# Low Bone Mineral Density and Impaired Bone Metabolism in Young Alcoholic Patients Without Liver Cirrhosis: A Cross-Sectional Study

Peter Malik, Rudolf W. Gasser, Georg Kemmler, Roy Moncayo, Gerd Finkenstedt, Martin Kurz, and W. Wolfgang Fleischhacker

**Background:** Osteoporosis is regularly mentioned as a consequence of alcoholism. Ethanol's direct effect on bone-modeling cells as well as alcoholism-related "life-style factors" such as malnutrition, lack of exercise, hormonal changes, and liver cirrhosis are discussed as potential causative factors.

**Methods:** In a cross-sectional study, we have examined 57 noncirrhotic alcoholic patients (37 male, 20 female) aged 27 to 50 years. Patients suffering from comorbid somatic diseases and with co-medication known to have an influence on bone mineral density (e.g., glucocorticoids, heparin, anticonvulsant agents, oral contraceptives) were excluded. We determined bone mineral density (BMD) by dual x-ray absorptiometry (DXA) in the lumbar spine (L1–L4) and the proximal right femur (femoral neck, total hip) as well as parameters of bone metabolism.

**Results:** In males but not females, BMD was significantly reduced in the lumbar region, as well as in the proximal femur (femoral neck, total hip). Nine male patients (24.3% of men) and 1 female patient (5% of women) had low BMD (defined as $Z$-score $\leq -2.0$). As expected, there was a positive correlation between body mass index (BMI) and BMD. Alcohol-related factors (e.g., duration of abuse, consumed amount of alcohol per day) as well as smoking were not associated with a significant effect on BMD. All of the 20 women examined showed elevated estradiol levels, which may have served as a protective factor. In this study, 75.7% of the men and 90% of the women had vitamin D insufficiency or deficiency (plasma levels of 25-hydroxy-vitamin D $< 30$ ng/ml).

**Conclusions:** Our study indicates that younger alcoholic patients without other diseases may suffer from an increased risk to develop low BMD and a disturbance of vitamin D metabolism. Nutritional factors or less exposure to sunlight may play an important role in bone loss in young alcoholic patients. BMD measurement and assessment of bone metabolism should be considered in all patients with chronic alcoholism.

**Key Words:** Osteoporosis, Bone Density, Body Mass Index, Young Alcoholics, Low BMD.

OSTEOPOROSIS IS OFTEN encountered as a comorbidity of alcoholism (Saville, 1965). It is defined as an absolute decrease in total bone mass, caused by an imbalance between osteoclastic bone resorption and osteoblastic bone formation, leading to an increased susceptibility to fractures (Nilsson, 1973). The most common primary forms of bone loss are postmenopausal and age-related osteoporosis. Secondary causes of metabolic bone disease have been related to drug treatment and to diseases which interfere with bone metabolism (e.g., malabsorption, hyperparathyroidism, or liver cirrhosis). Impaired vitamin D metabolism (Pitts and Van Thiel, 1986) and malnutrition (Lalor et al., 1986), risk factors for the development of bone loss, are common in alcoholic patients.

Few studies so far have focused on the direct effect of ethanol on bone metabolism and turnover in vivo. Reduction of bone formation through disturbances in osteoblast function seems to be a main factor (Turner, 2000). In vitro investigations point to a direct toxic effect of ethanol on osteoblasts (Giuliani et al., 1999). Some findings in animal models have also supported this hypothesis (Dai et al., 2000; Shankar et al., 2006; Turner et al., 1988). Immobility, dietary deficiency and decreased exposure to sunlight, resulting in vitamin D deficiency, have also been discussed to contribute to the risk of osteoporosis (Eastell et al., 1998).

While some authors have reported reduced bone mineral density (BMD) in alcoholic patients when compared with controls (Gonzalez-Calvin et al., 1993; Kim et al., 2003; Peris et al., 1994, 1995), others could not confirm these findings (Laitinen et al., 1990, 1992, 1993; Odvina et al., 1995). We have focused on younger noncirrhotic alcoholic patients. To the best of our knowledge, little evidence for reduced BMD is

*From the Departments of Biological Psychiatry (PM, GK, MK, WWF), Internal Medicine (RWG, GF), and Nuclear Medicine, Medical University Innsbruck (RM), Austria.*

*Received for publication March 11, 2008; accepted October 6, 2008.*

*Reprint requests: Peter Malik, MD, Department of Biological Psychiatry, Medical University Innsbruck, Anichstrasse 35, A-6020 Innsbruck; Fax: +43-512-504-25267; E-mail: peter.malik@i-med.ac.at*

*All authors report no competing interests.*



**DOI: 10.1111/j.1530-0277.2008.00847.x**

available for this group, in which less confounding factors are present.

In this study, we wanted to investigate the following questions:

Does our cohort of alcoholics have a reduced BMD compared with an age and sex-matched population?

Are potential reductions of BMD comparable in males and females?

Is there a relationship between alcohol-related variables or certain laboratory markers and BMD?

## METHODS

In a cross-sectional study, we investigated BMD in inpatients of an alcohol rehabilitation clinic suffering from alcohol dependence according to ICD 10. Women had to have had normal menstrual cycles over the course of the last 5 years. All patients were abstinent at the time of the examination, the duration of addiction was at least 1 year. To exclude patients with senile osteoporosis, we restricted inclusion to the age range from 19 to 50 years. Furthermore, we excluded patients suffering from comorbid somatic diseases, especially liver diseases (excluded by a combination of ultrasound and liver function testing), as well as patients treated with comedications known to have a potential influence on BMD (e.g., glucocorticoids, heparin, anticonvulsants, oral contraceptives) as well as bedridden patients or patients confined to a wheelchair. A semistructured clinical interview was conducted to evaluate smoking behavior (packyears). Severity of alcohol dependence was determined using the Alcohol Use Disorders Identification Test (AUDIT) and other alcohol-related variables (duration of abstinence and addiction, mean alcohol consumption per day for the last drinking period) by self-report.

After a thorough study description, informed consent was obtained. The study was approved by the Ethics Committee of Innsbruck Medical University.

Immediately after the interview and the consent process, we determined BMD by dual x-ray absorptiometry (DXA) with a QDR*4500-Hologic densitometer in the lumbar spine (L1–L4) and the proximal right femur (femoral neck, total hip). We also examined other regions, in the femur (greater trochanter, intertrochanteric region, and Ward's triangle), but did not use them to the determination of reduced BMD. BMD of individual patients was compared with a normative curve (obtained from data of a reference population included in the Hologic densitometer) and computed as *Z*-score (standardized difference from the mean) to enable comparisons of values across age and sex. A *Z*-score of −2.0 or lower is defined as "below the expected range for age" (the International Society for Clinical Densitometry—ISCD: 2007 official positions), which is the accepted term for low BMD or osteoporosis in premenopausal females or males younger than age 50 with risk factors for low bone density (secondary osteoporosis). Precision data from the densitometer are obtained via daily quality control by medical-technical personnel, highlighted through a so-called correlation variable with a value of about 0.4 (referring to a variability of 0.4% or lower between 2 separate measurements).

All patients had blood drawn for the analysis of liver function tests, calcium, phosphate, parathyroid hormone (PTH), 25-hydroxy vitamin D (25OHD), osteocalcin, serum crosslaps, sex hormones (estradiol, testosterone), and prolactin. Vitamin D insufficiency is defined as a 25OHD concentration of 20 to 30 ng/ml, whereas deficiency is defined as a 25OHD level $<20$ ng/ml (Dawson-Hughes B, *UpToDate in Endocrinology and Diabetes* 2008). Calcium and creatinine were determined in the urine.

Data were analysed with SPSS, version 12. Comparisons of male and female patients with regard to patient characteristics were performed by means of the Mann–Whitney *U*-test, as most sociodemographic variables were not normally distributed. Comparisons of the 2 groups with respect to bone density were conducted using analysis of covariance, adjusting for those covariates in which the 2 groups differed from each other. Comparison of patients' bone density (*Z*-scores) with normative values ($Z = 0$) was carried out by means of the 1-sample *t*-test. Associations between bone density and various laboratory measures and patient characteristics were analysed using Spearman correlation coefficients A *p*-value of ≤0.05 was considered to be statistically significant.

## RESULTS

Fifty-seven patients, 37 male (age range 27 to 49 years) and 20 female (age range 31 to 50 years), were recruited to the study. Demographic and clinical characteristics of the study group are summarized in Table 1. The mean time of abstinence was 53.1 days in men and 32.5 days in women. The mean amount of consumed alcohol for their last drinking period was 21.6 standard drinks (1 standard drink = 12 g ethanol) per day in men and 17.5 standard drinks per day in women.Thirty-two men (86.5%) and eighteen women (90%) were smokers. At a trend level ($p < 0.1$), males showed slightly higher body mass index (BMIs) than females and

**Table 1.** Demographic and Clinical Characteristics

| | Males ($N = 37$) | | | Females ($N = 20$) | | |
|---|---|---|---|---|---|---|
| | Mean | SD | Median | Mean | SD | Median |
| Age (years) | 40.4 | 5.3 | 40.0 | 41.1 | 5.5 | 42.0 |
| BMI[a] | 24.3 | 3.0 | 23.9 | 23.5 | 5.4 | 22.2 |
| Duration of addiction (years) | 15.7 | 8.6 | 15.7 | 11.7 | 7.1 | 10.3 |
| Mean consumed amount of alcohol/day (standard drinks)[b] | 21.6 | 11.1 | 18.0 | 17.5 | 8.6 | 14.5 |
| Duration of abstinence (days) | 53.1 | 53.3 | 30.0 | 32.5 | 19.0 | 27.5 |
| AUDIT score | 28.1 | 6.7 | 27.0 | 25.1 | 7.3 | 26.5 |
| Smoking (in packyears) | 28.6 | 22.2 | 25.0 | 21.5 | 14.1 | 17.5 |
| Positive family history of alcoholism [percent (*N*)][c] | 8.1% (3/37) | | | 30.0% (6/20) | | |

BMI: body mass index.
AUDIT: Alcohol Use Disorders Identification Test.
[a]$p = 0.088$, Z = 1.71 (males vs. females).
[b]$p = 0.058$, Z = 1.90 (males vs. females).
[c]$p = 0.054$, Z = 1.93 (males vs. females).

**Table 2.** BMD of 57 Alcohol-Dependent Patients (based on *Z*-scores)

| | | Normal (Z > 2.0) | | Reduced BMD (Z ≤ −2.0) | |
|---|---|---|---|---|---|
| | | *N* | % | *N* | % |
| Men (*N* = 37) | L1–L4 | 28 | 75.7 | 9 | 24.3 |
| | Femoral neck | 37 | 100 | 0 | 0.0 |
| | Total hip | 37 | 100 | 0 | 0.0 |
| Women (*N* = 20) | L1–L4 | 20 | 100 | 0 | 0.0 |
| | Femoral neck | 20 | 100 | 0 | 0.0 |
| | Total hip | 19 | 95.0 | 1 | 5.0 |

BMD: bone mineral density.

**Table 3.** Comparison of BMD (*Z*-scores) With Normative Values (*Z* = 0)

| | *Z*-score | | 95% Confidence interval for mean *Z*-score | Comparison with *Z* = 0 |
|---|---|---|---|---|
| Variable | Mean | Range | Lower/upper limit | *p*-value |
| Men | | | | |
| L1–L4 | −1.01 | −3.2/1.8 | −1.44/−0.59 | 0.000 |
| Femoral neck | −0.38 | −1.8/1.3 | −0.65/−0.12 | 0.005 |
| Total hip | −0.29 | −1.7/1.4 | −0.57/−0.01 | 0.045 |
| Women | | | | |
| L1–L4 | −0.23 | −1.5/3.1 | −0.69/0.22 | 0.294 |
| Femoral neck | −0.13 | −1.9/1.8 | −0.61/0.35 | 0.579 |
| Total hip | −0.43 | −2.1/2.2 | −0.88/0.02 | 0.061 |

BMD: bone mineral density.

reported larger amounts of consumed alcohol per day. Women reported a positive family history of alcoholism more frequently, but these differences did not reach statistical significance (details in Table 1).

Table 2 shows the BMD of male and female patients based on *Z*-Scores: 9 (24.3%) of the men met criteria for low BMD ($Z \leq -2.0$, i.e., below the expected range for age), all of them in the lumbar spine, and 28 (75.7%) were in the normal range ($Z > -2.0$). In female patients, only one (5%) showed a *Z*-score ≤ 2.0 in the total hip region.

In males, BMD (*Z*-scores) differed significantly from normal values, i.e., from $Z = 0$, in the lumbar spine ($p < 0.001$), the femoral neck ($p = 0.005$), and total hip ($p = 0.045$) (see Table 3). Women showed no significant differences in the measured regions of interest except in the intertrochanteric region (the latter result could also be found in male patients). Male patients had significantly lower BMD (*Z*-scores) at the lumbar spine than women ($F = 5.97$; df = 1,52; $p = 0.018$, analysis of covariance with adjustment for BMI, mean consumed amount of alcohol per day and positive family history). Men and women did not differ significantly in their BMD in the other regions.

We found 25OHD insufficiency or deficiency (< 30 ng/ml) in 75.7% of the male and 90% of the female patients (see Table 4), but no correlation between BMD and serum levels of 25OHD ($p = 0.578$ for lumbar spine and $p = 0.239$ for femoral neck). Two male patients had decreased testosterone

**Table 4.** Plasma Levels of Selected Laboratory Markers in Male and Female Alcohol-Dependent Patients

| | Lowered[a] | | Within normal range[a] | | Elevated[a] | |
|---|---|---|---|---|---|---|
| Parameter | *N* | % | *N* | % | *N* | % |
| Men (*N* = 37) | | | | | | |
| Calcium (2.10–2.70 mmol/l) | 0 | 0.0 | 37 | 100.0 | 0 | 0.0 |
| Phosphate (0.70–1.20 mmol/l) | 2 | 5.4 | 35 | 94.6 | 0 | 0.0 |
| GOT (10–50 U/l) | 0 | 0.0 | 33 | 89.2 | 4 | 10.8 |
| GPT (10–50 U/l) | 0 | 0.0 | 33 | 89.2 | 4 | 10.8 |
| GGT (10–66 U/l) | 0 | 0.0 | 34 | 91.9 | 3 | 8.1 |
| Alkaline phosphatase (40–129 U/l) | 2 | 5.4 | 35 | 94.6 | 0 | 0.0 |
| Ca/Creatinin (urine) [0.01–0.04 (mmol/l)/(mg/dl)] | 10 | 28.6 | 22 | 62.9 | 3 | 8.6 |
| 25-OH-Vitamin D3 (30–68 ng/ml)) | 28 | 75.7 | 8 | 21.6 | 1 | 2.7 |
| Prolactin (1.9–26 ng/ml) | 0 | 0.0 | 32 | 88.9 | 4 | 11.1 |
| PTH (10–65 pg/ml) | 1 | 2.7 | 34 | 91.9 | 2 | 5.4 |
| Osteocalcin (1.1–7.2 ng/ml) | 0 | 0.0 | 23 | 62.2 | 14 | 37.8 |
| Crosslaps (1100–4046 pmol/l) | 1 | 2.8 | 22 | 61.1 | 13 | 36.1 |
| Women (*N* = 20) | | | | | | |
| Calcium (2.10–2.70 mmol/l) | 0 | 0.0 | 20 | 100.0 | 0 | 0.0 |
| Phosphate (0.70–1.20 mmol/l) | 0 | 0.0 | 20 | 100.0 | 0 | 0.0 |
| GOT (10–50 U/l) | 0 | 0.0 | 20 | 100.0 | 0 | 0.0 |
| GPT (10–50 U/l) | 0 | 0.0 | 19 | 95.0 | 1 | 5.0 |
| GGT (10–66 U/l) | 0 | 0.0 | 16 | 80.0 | 4 | 20.0 |
| Alkaline phosphatase (40–129 U/l) | 1 | 5.0 | 19 | 95.0 | 0 | 0.0 |
| Ca/Creatinin (urine) [0.01–0.04 (mmol/l)/(mg/dl)] | 7 | 35.0 | 12 | 60.0 | 1 | 5.0 |
| 25-OH-Vitamin D3 (30–68 ng/ml) | 18 | 90.0 | 2 | 10.0 | 0 | 0.0 |
| Prolactin (1.9–26 ng/ml) | 0 | 0.0 | 18 | 94.7 | 1 | 5.3 |
| PTH (10–65 pg/ml) | 0 | 0.0 | 18 | 90.0 | 2 | 10.0 |
| Osteocalcin (0.5–7.0 ng/ml) | 0 | 0.0 | 14 | 70.0 | 6 | 30.0 |
| Crosslaps (1287–3689 pmol/l) | 1 | 5.0 | 9 | 45.0 | 10 | 50.0 |

Ca: calcium.
PTH: parathyroid hormone.
[a]Based on the normal ranges given in parenthesis.

levels. All of the twenty women had elevated estradiol levels for the reported phase of their menstrual cycle at the time of sampling, but we did not find estradiol levels above normal in men. 50% of the women and 36.1% of the men had elevated serum crosslaps, a marker of bone resorption. Osteocalcin, a marker of bone formation, was increased in 37.8% of the men and 30% of the women, none of them showed lowered levels. All other laboratory findings are summarized in Table 4.

Osteocalcin and crosslaps showed significant negative correlations with BMD in all measured areas (see Table 5, Figs. 1 and 2). All other biochemical variables as well as smoking showed no correlations with BMD.

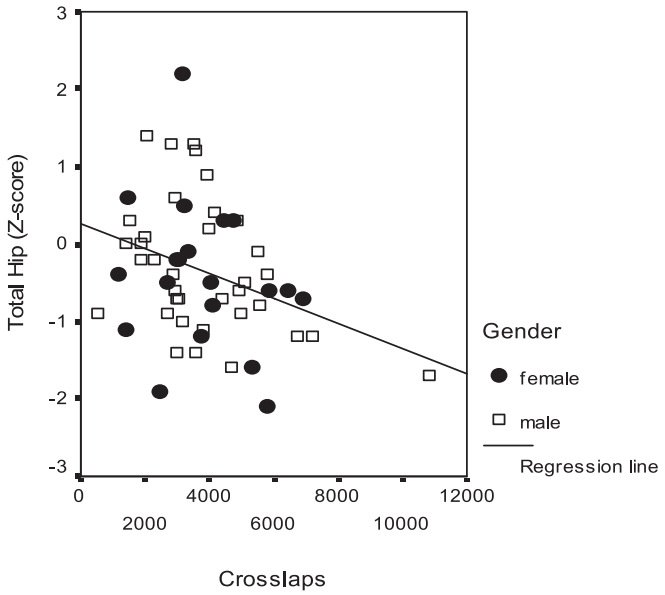
Body mass index was correlated positively with BMD in the femur (total hip, see Table 5 and Fig. 3). None of the other potential predictors studied (duration of abstinence, duration of addiction, consumed alcohol per day, AUDIT score) showed a significant correlation with BMD.

In order to demonstrate that the reduction in BMD is not a mere consequence of the low BMI values in underweight subjects, an additional analysis was performed excluding all patients with BMI < 19. In males, the significant reduction

**Table 5.** Correlation Between BMD (*Z*-score) and Laboratory Markers, BMI (*r* = Spearman Rank Correlation)

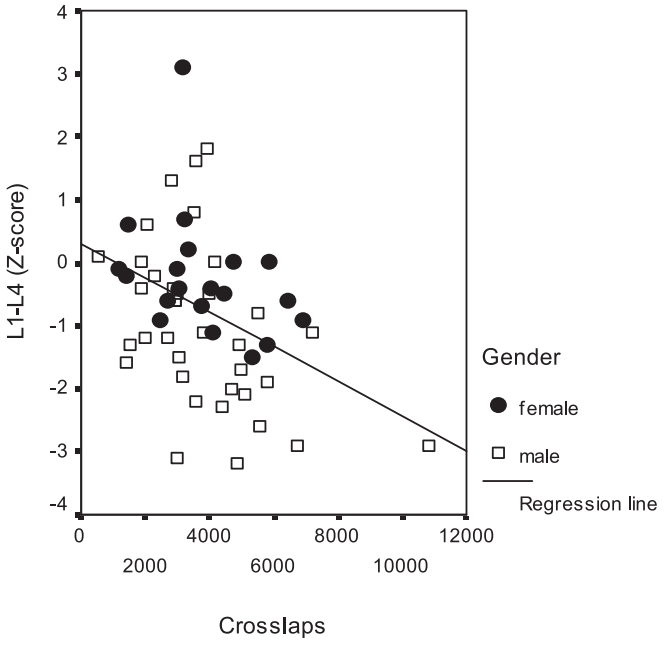
| | L1–L4 | Femoral neck | Total hip |
|---|---|---|---|
| BMI | 0.126 | 0.196 | 0.381** |
| Duration of addiction (years) | −0.078 | −0.157 | 0.026 |
| Duration of abstinence (days) | −0.249 | −0.069 | −0.060 |
| Mean amount of alcohol p. day | −0.225 | −0.190 | −0.099 |
| Smoking (packyears) | −0.007 | −0.034 | 0.000 |
| AUDIT score | −0.093 | 0.011 | −0.016 |
| 25-OH-Vitamin D3 | 0.075 | 0.158 | 0.248 |
| Osteocalcin | −0.347** | −0.417** | −0.294* |
| Crosslaps | −0.395** | −0.380** | −0.297* |

BMD: bone mineral density.
BMI: body mass index.
AUDIT: Alcohol Use Disorders Identification Test.
*$p < 0.05$; **$p < 0.01$.



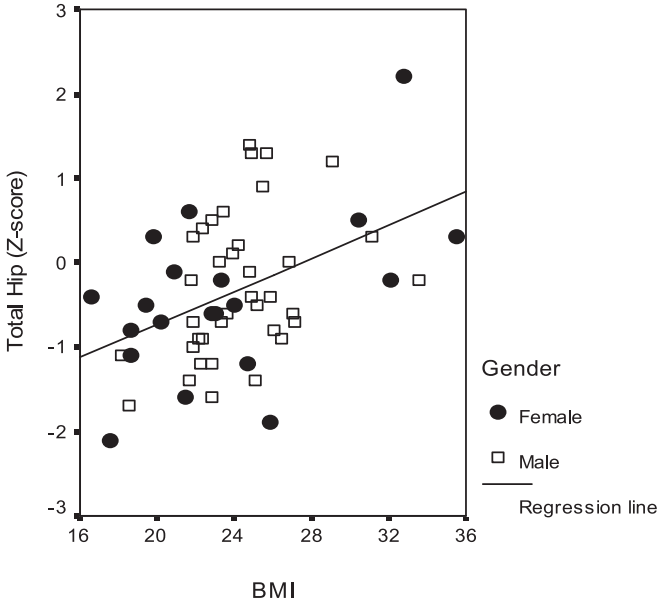

$r_{Spearman} = -0.297$, $p = 0.026$

**Fig. 1.** Correlation between crosslaps and total hip (*Z*-score).




$r_{Spearman} = -0.395$ $p = 0.003$

**Fig. 2.** Correlation between crosslaps and L1–L4 (*Z*-score).




$r_{Spearman} = 0.381$, $p = 0.003$

**Fig. 3.** Correlation between BMI and total hip (*Z*-score).

of BMD $Z$-scores in comparison to the norm ($Z = 0$) could be confirmed both for the lumbar spine [mean $Z$-score = −0.95, 95% confidence interval (CI): −1.39/−0.52, $p < 0.001$] and the femoral neck (mean $Z$-score = −0.35, 95% CI: −0.63/−0.08, $p = 0.013$). The analysis of regions which were not our primary focus of interest, yielded the following results: For the intertrochanteric region, statistical significance was lost. In females, the only statistically significant result (reduced $Z$-score for the intertrochanteric region) could also not be upheld, when corrected for BMI. When pooling males and females, BMD $Z$-scores for the intertrochanteric region were found to be significantly lower than 0 (mean $Z$-score = −0.24, 95% CI: −0.48/−0.01, $p = 0.045$). However, one needs to consider the reduced sample size of this post hoc analysis.

## DISCUSSION

Our data, obtained in a sample of relatively young patients, demonstrate that the investigated patients had low BMD, as previously found in other studies (Gonzalez-Calvin et al., 1993; Kim et al., 2003; Peris et al., 1994, 1995). Nine of the male patients (24.3%), but only 1 female patient (5%) met criteria for low BMD ($Z$-score ≤ −2.0), defined by a value below the expected range for age. In males, $Z$-scores differed significantly from normal in the lumbar spine, the femoral neck and in total hip. In the group of female patients, $Z$-scores did not differ significantly from normal values in the regions of interest.

Concerning laboratory markers, a large number of our patients had 25OHD insufficiency or deficiency. Other interesting results in this group include elevated estradiol levels in all women and high percentages of elevated osteocalcin and crosslaps levels. The latter correlated negatively with BMD. If both osteocalcin, a marker of bone formation, and crosslaps, a marker of bone resorption, are elevated, this is a sign indicative of a high bone turnover. BMI showed a positive correlation with BMD in the femoral region, which could be explained considering the protective role of estrogen, which is produced in fat cells, for bone. On the other hand, a recent study (Hsu et al., 2006) suggested that a higher percentage of body fat increases the risk of developing reduced BMD. In contrast, the higher weight which comes with higher BMI places mechanical strain on bone and promotes bone formation in these patients. As we did not determine the percentage of body fat in our patients, we cannot substantiate either of these controversial pathophysiological explanations.

Throughout the literature (Bikle, 1988), elevated PTH levels are discussed as a possible cause for bone loss. In our study, over 90% of the patients had normal PTH levels, therefore frank hyperparathyreoidism can be excluded as a cause for low BMD. But mild secondary hyperparathyreoidism with PTH values in the upper normal range could explain low BMD in some patients of our sample, taking into account the high prevalence of low 25OHD-levels in the study patients.

A Finnish group (Laitinen et al., 1990), in an earlier study, has shown that if confounding factors such as liver disease or hypogonadism are excluded, BMD in alcoholics does not decrease, which is in contrast to our finding a significantly reduced BMD, also having excluded these 2 risk factors. This could be the result of the lower mean body weight in the Laitinen study. Also, patients in their sample had a high calcium intake, as measured through a structured interview by a trained nutritionist, which could explain the discrepancy to our results, as we have not investigated nutritive factors.

In another investigation (Laitinen et al., 1992), the same group showed a association between duration of addiction and decreased BMD, which, again, is not confirmed by the present study. Maybe the fact that our patients had been abstinent for a considerably longer period of time could account for this, even though the difference of about 40 to 50 days should have a relatively small impact. The modest sample size may also account for not being able to demonstrate such a correlation.

Peris and colleagues (1994) have investigated bone density in male alcoholics as well as levels of osteocalcin and 25OHD. BMD in alcoholics was significantly lower than in controls. As initially low osteocalcin levels increased over a period of 2 years in abstinent patients, one could conclude that ethanol has damaging effects on bone formation which can remit after a certain period of abstinence. BMD improved significantly after 2 years of abstinence as well. It has been suggested that osteoblastic dysfunction resulting in diminished bone formation and reduced bone mineralization could be the reason for reduced BMD in alcoholic patients (Diamond et al., 1989; Turner, 2000).

One of the prevailing theories of the etiology of decreased BMD in alcoholics is a direct toxic effect of ethanol on osteoblasts and the subsequent inhibition of bone formation, as demonstrated in animal models and in-vitro studies (Giuliani et al., 1999; Shankar et al., 2006). This would suggest that a higher amount of consumed alcohol and longer duration of addiction would lead to lower bone mass. In this context, one would also expect decreased levels of osteocalcin. As all of our patients had normal or elevated levels and we did not detect a relationship between the amount of alcohol consumption and BMD, we assume that this is a consequence of the relatively long duration of abstinence (mean 53 days in men and 32 days in women) in our sample.

Peris and colleagues (1995) have also studied vertebral fractures. 29% of their sample showed osteopenia and many had fractures, but mostly asymptomatic. We found no clinical fractures in our patients, but detection of (radiologic) fractures was not an endpoint of our study. Another group (Clark et al., 2003) has also examined BMD and the risk for fractures in a large sample of alcohol-dependent women. Elderly women and women with liver disease were also included, and concomitant medication or comorbidity affecting bone status were not ruled out, thereby studying a higher risk sample than we have. They reported lower BMD and more fractures in alcohol-dependent women than in a control group. Regarding fractures one also needs to consider that ethanol itself my be a risk factor not only via any direct effect on bone, but also

by increasing the risk for falls when intoxicated, by inducing peripheral neuropathy, or decreased strength by malnourishment.

Next to a direct toxic effect of alcohol, indirect causative factors may be relevant. These include, among others, nutrition, physical activity and hormonal changes. Santolaria and colleagues (2000) conducted a study on malnutrition in male alcohol-dependent patients. Again, senile osteoporosis was not excluded, and neither was concomitant liver disease. These authors reported a correlation between impaired nutritional status and BMI. Like in our sample, patients with lower BMI showed lower BMD, and there was no connection between duration and amount of ethanol intake and BMD.

A considerable number of our patients showed 25OHD insufficiency or deficiency. This has been found in a number of previous studies in alcoholics (Bjorneboe et al., 1988; Hickish et al., 1989; Lindholm et al., 1991) as well as in other psychiatric patients (Hummer et al., 2005). The supply of vitamin D is mainly secured by the formation of cholecalciferol (vitamin D 3) in the skin through the action of ultraviolet light. Only a small fraction is obtained via food intake. Therefore, malnutrition or a reduced duration of exposition to sunlight or both are possible mechanisms responsible for low 25OHD in patients with alcoholism. We found no correlation between low 25OHD levels and BMD, which could be explained—as already discussed by Laitinen and colleagues (1990)—by the fact that the patients had likely ingested enough calcium, although we did not conduct a detailed nutritional intake survey.

Additive effects of alcohol and hindlimb unloading, a test used to simulate reduced physical activity in rats, on inhibition of bone formation have been demonstrated recently (Hefferan et al., 2003). This preclinical finding—though not confirmed in humans yet—suggests that reduced physical activity could be a comorbidity factor for osteoporosis in alcoholic patients. Consequently, exercise should contribute to a higher bone formation and subsequently to higher BMD.

In women, BMD seems to be less affected than in men. One explanation for these differences may be that the duration of addiction in females is on average about 5 years less. An important protective factor for women is a high estrogen level. This was also shown in an animal study (Chen et al., 2006). Our patients did have high estrogen levels as well. Lower amounts of consumed alcohol or nicotine, even though we were not able to show a significant correlation between these 2 variables and BMD, could also contribute. Unfortunately, very few studies on alcoholism and osteoporosis have included female patients.

The potential reversibility of osteopenia and osteoporosis is a matter of major interest. Some previous findings strengthen the assumption that bone metabolism may recover following abstinence (Lindholm et al., 1991; Peris et al., 1994). Interestingly, in 1 study (Laitinen et al., 1992), the authors found that decreased bone formation normalized within 2 weeks of abstinence. Clearly, longitudinal studies comparing larger samples of abstinent patients to continously consuming control groups are needed to confirm these assumptions.

Although smoking has been described frequently as risk factor for developing osteoporosis (Szulc et al., 2002), we did not find a correlation between lifetime history of consumed nicotine and BMD. Despite this, as nicotine abuse is very common in alcoholic patients (Sampson, 2002), it has to be taken into account in affecting bone metabolism.

In summary, our study demonstrates that young male alcoholic patients might suffer from a higher risk of developing low BMD. Although our sample was relatively small, which limits the conclusions that can be drawn from our findings, we have, in contrast to most other studies conducted so far, been able to rule out a number of potentially confounding variables. This lowers the likelihood that postmenopausal and senile osteoporosis or BMD changes due to secondary factors, such as medication or liver cirrhosis, are responsible for the BMD affection found. As disturbances of bone metabolism can lead to fractures, thereby amplifying comorbidity in patients whose somatic health is already severely challenged, they warrant further clinical and research interest. In this context, we would also like to emphasize the need of further studies focusing on "life-style" factors (e.g., nutrition, exercise) in alcoholic patients. Lastly, potential preventive measures have to be the subject of future focus.

## REFERENCES


Bikle DD (1988) Effects of alcohol abuse on bone. Compr Ther 14:16–20. Review.

Bjorneboe GE, Bjorneboe A, Johnsen J, Skylv N, Oftebro H, Gautvik KM, Hoiseth A, Morland J, Drevon CA (1988) Calcium status and calcium-regulating hormones in alcoholics. Alcohol Clin Exp Res 12:229–232.

Chen JR, Haley RL, Hidestrand M, Shankar K, Liu X, Lumpkin CK, Simpson PM, Badger TM, Ronis MJ (2006) Estradiol protects against ethanol-induced bone loss by inhibiting up-regulation of receptor activator of nuclear factor-kappaB ligand in osteoblasts. J Pharmacol Exp Ther 319:1182–1190. Epub 2006 Sep. 13.

Clark MK, Sowers MF, Dekordi F, Nichols S (2003) Bone mineral density and fractures among alcohol-dependent women in treatment and in recovery. Osteoporos Int 14:396–403.

Dai J, Lin D, Zhang J, Habib P, Smith P, Murtha J, Fu Z, Yao Z, Qi Y, Keller ET (2000) Chronic alcohol ingestion induces osteoclastogenesis and bone loss through IL-6 in mice. J Clin Invest 106:887–895.

Diamond T, Stiel D, Lunzer M, Wilkinson M, Posen S (1989) Ethanol reduces bone formation and may cause osteoporosis. Am J Med 86:282–288.

Eastell R, Boyle IT, Compston J, Cooper C, Fogelman I, Francis RM, Hosking DJ, Purdie DW, Ralston S, Reeve J, Reid DM, Russell RG, Stevenson JC (1998) Management of male osteoporosis: report of the UK Consensus Group. QJM 91:71–92. Review.

Giuliani N, Girasole G, Vescovi PP, Passeri G, Pedrazzoni M (1999) Ethanol and acetaldehyde inhibit the formation of early osteoblast progenitors in murine and human bone marrow cultures. Alcohol Clin Exp Res 23:381–385.

Gonzalez-Calvin JL, Garcia-Sanchez A, Bellot V, Munoz-Torres M, Raya-Alvarez E, Salvatierra-Rios D (1993) Mineral metabolism, osteoblastic function and bone mass in chronic alcoholism. Alcohol Alcohol 28:571–579.

Hefferan TE, Kennedy AM, Evans GL, Turner RT (2003) Disuse exaggerates the detrimental effects of alcohol on cortical bone. Alcohol Clin Exp Res 27:111–117.

Hickish T, Colston KW, Bland JM, Maxwell JD (1989) Vitamin D deficiency and muscle strength in male alcoholics. Clin Sci (Lond) 77:171–176.

Hsu YH, Venners SA, Terwedow HA, Feng Y, Niu T, Li Z, Laird N, Brain JD, Cummings SR, Bouxsein ML, Rosen CJ, Xu X (2006) Relation of body

composition, fat mass, and serum lipids to osteoporotic fractures and bone mineral density in Chinese men and women. Am J Clin Nutr 83:146–154.

Hummer M, Malik P, Gasser RW, Hofer A, Kemmler G, Moncayo Naveda RC, Rettenbacher MA, Fleischhacker WW (2005) Osteoporosis in patients with schizophrenia. Am J Psychiatry 162:162–167.

Kim MJ, Shim MS, Kim MK, Lee Y, Shin YG, Chung CH, Kwon SO (2003) Effect of chronic alcohol ingestion on bone mineral density in males without liver cirrhosis. Korean J Intern Med 18:174–180.

Laitinen K, Karkkainen M, Lalla M, Lamberg-Allardt C, Tunninen R, Tahtela R, Valimaki M (1993) Is alcohol an osteoporosis-inducing agent for young and middle-aged women? Metabolism 42:875–881.

Laitinen K, Lamberg-Allardt C, Tunninen R, Harkonen M, Valimaki M (1992) Bone mineral density and abstention-induced changes in bone and mineral metabolism in noncirrhotic male alcoholics. Am J Med 93:642–650.

Laitinen K, Välimäki M, Lamberg-Allardt C, Kivisaari L, Lalla M, Kärkkäinen M, Ylikahri R (1990) Deranged vitamin D metabolism but normal bone mineral density in Finnish noncirrhotic male alcoholics. Alcohol Clin Exp Res 14:551–556.

Lalor BC, France MW, Powell D, Adams PH, Counihan TB (1986) Bone and mineral metabolism and chronic alcohol abuse. Q J Med 59:497–511.

Lindholm J, Steiniche T, Rasmussen E, Thamsborg G, Nielsen IO, Brockstedt-Rasmussen H, Storm T, Hyldstrup L, Schou C (1991) Bone disorder in men with chronic alcoholism: a reversible disease? J Clin Endocrinol Metab 73:118–124.

Nilsson BE (1973) Changes in bone mass in alcoholics. Clin Orthop Relat Res 90(Jan-Feb):229–232.

Odvina CV, Safi I, Wojtowicz CH, Barengolts EI, Lathon P, Skapars A, Desai PN, Kukreja SC (1995) Effect of heavy alcohol intake in the absence of liver disease on bone mass in black and white men. J Clin Endocrinol Metab 80:2499–2503.

Peris P, Guanabens N, Pares A, Pons F, del Rio L, Monegal A, Suris X, Caballeria J, Rodes J, Munoz-Gomez J (1995) Vertebral fractures and osteopenia in chronic alcoholic patients. Calcif Tissue Int 57: 111–114.

Peris P, Pares A, Guanabens N, Del Rio L, Pons F, Martinez de Osaba MJ, Monegal A, Caballeria J, Rodes J, Munoz-Gomez J (1994) Bone mass improves in alcoholics after 2 years of abstinence. J Bone Miner Res 9:1607–1612.

Pitts TO, Van Thiel DH (1986) Disorders of divalent ions and vitamin D metabolism in chronic alcoholism. Recent Dev Alcohol 4:357–377.

Sampson HW (2002) Alcohol and other factors affecting osteoporosis risk in women. Alcohol Res Health 26:292–298.

Santolaria F, Gonzalez-Reimers E, Perez-Manzano JL, Milena A, Gomez-Rodriguez MA, Gonzalez-Diaz A, de la Vega MJ, Martinez-Riera A (2000) Osteopenia assessed by body composition analysis is related to malnutrition in alcoholic patients. Alcohol 22:147–157.

Saville PD (1965) Changes in bone mass with age and alcoholism. J Bone Joint Surg Am 47:492–499.

Shankar K, Hidestrand M, Haley R, Skinner RA, Hogue W, Jo CH, Simpson P, Lumpkin CK Jr, Aronson J, Badger TM, Ronis MJ (2006) Different molecular mechanisms underlie ethanol-induced bone loss in cycling and pregnant rats. Endocrinology 147:166–178.

Szulc P, Garnero P, Claustrat B, Marchand F, Duboeuf F, Delmas PD (2002) Increased bone resorption in moderate smokers with low body weight: the Minos study. J Clin Endocrinol Metab 87:666–674.

Turner RT (2000) Skeletal response to alcohol. Alcohol Clin Exp Res 24:1693–1701. Review.

Turner RT, Aloia RC, Segel LD, Hannon KS, Bell NH (1988) Chronic alcohol treatment results in disturbed vitamin D metabolism and skeletal abnormalities in rats. Alcohol Clin Exp Res 12:159–162.