
<td>0.43</td>
<td>0.32</td>
<td>0.18</td>
</tr>
<tr>
<td>F (P)</td>
<td>OPG F = 45.908 (p=0.001)</td>
<td>RANKL F=50.761 (p=0.001)</td>
<td></td>
</tr>
<tr>
<td>q</td>
<td>6.5*</td>
<td>20.06*</td>
<td>6.67*</td>
</tr>
<tr>
<td>q1</td>
<td>9.9*</td>
<td></td>
<td>13.1*</td>
</tr>
<tr>
<td>q2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Where:
q = Control versus other groups
q1 = Control with pathological BMD versus cirrhosis with or without normal MD.
q2 = Cirrhosis with normal BMD versus cirrhosis with pathological BMD.
* = Significant (p< 0.05).

The healthy controls showed T score of 0.34± 0.33, 0.59±0.13, and 0.71±0.41, while cirrhotic with normal BMD showed a T score of -0.87± 0.94, -0.62±0.43, and -0.5±0.24 at lumbar spine, femoral neck, and lower end of radius respectively. The decrease in T score was non significant (p>0.05). On the other hand, cirrhotics with low BMD show T score of -2.4± 0.67, -1.93±0.5, and -1.71±0.98 which was non significantly lower at the three levels (p>0.05) than non cirrhotic patients with low BMD who
show T score of -1.69± 0.98, -1.52±0.41, and -1.31±0.84 at lumber spine, femoral neck, and lower end of radius respectively.

Table (3): Correlation between OPG, RANKL and other parameters among cirrhotic patients.

<table>
<thead>
<tr>
<th></th>
<th>Cirrhosis with normal BMD</th>
<th>Cirrhosis with pathological BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OPG (Pmol/L)</td>
<td>RANKL (Pmol/L)</td>
</tr>
<tr>
<td></td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>BMD</td>
<td>0.402</td>
<td>0.057</td>
</tr>
<tr>
<td>Ca</td>
<td>-0.775*</td>
<td>0.008</td>
</tr>
<tr>
<td>Albumin</td>
<td>-0.841*</td>
<td>0.002</td>
</tr>
<tr>
<td>PT(INR)</td>
<td>-0.756*</td>
<td>0.01</td>
</tr>
<tr>
<td>Alk. Ph.</td>
<td>0.97*</td>
<td>0.000</td>
</tr>
<tr>
<td>AST</td>
<td>0.871*</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* = Significant (p< 0.01).

BMD in all studied groups.  
RANKL/OPG in all studied groups.

It is observed that the T score of BMD has its lowest values at the lumber spine, femoral neck, and lastly lower end of radius in all studied groups.

BMD was not correlated to OPG (r=-0.402, p=0.057; r=0.328, p=0.233) or RANKL (r=-0.398, p=0.060; r=-0.303, p=0.195) either in cirrhosis with normal BMD, or in cirrhosis with pathological BMD respectively.
In this study, there was a significant decrease in OPG in osteopenic/osteoporotic non cirrhotic patients (0.49±0.18) compared to control group (1.15±0.43) (q=6.5, p=0.041), while cirrhotic groups showed significant increase in both osteopenic osteopenic/osteoporotic (4.4±1.3) and non osteopenic/osteoporotic (2.49±0.89) compared to control group (q = 13.8, p=0.02; and q=6.67, p= 0.04 respectively).

OPG was significantly higher in cirrhotic groups osteopenic (4.4±1.3) and non osteopenic/osteoporotic (2.49±0.89) versus non-cirrhotic osteopenic/osteoporotic patients (q=12.9, p= 0.028; and q=9.9, p=0.032). Lastly, OPG was significantly higher in cirrhotic osteopenic/osteoporotic (4.4±1.3) than non cirrhotic osteopenic/osteoporotic (2.49±0.89) (q=15.8, p=0.015).

Regarding serum RANKL, it was significantly higher in non cirrhotic patients with pathological BMD (2.07±0.16) compared to control group (1.4±0.32) (q=20.06, p =0.009). On the other hand, it was lower than control in cirrhotic groups both with normal BMD (1.3±0.25) and with pathological BMD (0.72±0.14), with significant difference in cirrhotic with pathological BMD and non significant in those with normal BMD compared to control (q=11.2, p = 0.03; and q= 1.4 ,p= 0.41 respectively).

Osteopenic/osteoporotic non cirrhotic patients had significantly higher RANKL compared to control, cirrhotic with normal BMD and cirrhotic with pathological BMD (q=20.06, p =0.009; q= 13.1, p = 0.024; and q =15.8, p = 0.021 respectively).

Osteopenic/osteoporotic cirrhotic patients had significantly lower RANKL (0.72±0.14) compared to cirrhotic with normal BMD (1.3±0.25) (q=18.5, p=0.016). In cirrhotic patients with normal BMD the increase in serum OPG was negatively correlated to serum calcium (r=-0.775, p=0.008), albumin (r=−0.841, p=0.002) and INR (r=−0.756, p=0.01), but positively correlated to bone alkaline phosphatase (r=0.97, p= 000) and AST (r=0.871, p=0.001).

In the same group, RANKL was not correlated to all parameters; serum calcium (r=0.394, p=0.146), albumin (r=0.336, p=0.22), INR(r=0.388, p=0.153), bone alkaline phosphatase (r=0.467, p= 0.08) and AST (r=0.415, p=0.124).

In cirrhotic patients with pathological BMD, the increase in serum OPG was negatively correlated to serum calcium (r=0.807, p=0.001), albumin (r=−0.703, p=0.003) and INR (r=−0.761, p=0.001), but positively
correlated to bone alkaline phosphatase \( (r=0.935, p=0.000) \) and AST \( (r=0.772, p=0.001) \).

In same group, RANKL was not correlated to all parameters; serum calcium \( (r=0.286, p=0.301) \), albumin \( (r=0.455, p=0.088) \), INR \( (r=0.328, p=0.233) \), bone alkaline phosphatase \( (r=0.421, p=0.118) \) and AST \( (r=0.442, p=0.09) \).

**DISCUSSION**

Although metabolic bone disease is a systemic condition, BMD assessments at one site correlated imperfectly with measurement at another site in the same patient and screening for low BMD at a single site can underestimate its frequency and severity (Kalef-Ezra et al., 1996). In this work, we studied BMD at three sites; L 2-4, femoral neck, and lower end of the radius to assess both central and peripheral affection. It was observed that BMD has its lowest values at the lumbar spine, then femoral neck and lastly lower end of radius in all studied groups, with non significant difference between cirrhotic and non cirrhotic patients with low BMD.

These findings mean that axial bone is affected earlier than peripheral bone in both cirrhotic and non hepatic cases. This was in agreement with Figeiredo et al. (2003) and can be explained by the faster rate of renewal in trabecular bone than cortical bone (up to 8 times), which makes sites with high proportion of trabecular bone such as vertebrae and femoral neck affected earlier. On the other hand the alteration is less in the sites with less in trabecular bone than cortical bone as in lower end of the radius (Lan & Boff 2006), so these alteration will be apparent earlier and more intense at lumbar spine, than femoral neck, and lower end of radius explaining the observed results.

BMD was not correlated to OPG or RANKL either in cirrhosis with normal BMD, or in cirrhosis with pathological BMD, which was in agreement with other authors (Figeiredo et al., 2003, Moschen et al., 2005 and Szalay, 2003).

The OPG/RANKL system is the key regulator of osteoclastogenesis. Some of the cytokines involved in the pathogenesis of cirrhosis (IL-1, IL-6, and TNFα) are linked to osteoclastogenic through potentiating RANKL inducing stromal/osteoblastic cells (Hofbauer et al., 1999). The activated osteoblasts produce OPG as well which can bind to RANK on the osteoclast surface blocking it and prevent its activation with RANKL, preventing osteoclast maturation with subsequent stoppage of resorption.
OPG is produced mostly by osteoblast, so if there is a reduced osteoblast function in cirrhosis, one would expect lower OPG levels in cirrhotic than in healthy, and in osteopenic/osteoporotic than in non osteopenic/osteoporotic individuals. In this work, non cirrhotic patients obey this logic rule, but cirrhotic patients don't. Cirrhotic patients have significantly higher OPG compared to non-cirrhotics. Enhanced activity of the OPG system in cirrhotic cases may be the consequence of increased activity of other members of the TNF family and elevated serum level of pro-inflammatory cytokines, such as TNF-a and IL-6, also reported in cirrhosis (Hofbauer et al., 1999).

Cirrhotic osteopenic/osteoporotic patients have significantly higher OPG compared to cirrhotic non osteopenic/osteoporotic. the high OPG level found in this study was reported by other researchers (Szalay et al., 2003 and Moschen et al., 2005) and can implicate that other tissues or cells, such as T- or B-cells or fibroblasts in the liver, may also contribute to the production of this molecule as a consequence of the inflammatory process (Hofbauer et al., 2000), or dysfunctional osteoblasts themselves produce excessive amount of OPG (Moschen et al., 2005). Uelad et al. (2001) hypothesized that increased serum OPG levels found in Cushing’s syndrome may reflect a compensatory response to enhanced osteoclast activity or negative bone remodeling balance. Similar mechanisms may be present in cirrhosis as well.

In this study, RANKL was significantly higher in non-cirrhotic osteopenic/osteoporotic patients compared to control. This was in accordance with other authors who studied RANKL in post menopausal osteoporosis (McClung, 2006 & McClung et al., 2006).

On the contrary, RANKL was significantly lower in cirrhotic osteopenic/osteoporotic patients compared to cirrhotic non osteopenic/osteoporotic, which is surprising. High levels of bone protecting OPG and low levels of osteoclastogenic RANKL in osteopenic/osteoporotic patients are unexpected at first glance and query a role for the OPG/RANKL system in the development of bone loss in cirrhosis. However, similar results were obtained in patients with primary biliary cirrhosis without definite cause (Szalay et al., 2003), in the same study patients with chronic hepatitis C (CHC) had elevated RANKL but their patients were not matched with this study as they were not cirrhotic.

Recently, RANK/RANKL interaction was found to activate monocytes/macrophages, enhances cytokine secretion, and promotes stimulatory capacity and survival of these cells (Seshasayee et al., 2004).
This could suggest a possible role for RANK/RANKL in hepatic Kupffer cells which are the resident macrophages of the liver. As Kupffer cells are widely implicated in hepatic inflammation (Canbay et al., 2003), so RANK/RANKL interaction per se could theoretically contribute to the perpetuation of hepatic inflammation.

So it can be suggested that in hepatic osteodystrophy, there is increased RANK/RANKL affinity. RANK/RANKL complex is not measurable, and consumes part of total RANKL leaving a less amount of measurable soluble RANKL to be assessed, which explain its lower level in serum despite increase osteoporotic changes in bone. The same suggestion can explain the higher levels of OPG. As RANK/RANKL interaction stimulate OPG production (Tanaka et al., 2005), so higher level of OPG will follow RANK/RANKL complex formation. Accordingly, OPG couldn't beat the RANK/RANKL affinity resulting osteoporosis with elevated serum OPG level.

OPG was inversely correlated to albumin and INR, and positively correlated to AST but not ALT in both cirrhotic groups. This was a little different from (Szalay et al., 2003) who reported similar results except for positively correlated ALT in CHC. This variation could be explained by the parallel level of both enzymes in hepatitis which vary greatly in cirrhosis. These results were also in accordance with (Moschen et al., 2005) who reported similar results in post viral cirrhotic cases.

The inverse correlation between OPG and calcium, and positive correlation to bone alkaline phosphatase (AP), reported in this study are supported by similar reports for calcium by (Moschen et al., 2005 and Szalay et al., 2003) reported similar results for total rather than bone derived AP. RANKL did not correlate to any of these parameters. This was different from (Moschen et al., 2005) who reported positive correlation between calcium and RANKL in his patients, but agree with the rest of our results.

Conclusion:

In cirrhotic patients, hepatic osteodystrophy has a tendency to affect axial bone earlier than peripheral, which is similar to postmenopausal osteoporosis. On the contrary, cirrhotic osteopenic/osteoporotic patients have significantly higher OPG and lower RANKL than control, which is opposite to postmenopausal osteoporosis. This difference indicates that: OPG/RANKL system is activated in a different way in cirrhosis. We suggest an increased RANK/RANKL affinity to make this difference in hepatic osteodystrophy.
REFERENCES


Ueland T, Bollerslev J, Godang K, Muller F, Froland SS, Aukrust P (2001): Increased serum osteoprotegerin level in disorders characterized by persistent...
immune activation or glucocorticoid excess-possible role in bone homeostasis.

osteodystrophy: the influence of liver disease and portal hypertension on

WHO Study Group (1994): Assessment of fracture risk and its application to screening
Organ Tech Rep Ser 843: 1–129.

Yasuda H, Shima N, Nakagawa N, Yamaguchi K, Kinosaki M, Mochizuki S-I, et
al. (1998): Osteoclast differentiation factor is a ligand for osteoprotegerin
osteoclastogenesis inhibitory factor and is identical to TRANCE/-RANKL.

نظام (رابط المستقبلات المنثة للعظام النوي) كتامب/العظام المحفزة
للتعظم) مختل في حالات التأكل العظمي الناجم عن أمراض الكبد المزمنة.

ينان السدعي، حنان سليمان*، فريال القلاً، جمال قاسم*، هالة ناجي**، هبة
مراد**، أمل البنداري***

أهمية النظام: إن ارتباط ظهور أمراض العظام الأيضية، وخصوصاً الشائعة، بأمراض الكبد
المزمنة أمر ثابت.は何دها تم إكتشاف نظام رابط المستقبلات المنثة للعظام النوي كتامب/العظام
المحفزة للتعظم، ووجد أنه يلعب دوراً محورياً في تنظيم عملية التعظم والإصابة بالتشقية، لكن
دراسته في أمراض الكبد المزمنة محدودة للغاية.

الهدف: استهدف هذا البحث دراسة نظام رابط المستقبلات المنثة للعظام النوي
كتامب/العظام المحفزة للتعظم في مرضى التشيم الكبدي الذين يعانون من ألم الظهر.

الطريقة: ضمت الدراسة 50 شخصاً تم تقسيمهم إلى أربع مجموعات المجموعة الأولى
التي تآثرت 10 أشخاصاً كمجموعة ضابطة، والثانية 15 أشخاصاً مصابين بتشيش الكبد،
والثالثة 15 أشخاصاً مصابين بالتشيش الكبد، وعالية عظامهم طبيعية، والرابعة 15 أشخاصاً مصابين بالتشيش
الكل، وهشاشة العظام. وقد تم أخذ التأثيرات المرضية بناءاً على الشروط الإلكترونية لإنشاء الاستفادة
والاختبارات الفعلية العظام الكاملة للتشيش الفيروسي التي تأخذ النواة بالتشيش
قيمة رابط المستقبلات المنثة للعظام النوي كتامب/العظام المحفزة للتعظم بالإضافة إلى تقيس
كفاءة العظام والتي تتم على أساسها اختيار الحالات.

النتائج: سجلت الدراسة وجود أقل قراءة لكلائمة العظام في المرضى المصابين بتشيش
العظام في الفترات القطنية تليها رقية عظامها الفخذ ثم النهاية الطفيفة لنظامها الرحم.

كما أظهرت النتائج زيادة ذات دلالة إحصائية في مستوى العظام المحفزة للتعظم في
المرضى المصابين بالتشيش يوجد المرض مع الشائعة لدى مقارنتها بالمجموعة
المجموعة النموذجية. للعظام المحفزة للتعظم

نظام (رابط المستقبلات المنثة للعظام النوي) كتامب/العظام المحفزة
للتعظم) مختل في حالات التأكل العظمي الناجم عن أمراض الكبد المزمنة.

ينان السدعي، حنان سليمان*، فريال القلاً، جمال قاسم*، هالة ناجي**، هبة
مراد**، أمل البنداري***

أهمية النظام: إن ارتباط ظهور أمراض العظام الأيضية، وخصوصاً الشائعة، بأمراض الكبد
المزمنة أمر ثابت.は何دها تم إكتشاف نظام رابط المستقبلات المنثة للعظام النوي كتامب/العظام
المحفزة للتعظم، ووجد أنه يلعب دوراً محورياً في تنظيم عملية التعظم والإصابة بالتشقية، لكن
دراسته في أمراض الكبد المزمنة محدودة للغاية.

الهدف: استهدف هذا البحث دراسة نظام رابط المستقبلات المنثة للعظام النوي
كتامب/العظام المحفزة للتعظم في مرضى التشيم الكبدي الذين يعانون من ألم الظهر.

الطريقة: ضمت الدراسة 50 شخصاً تم تقسيمهم إلى أربع مجموعات المجموعة الأولى
التي تآثرت 10 أشخاصاً كمجموعة ضابطة، والثانية 15 أشخاصاً مصابين بتشيش الكبد،
والثالثة 15 أشخاصاً مصابين بالتشيش الكبد، وعالية عظامهم طبيعية، والرابعة 15 أشخاصاً مصابين بالتشيش
الكل، وهشاشة العظام. وقد تم أخذ التأثيرات المرضية بناءاً على الشروط الإلكترونية لإنشاء الاستفادة
والاختبارات الفعلية العظام الكاملة للتشيش الفيروسي التي تأخذ النواة بالتشيش
قيمة رابط المستقبلات المنثة للعظام النوي كتامب/العظام المحفزة للتعظم بالإضافة إلى تقيس
كفاءة العظام والتي تتم على أساسها اختيار الحالات.

النتائج: سجلت الدراسة وجود أقل قراءة لكلائمة العظام في المرضى المصابين بتشيش
العظام في الفترات القطنية تليها رقية عظامها الفخذ ثم النهاية الطفيفة لنظامها الرحم.

كما أظهرت النتائج زيادة ذات دلالة إحصائية في مستوى العظام المحفزة للتعظم في
المرضى المصابين بالتشيش يوجد المرض مع الشائعة لدى مقارنتها بالمجموعة
المجموعة النموذجية. للعظام المحفزة للتعظم
الضابطة، على حين كان هذا العامل المنخفض بصورة ذات دلالات إحصائية في مرضى الهشاشة.

أما رابط المستقبلات المنخفضة للعامل النووي كابا فقد زاد زيادة ذات دلالات إحصائية في مرضى الهشاشة الغير مصابين بأمراض الكبد مقارنة بالمجموعة الضابطة، بينما كان هذا الرابط منخفضاً في المرضى المصابين بالتشمع الكبدي مقارنة بالمجموعة الضابطة وكان هذا انخفاضًا ذا داللة إحصائية فقط في مرضى التشمع الكبدي المصابين بهشاشة العظام.

وقد وجد أن العلاقة الإرتباطية عكسية بين العامل المحفز للتعظم وكلاً من الكالسيوم والألبومين وكفاءة التجلط، وترددي بينه وبين فوسفاتي العظام القاعدي وإنزيم الإسبرتات الداقل للأمن في مرضى التشمع الكبدي.

الخلاصة: مما سبق نخلص إلى ما يلي: في مرضى التشمع الكبدي تميل هشاشة العظام لإصابة العظام المركزية مبكراً عن الطرفية، وهو أمر مشابه للهشاشة المصاحبة للإياس والتي تحدث دون وجود أمراض في الكبد. بينما يشير نظام رابط المستقبلات المنخفضة للعامل النووي كابا/العامل المحفز للتعظم في مرضى التشمع الكبدي المصابين بهشاشة العظام في إجابة معاكسة لما يشير عليه في الهشاشة الغير مصحوبة بالتشمع، مما يدل على أن التشمع الكبدي أدي تنشيط هذا النظام بصورة مختلفة قد تكون جزءًا من التطور المرضي للتأكل العظمي الكبدي المنشأ.