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Increased Bone Mineral Density after Abstinence in Male Patients with Alcohol Dependence

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Objective: This study aimed to compare the bone mineral density of male patients with alcohol dependence with that in healthy controls and to assess changes in bone density after abstinence.
Methods: Forty-four inpatients with confirmed the Diagnostic and Statistical Manual of Mental Disorders, fourth edition diagnosis of alcohol abuse and 42 controls were recruited. Bone density was determined with dual-energy X-ray absorptiometry in the lumbar spine as well as in the femoral neck, trochanter, and Ward's triangle regions of the proximal right femur.
Results: There were no significant differences in age and body mass index between patients with alcohol dependence and healthy controls. In the alcohol dependence group, osteopenia and osteoporosis were found in 54.5% and 34.1% of the patients, respectively, whereas in the control group, the corresponding values were 45.2% and 11.9% (p=0.001). Although the actual bone density in the femur and the corresponding T-scores were significantly lower in the alcohol dependence group, no significant differences were found in the lumbar spine. In both groups, body mass index showed a significant correlation with bone mineral density in all areas. After 3 to 4 years of abstinence, bone density significantly increased in the lumbar and femur.
Conclusion: We conclude that bone mineral density in patients with alcohol dependence was significantly lower than that in healthy controls, and the rates of osteopenia and osteoporosis are higher. Importantly, abstinence from alcohol increases bone density.

KEY WORDS: Alcohol abstinence; Alcoholism; Bone density; Osteoporosis.

INTRODUCTION

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. According to the World Health Organization (WHO), osteoporosis affects more than 75 million people in the United States, Europe, and Japan.[1] Osteoporosis causes more than 8.9 million fractures annually worldwide, and it may be life-threatening in elderly people owing to complications such as a fracture.[1] Although osteoporosis has been known as a disease affecting postmenopausal women, recently published epidemiologic studies have emphasized that osteoporosis and related fractures in men are an increasing public health problem, in part because of increased longevity and public awareness.[2,3]

People with chronic mental disorders, such as schizophrenia and alcohol dependence, are at high risk of developing osteoporosis because of lack of exercise, poor nutrition, medication, and high rate of smoking.[4-6] In particular, excessive alcohol consumption is a secondary common cause of osteoporosis in men.[7] Although moderate alcohol intake has been reported to be associated with an increase in bone mineral density (BMD),[8,9] chronic alcohol consumption is considered to be a risk factor for osteoporosis and fracture.[10,11] Overall, fractures in chronic alcoholism are more than 4 times more common than in age-matched controls.[12] Some authors have re-

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ported low BMD in chronic alcoholism,[13-15] which is associated with increased fracture incidence and complication rates.[16]

Alcohol dependence results in several medical problems, such as liver dysfunction, vitamin D deficiency, and hyperparathyroidism, and all these medical conditions increase the risk for developing osteoporosis.[17] Furthermore, alcohol itself can also increase bone loss by disturbing bone remodeling and enhancing bone fragility.[18,19] In particular, a direct toxic effect of alcohol on osteoblasts impairs bone formation.[20,21]

Few studies suggested that alcohol abstinence may improve BMD. It was shown that abstaining women had higher bone mass than women who consumed alcohol.[22] Another study reported that lumbar and femoral neck BMD increased in alcoholic patients after abstinence, but not in controls.[14]

The prevalence of BMD loss is different among ethnic populations. The higher sensitivity of Asians to the effects of alcohol is due to the delayed oxidation of acetaldehyde by the atypical aldehyde dehydrogenase.[23] Therefore, there may also be racial differences in the association between alcohol intake and osteoporotic fracture or bone density.[9]

In this study, we investigated whether Korean alcoholic male patients have reduced BMD compared with age-matched healthy controls and whether there is a relationship between alcohol-related parameters and BMD. In addition, we evaluated the changes in BMD after abstinence from alcohol.

METHODS

Forty-four male patients with alcohol dependence diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)[24] and 42 age-matched healthy controls participated in this cross-sectional study. Subjects aged between 25 and 60 years were included. All patients admitted to a chronic mental hospital and had no withdrawal symptoms and psychiatric comorbidity, except personality disorder. They were clinically stable and participated in the inpatient program, which included daily exercise. Patients who were abusing other substances, with the exception of cigarette smoking, had impaired liver functions, nutritional impairments, or were taking any medication or had a known medical disorder linked to the risk of osteoporosis were excluded. Those with clinical signs suggesting an endocrinological disorder were also excluded. Three years after the study, patients who were enrolled in this study were re-examined, with 18 patients hospitalized. Twelve patients were still in the hospital, and six were re-hospitalized. The duration of the problem drinking of patients who were re-admitted did not exceed one month for three years.

Age- and sex-matched healthy controls were recruited during their visits to the medical examination center for routine medical checkups. They did not have any medical illnesses, including any known nutritional impairments and disorders related to osteoporosis. Healthy controls met the criteria for under moderate drinking. According to the "Dietary Guidelines for Americans 2015-2020," U.S. Department of Health and Human Services and U.S. Department of Agriculture, moderate drinking is up to 1 drink per day for women and up to 2 drinks per day for men. One alcoholic drink-equivalent is 12 fluid ounces of regular beer (5% alcohol).[25]

All subjects were interviewed for smoking and alcohol use history, demographic data, and history of fractures. Smokers were defined as those who smoked more than 5 cigarettes per day for more than 1 year. The lifetime frequency of fracture was examined by medical records of patient group and interview by control group. All subjects enrolled after giving written informed consent. This study was approved by the institutional review board of Busan Paik Hospital, Inje University College of Medicine.

Bone densitometry testing was performed with dual-energy X-ray absorptiometry (GE Lunar 4500 scanner; General Electric Healthcare, Madison, WI, USA). The lumbar spine (L1-L4) and the neck, trochanter, and intertrochanteric regions of the proximal right femur were evaluated. According to the WHO guidelines,[26] a T-score ≥ -1.0 represents normal bone mass. For the study purposes, we defined BMD loss as either the presence of osteopenia or osteoporosis (BMD < -1.0). Osteopenia was defined as a T-score between -1 and -2.5, and osteoporosis was defined as a T-score < -2.5.

Student's *t*-test and Wilcoxon rank sum test were used for comparing the 2 groups after normality test. The Pearson's correlation analysis was conducted for evaluating the association between BMD and body mass index (BMI). All tests were two-tailed, and a p value <0.05 was

considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

There were no significant differences in age (53.93±5.65 vs. 53.63±4.42) and BMI (23.87±3.23 vs. 24.27±2.81) between the patients with alcohol dependence and healthy controls. Underweight, normal, overweight, and obese subjects represented 9.1% (4/44), 59.1% (26/44), 27.3% (12/44), and 4.5% (2/44) of the patients in the alcohol dependence group, respectively. The corresponding values in the healthy control group were 4.8% (2/42), 61.9% (26/42), 28.6% (12/42), and 4.8% (2/42). The mean duration of illness in the alcohol dependence group was 93.34±55.44 months, and the mean age of starting problem drinking was 21.56±7.14 years. The average number of hospitalizations is 4.41±2.60. Patients taking antidepressants are used for the treatment of mild depressive mood and insomnia but do not meet the diagnostic criteria for major depressive disorder or other mood disorders. Mood stabilizers and antipsychotics are used for symptom control such as aggressive behavior and insomnia, but antipsychotics do not exceed 1 mg of risperidone equivalent. The number of smokers was higher in the alcohol dependence group ($p \leq 0.001$), but there was no difference in the number of cigarettes smoked daily.

Lifetime frequency of fracture was higher in the alcohol dependence group, and 16 of 44 patients experienced more than one fracture. In the fracture site, there were 4 lumbar spine compression fractures, 8 extremities fractures (humerus, ankle, finger etc.), and 7 rib fractures. In control group, there were two ankle and tibia fractures respectively. The bone fracture was more frequent in the

Table 1. Demographic and clinical characteristics of male patients with alcohol dependence and healthy controls

Characteristic	Alcohol dependence (n=44)	Healthy controls (n=42)	*p* value
Age (yr)	53.93±5.65	53.63±4.42	0.695
Body mass index (kg/m^2)	23.87±3.23	24.27±2.81	0.512
Duration of illness (mo)	93.34±55.44	ND	NA
Number of hospitalization	4.41±2.60	ND	NA
Medication			
Anti-craving	42 (95.5)	ND	NA
Benzodiazepine	19 (43.2)	ND	NA
Antidepressants	7 (15.9)	ND	NA
Mood stabilizers	3 (6.8)	ND	NA
Antipsychotics	4 (9.1)	ND	NA
Smoking (pack years)	27.04±11.01	20.86±5.46	0.162
Numbers of smokers			
Smokers	28 (63.6)	6 (14.3)	<0.001
Non-smokers	16 (36.4)	36 (85.7)	
Lifetime frequency of fracture	16 (36.4)	2 (4.8)	<0.001
1 fracture	10 (22.7)	2 (4.8)	
2 fractures	4 (9.1)	0 (0)	
3 fractures	2 (4.5)	0 (0)	

Values are presented as mean±standard deviation or number (%).
ND, not detected; NA, not applicable.

Table 2. Comparison of actual bone density and t-scores of bone mineral density in the lumbar and femur between male patients with alcohol dependence and healthy controls

	Alcohol dependence (n=44)	Healthy controls (n=42)	Alcohol dependence (n=44)		Healthy controls (n=42)	
			Smokers (n=28)	Non-smokers (n=16)	Smokers (n=6)	Non-smokers (n=36)
Actual bone density (g/cm^2)						
L1-L4	1.10±0.18	1.16±0.21	1.12±0.18	1.06±0.16	1.14±0.17	1.17±0.22
Femur						
Neck	0.81±0.15*	0.94±0.18	0.81±0.16	0.81±0.10	0.95±0.18	0.94±0.18
Ward's triangle	0.66±0.11*	0.76±0.14	0.66±0.12	0.67±0.11	0.80±0.13	0.76±0.15
Trochanter	0.75±0.14*	0.85±0.15	0.76±0.15	0.75±0.12	0.86±0.09	0.84±0.16
T-score						
L1-L4	−0.69±1.47	−0.26±1.54	−0.53±1.52	−1.03±1.36	−0.34±1.36	−0.20±1.58
Femur						
Neck	−1.07±1.12*	0.06±1.05	−1.05±1.26	−1.11±0.79	−0.01±1.43	0.08±1.02
Ward's triangle	−1.66±0.88*	−0.91±1.10	−1.67±0.89	−1.65±0.87	−0.63±0.99	−0.94±1.13
Trochanter	−0.24±1.26*	0.75±1.10	−0.22±1.34	−0.28±1.10	−0.76±0.83	0.75±1.15

Values are presented as mean±standard deviation.
*$p<0.001$.

Table 3. Correlations between bone mineral density, body mass index, and starting problem drinking age after correction for age

	Body mass index		Starting problem drinking age (in alcohol dependence group)		
	Alcohol dependence (n=44)	Healthy controls (n=42)	Alcohol dependence with smoking (n=28)	Alcohol dependence without smoking (n=16)	Total (n=44)
Actual bone density					
L1-L4	0.447†	0.343†	0.334	−0.025	0.241
Femur					
Neck	0.353*	0.282*	0.554†	−0.149	0.399*
Ward's triangle	0.145†	0.421‡	0.438*	−0.041	0.289
Trochanter	0.464†	0.440‡	0.403*	0.160	0.336*
T-score					
L1-L4	0.448†	0.460‡	0.335	−0.025	0.241
Femur					
Neck	0.353*	0.484‡	0.555†	−0.150	0.399*
Ward's triangle	0.415†	0.420‡	0.438*	−0.041	0.290
Trochanter	0.465†	0.559‡	0.402*	0.161	0.336*

*$p<0.05$, †$p<0.01$, ‡$p<0.001$.

alcohol dependence group ($p<0.001$). The demographic and clinical characteristics of the subjects are presented in Table 1.

Bone Mineral Density Assessment

BMD loss was present in 88.6% of the patients with alcohol dependence and 57.1% of the controls. There was a significant difference in the extent of bone loss between the 2 groups. In the alcohol dependence group, 54.5% (24/44) of the patients had osteopenia and 34.1% (15/44) had osteoporosis, whereas in the healthy control group these numbers were 45.2% (19/42) and 11.9% (5/42), respectively ($p=0.001$).

There were no significant differences between the 2 groups in bone density of the L1–L4 spinal segments. In contrast, bone density in the neck, Ward's triangle, and trochanter of the proximal right femur was significantly lower in the alcohol dependence group ($p<0.001$). A comparison of the T-scores between the 2 groups produced similar results: no differences were detected in the L1-L4 vertebrae while significantly lower T-scores of the femur were found in the alcohol dependence group ($p<0.001$). Smoking was not associated with differences in bone density (Table 2).

In both groups, BMI showed a significant correlation with BMD in all areas. After correction for age, the age of starting problem alcohol use correlated with bone mineral loss in the neck ($p=0.012$) and trochanter ($p=0.037$) of the femur, especially in smokers (Table 3).

The patients who maintained abstinence from alcohol (n=18) were followed up 3-4 years after the initial study. Significantly increased BMD in the lumbar and femur areas was detected in these individuals (Table 4).

Table 4. Changes in bone mineral density after 3-4 years of abstinence in male patients with alcohol dependence (paired *t* test)

	Patients with alcohol dependence (n=18)		
	Baseline	Follow-up	*p* value
Actual bone density (g/cm^2)			
L1-L4	1.11±0.17	1.15±0.21	0.018*
Femur			
Neck	0.78±0.16	0.81±0.12	0.099
Ward's triangle	0.66±0.10	0.72±0.10	0.042*
Trochanter	0.74±0.13	0.77±0.13	0.033*
T-score			
L1-L4	−0.34±1.27	−0.22±1.78	0.006†
Femur			
Neck	−1.27±1.21	−1.03±0.95	0.073
Ward's triangle	−1.70±0.75	−1.22±0.74	0.042*
Trochanter	−0.33±1.18	−0.12±1.23	0.025*

Values are presented as mean±standard deviation.
*$p<0.05$, †$p<0.01$.

DISCUSSION

Alcohol dependence is a chronic, debilitating illness requiring long-term treatment, and this illness has been associated with a high risk for developing osteoporosis. In the present study, 88.6% of male patients with alcohol dependence and 57.1% of healthy controls showed bone density loss. Osteoporosis was detected in 34.1% of the subjects in the alcohol dependence group and 11.9% in

the healthy control group. Thus, the patients with alcohol dependence showed more dramatic bone density loss.

The prevalence of bone density loss in men has not been well established. Radiographic evidence of extensive bone loss was found in 47% of 96 fully ambulatory male patients aged 24 to 62 years who were admitted to a rehabilitation center.[11] An Indian study reported that osteopenia was present in 42% and osteoporosis in 8.5% of healthy men over 50 years old.[27] Two studies revealed bone loss in 39-50% of middle-aged healthy Korean men.[5,28] Furthermore, it has been demonstrated that alcoholic patients had lower BMD in Ward's triangle and trochanter of the femur than the control group.[29] Overall, these results are similar to those obtained for the healthy controls in this study.

Although the mechanism of osteoporosis in men is not well established, many studies demonstrated that, like in women, sexual hormones, such as estrogen and testosterone, affect bone formation and resorption.[30,31] It is important to understand the effect of alcohol on bones because alcohol dependence frequently occurs in men.[32] In this regard, excluding underlying pathological causes is particularly critical as these are much more likely to be present in men than in women.[33] The alcohol-induced bone loss is distinct from postmenopausal osteoporosis. In particular, gonadal insufficiency related to menopause increases the rate of bone remodeling, whereas alcohol decreases this rate.[21,34] Testosterone and other androgens mediate protective effects on bone through suppression of osteoclastogenesis and bone resorption, although the molecular mechanisms of this remain unclear.[35] We did not focus on the role of hormones because gonadal state and markers of bone turnover were not evaluated in our patients.

BMD can be measured at several skeletal sites, such as the fingers, arm, and ankle. However, the definition of osteoporosis is based on an evaluation of the lumbar and femoral regions, the 2 major clinically accepted sites. Although bone densitometry at multiple sites is recommended for enhancing the accuracy of diagnosis,[36] some studies suggested that bone densitometry in the femoral region is sufficient because of low accuracy error ($<5\%$) at this site.[37] The lumbar spine is composed of 60-70% cancellous bone, whereas the femur consists mostly of cortical bone. Although an animal study suggested that the femur is more strongly affected by alcohol,[38] whether the cancellous or cortical bone is more susceptible to alcohol dependence-related damage has not been sufficiently investigated in humans. In our study, bone density was measured in 3 regions of the femur as well as in the lumbar. Remarkably, significant differences between the groups were detected only in the femur. In this regard, another Korean study reported that BMD in the femoral trochanter and Ward's triangle but not in the lumbar spine was significantly lower in the chronic alcohol consumption group than in the control group.[29] Other studies will be needed to unequivocally confirm that the femur is more sensitive to bone loss related to alcohol dependence.

In this study, lower BMD correlated with early onset of drinking, especially in smokers. Drinking alcohol at an early age has been associated with alcohol use disorder and other related problems. Furthermore, early initiation of smoking and alcohol drinking is a relevant marker of lower BMD in late adolescence.[39]

Some previous studies suggested that low BMI is related to BMD loss in men.[27,40,41] In this study, mean BMI was significantly associated with BMD in both groups. In this regard, the Osteoporotic Fractures in Men study (MrOS) demonstrated the relationship between high BMI and increased fracture risk in older men.[42]

Although the accurate mechanism of action of cigarette smoking on bone physiology is unknown, several studies have found a significant difference in BMD between smokers and non-smokers.[43,44] Smoking alone was not associated with BMD in the present study, which may be a consequence of the small sample size. However, early onset of alcohol drinking and smoking was correlated with lower BMD.

Overall, fractures are 4 times more common in chronic alcohol dependence than in age-matched controls.[45] Importantly, men who suffer a major fracture have higher mortality rates than both the general population and women with fractures.[7] In this study, lifetime frequency of fracture was higher in the alcohol dependence group than in the healthy controls (36.4% vs. 4.8%, respectively). However, it is not possible to conclude that a high percentage of fractures is due to low bone density, as there is a possibility that a fracture may have occurred for reasons not associated with BMD (falls or other injuries etc.) except compression fracture of the lumbar spine.

Age is the most reliable risk factor for developing osteo-

porosis in both sexes,[37] and osteoporosis and osteoporotic fractures increase with increasing age.[27] The narrow age range in this study prevented the evaluation of the effect of aging on bone loss. Thus, sample bias may contribute to the differences between the results of our study and those of published reports.

We observed increased BMD in the lumbar spine and femur in 18 alcoholic patients after 3-4 years of abstinence. In a previous study, abstainers showed either no change or an increase in bone mass after 6 months of abstinence.[46] In agreement, other researchers demonstrated that lumbar and femoral neck BMD increased in alcoholics after 2 years of abstinence.[14]

Some studies showed that reduced BMD in these patients being reversible with abstinence through an excess of bone formation over resorption.[47,48] According to the studies, Osteoprotegerin, a parameter of reduced BMD, levels decreased significantly, while osteocalcin, a marker of bone formation, increased significantly over the course of 8 abstinent weeks. Increased osteocalcin levels indicating a higher rate of bone formation during continuous abstinence. The prevention of bone loss through osteoprotegerin has been postulated to result from the inhibition of osteoclastogenesis.[49]

The association between prolonged abstinence and increasing BMD should be interpreted with caution. The rate of abstainers in this study was higher than usual because the patients were hospitalized for extended periods of time for a number of reasons. During hospitalization, they ate well-balanced meals, exercised regularly, and were provided regular health checkups. We believe that such a big change in their daily life could be sufficient to improve BMD.

Several other limitations should be considered when interpreting the findings of this report. In addition to the effect of the disease itself, several factors, such as smoking, nutrition, activity level, and deficiency of calcium and vitamin D, can influence bone density. We could not exclude the effect of these variables because of the cross-sectional design of this study. Long-term, prospective studies are needed to exclude the potential effects of these factors. Furthermore, there were much more smokers in the alcohol dependence group. This may explain the discrepancy between our data and published results with respect to the association between smoking and BMD. Additionally, the present study was the relatively small sample size and the lack of healthy controls for follow-up evaluation. Finally, all the patients in this study participated in an inpatient program. This limits the generalization of our results.

In summary, male patients with alcohol dependence showed a high prevalence of bone loss, and bone density in the alcohol dependence group was lower than that in healthy controls. These results suggest that male patients with alcohol dependence are at high risk of osteoporosis and bone fracture. Furthermore, abstinence may improve BMD in patients with alcohol dependence.

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