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Prevalence of osteoporosis in liver cirrhosis

Karaciğer sirozunda osteoporoz sıklığı

Ümit Bilge DOĞAN MD[1], Seren ÖZENİRLER MD[1], Mehmet ARAÇ MD[2], Ayhan KARAKOÇ MD[3], Ziya ÖZTÜRK MD[1], Mehmet CİNDORUK MD[1], Uğur KANDİLCİ MD[1]

Department of Gastroenterology[1], Radiology[2] and Internal Medicine[3], Gazi University Medical Faculty, Ankara

ÖZET: *Osteoporoz, alkolik karaciğer hastalığının, primer ve sekonder bilier sirozun iyi bilinen bir komplikasyonudur. Patogenezde safra tuzları, alkol ve beslenme yetersizliği suçlanmakla birlikte, hepatosellüler hasarla kemik kaybı arasıdaki ilişki hala iyi anlaşılmış değildir. Hepatik osteodistrofinin sıklığını ve ciddiyetini invaziv olmayan metodlarla tesbit etmek için, histolojik olarak kronik karaciğer hastalığı tanısı konmuş 37 hastayı, yaşı ve cinsiyeti uygun 19 kişiyle mukayese ettik. Otuzyedi hastanın 26'sında posthepatitik siroz, 4'ünde alkolik karaciğer hastalığı, 3'ünde kriptojenik, 3'ünde otoimmün ve birinde primer bilier siroz vardı. Kullanılan metodlar kırık insidansının spinal radyografi ile değerlendirilmesini ve vertebral kemik dansitesinin kantitatif tomografi ile ölçümünü içerdi. Sadece, alkolik karaciğer hastalığı olan bir hastada spinal fraktür vardı. Vertebraların kemik mineral dansiteleri, alkolik karaciğer hastalığı olanlarda belirgin derecede azalmıştı. Sirozu olan diğer hastalarla sağlıklı kontrol grubu arasında spinal osteoporoz sıklığı açısından (%18.18 ve %10.53) fark bulunmadı. İskelet kırıklarının sıklığı veya kemik dansitesi üzerine, serum kalsiyum ve fosfat değerlerinin etkisi saptanmadı. Osteoporozun, alkolik sirozdakinin aksine, posthepatitik sirozda major bir komplikasyon olmadığı kanaatine vardık.*

Anahtar Kelimeler: **Karaciğer sirozu, osteoporoz**

SUMMARY: *Osteoporosis is a well known complication of primary and secondary biliary cirrhosis, and alcoholic liver disease. Although, factors such as bile salts, alcohol, low nutritional state have been incriminated in the pathogenesis, the association of bone loss with hepatocellular injury is still poorly understood. In order to determine the prevalence and severity of hepatic osteodystropy by non-invasive means we compared 37 patients with histologically proven chronic liver disease to 19 age and sex matched control subjects. In 37 patients, 26 had posthepatitic cirrhosis, 4 had alcoholic liver disease, 3 had cryptogenic cirrhosis, 3 had autoimmune cirrhosis and one had primary biliary cirrhosis. Methods used included the assessment of fracture prevalence rates with spinal radiography, and measurements of bone mineral density with quantitative computed tomography in the spine. Only, one patient who had alcoholic liver disease had spinal fracture. The bone mineral densities of the spines were significantly reduced in patients with alcoholic liver disease. No difference was seen in prevalence rates of spinal osteoporosis between other patients with cirrhosis (18.18%) and healthy control group (10.53%). The concentrations of serum calcium and phosphate were apparently without effect on the prevalence of skeletal fractures or bone density. We conclude that osteoporosis is not a major complication of posthepatitic cirrhosis, but alcoholic cirrhosis.*

Key Words: **Liver cirrhosis, osteoporosis.**

OSTEOPENIA has long been recognized as a potential complication of chronic liver disease. Initially, it was thought that the osteopenia was caused chiefly by osteomalacia (1-3), which does occur occasionally in the setting of vitamin D deficiency or limited exposure to UV light (4). Recent studies, chiefly in patients with cholestatic liver diseases such as PBC, indicate that osteoporosis is the most common abnormality of bone in osteopenic patients with liver disease (5-7).

Alcoholics have a higher prevalence of fractures than age-matched controls (8). Prolonged alcohol consumption induces calcium metabolism disturbances (9) leading to reduction of bone mass (10). In patients with alcoholic cirrhosis, osteoporosis is the most striking form of bone disease when histomorphometric analysis of bones are performed (11). However, the pathogenic mechanisms of trabecular bone loss remain poorly understood in lacohol abusers: whether alcohol directly affects bone remodeling cells or indirectly acts on calcium-regulating hormones is still a puzzling question. A secondary hyperparathyroidism (to chronic hypocalcemia) has been thought to be responsible for

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Table 1. Demographic and general features of subjects studied

	Posthep. cirrhosis	*Alcoholic cirrhosis*	*Other cirrhosis*	*All patients*	*Healthy controls*
Age (years)	51.1 ± 11.3	55.2±12.9	39.6±14.8	49.3±12.8	50.2±12.8
Male/Female	19/7	4/0	3/4	26/11	13/6
Child-A n(%)	13(50)	1(25)	4(57.11)	18(48.7)	0
Child-B n(%)	10(38.5)	2(50)	1(14.3)	13(35.1)	0
Child-C n(%)	3(11.5)	1(25)	2(28.6)	6(16.2)	0
PTZ (above control)	4±3.5	6±4.4	4.8±6	4.4±4	0.4±0.8
AST (IU/L)	67.8±75.1	55.3±46.6	56.6±37	64.3±66	27.4±0.8
ALT (IU/L)	49.2±41.6	56.5±70	47.3±36.4	49.6±42.9	30±10.7
GGT (IU/L)	107±102	110±163	126±108	111±107	64.4±35
AF (IU/L)	175±77	129±63	280±343	190±162	83.3±30.3
Bilirubin (mg/dl)	1.84 ±1.63	2.95±1.72	2.18±1.26	2.02±1.57	0.74±0.15
Albumin (g/dl)	3.25±0.74	3.37±0.68	3.67±0.94	3.35±0.77	4.22±0.25
Calcium (mg/dl)	9.35±0.82	8.85±0.68	8.96±0.65	9.22±0.79	9.98±0.50
Phosphorus (mg/dl)	3.74±0.67	3.52±0.41	3.57±0.72	3.69±0.65	3.78±0.42
Bone density (mg/cm3)	122±33.5	92.5±30.7	132±20.8	121±32.4	127±31.5
Osteoporosis, n(%)	5(19.23)	3(75)	1(14.29)	9(24.32)	2(10.53)

increased osteoclastic activity. However, biochemical studies have shown controversial results: an increased parathyroid hormone secretion is advocated by Bikle et al. (11), while normal and even reduced levels are noted by others (12). The reduced osteoblastic activity associated with normal osteoclastic function appears to play a major role in the pathogenesis of alcoholic osteoporosis leading to decreased bone mass with thinner trabeculae (13).

Severe osteopenia, regardless of cause, is a risk factor for development of fractures, which may be a source of morbidity and contribute to mortality in patients already debilitated by chronic liver disease. A first step toward prevention of this morbidity and mortality is to identify those patients with liver disease who have significant osteopenia. There are many studies concerning bone metabolism with chronic liver disease (1, 5-7, 11-12). Most of these relate to those who have had a bone biopsy, although non-invasive skeletal measurements have also been done in small numbers of selected patients (5-7, 11-12) or unselected ambulant individuals (14).

We assessed the prevalence of spinal fractures with standard spinal radiography. Bone mineral density was assessed by spinal quantitative computed tomography. The patients who suffered from various hepatic disorder were compared with appropritaly matched healthy controls.

METHODS

Subjects and controls: Thirty-seven patients with histologically proven chronic liver disease were studied. There were 26 men and 11 women aged 22-72 years (mean 49.35+12.77). Twenty-six patients had posthepatitic cirrhosis, 4 had alcoholic liver disease, 3 had cryptogenic cirrhosis, 3 had otoimmune cirrhosis and one had primary biliary cirrhosis. Hepatic cirrhosis was diagnosed by the usual histological criteria. No patient was taking cholestyramine, vitamin D, oestrogens, or calcium supplements. Control subjects were collected concurrently with the patients and were matched for age, sex, and menopausal status.

Women were specially questioned regarding their menstrual history. Menopause was defined as amenorrhoea of at least six months' duration. Five of the 11 female patients and 3 of the 6 female controls were menopausal.

A detailed fracture history was obtained. No peripheral fractures involving major long bones were found.

Spinal radiography and bone mineral density: Lateral thoracolumbar radiographs were evaluated from T3 to L5 for the presence of spinal compression fractures. Vertebral bone mineral density was measured with computed tomography. Repre-

sentative volumes of trabecular bone in the bodies of lumbar vertebrae L1-L4 were measured, averaged and expressed as mineral equivalents of dipotassium phosphate in mg/cm3. If a compression fracture was noted on the scout film in one of these vertebrea, an adjacent vertebra was measured instead. Although there is no sensitivity and specificity reported, osteoporosis of the lumber spine was defined as a mean spinal bone density measurement grater than 2 standard deviations below the mean value obtained in an age and sex matched control group.

Serum biochemical determinations: Serum calcium, serum inorganic phosphate, serum albumin, serum bilirubin and the activities of three serum enzymes (aspartate amino transferase, alkaline phosphatase, and gama glutamyl transferase) were measured with standard Auto-Analyzer methods. Serum levels of oestradiol and testosterone was measured by radioimmunoassasy.

Statistical analysis: All results were expressed as means. Group mean values were compared by student's t test.

RESULTS

The patient groups were of similar ages. All patients were ambulant. Standard liver function tests, mean serum oestradiol and testosterone concentrations were similar in all patient groups. To Child-Pugh score, 18 patients (48.65%) were in Chid-A, 13(35.14%) were in Child-B and 6 (16.22%) were in Child-C.

Table 1 summarizes general clinical features, values of laboratory variables and measurements of spinal bone densities of patients and normal controls. As a group, compared with normal controls, the patients had significant decreases in mean serum albumin and total serum calcium. Mean serum bilirubin, total alkaline phosphatase (AF), g-glutamyl transpeptidase (GGT), AST, ALT and prothrombin time were increased significantly. Mean serum phosphorus was normal in all instances. There were no significant differences between patients and conrols for oestradiol and testosterone levels.

The groups with posthepatitic and other cirrhosis had bone densities nearly the same as controls ($p>0.05$), whereas patients with alcoholic liver disease had significant decreases in bone densities. Only, one patient who had alcoholic liver disease had spinal fracture.

DISCUSSION

Although metabolic bone disease is recognized as a complication of advanced liver disease (1-7), only recently has it become feasible to assess its prevalence easily with newer noninvasive methods (dual-energy, computed tomographic scan, photon absorptiometry). A high prevalence of osteopenia was demonstrated in a diverse group of patients with liver disease (15). But most studies were done in decompensated cirrhotic patients because the calcium metabolic changes and the bone abnormalities were known to be maximized. In a study done in unselected ambulant patients, most of patients had alcoholic liver disease (14). The group to patients with posthepatitic cirrhosis is small in most studies.

In this study, all patients were ambulant and most of them had compensated cirrhosis. In patients with posthepatitic cirrhosis, Hepatitis-B virus was the most commonly seen agent (96.15%). We found no difference of osteoporosis between patients with posthepatitic cirrhosis and healthy controls. These data were similar to another study from Turkey (16). In that study, Ersöz et al. reported an increased bone turn-over without bone loss in patients with posthepatitic liver cirrhosis. Although the reason or reasons for the same prevalence of osteoporosis in our patients with posthepatitic cirrhosis are unknown, some possible explanations may be proposed: (a) Most of our patients had compensated cirrhosis and all of them were ambulant, and (b) as a group their nutrition was better and severity of liver disease less than the patients with posthepatitic cirrhosis previously studied by other groups.

Among subgroups of patients with liver disease in our study, those with alcoholic liver disease had significant osteoporosis. However, more patients in this category are needed to talk about the real prevalence of osteoporosis in alcoholic liver disease. Osteopenia in alcohol abusers is not caused simply by liver disease but also by alcohol ingestion itself (17) and perhaps by other factors often associated with alcoholism such as malnutrition, gonadal failure and physical inactivity. Only, one patient who had alcoholic liver disease had spinal fracture. Hodgson et al (7) who studied spinal fractures in 15 patients with primary biliary cirrhosis reported a prevalence rate of 13%, while Wilkinson et al (18) who studied peripheral fractures in 31 patients with alcoholic liver disease reported a prevalence rate of 32%. And, Diamond

et al (14) who studied spinal and peripheral fractures in 115 patients reported that the type of liver disease was without effect on the prevalence of spinal fractures, whereas peripheral fractures were more common in the alcoholic patients than in the other patients. We found no peripheral fractures.

Noteworthy was the lack of correlation between bone mineral densities and levels of serum calcium and phosphorus. These results are compatible with studies indicating that the osteopenia of chronic liver disease is chiefly caused by osteoporosis rather than osteomalacia (5-7).

According to our study, we concluded that osteoporosis is not a major complication of posthepatitic cirrhosis, but alcoholic cirrhosis.

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