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Spine bone mineral density and vertebral body height are altered by alcohol consumption in growing male and female rats

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Abstract

Alcohol, consumed for extended periods by growing male and female rats, impairs osteogenesis and reduces bone size and mass. The skeletal sites of experimental animals commonly chosen for an evaluation of bone mechanical characteristics and architectural properties, bone matrix gene expression, tissue concentrations of growth factors, and bone mineral density (BMD) have been the tibiae and femora. Far less attention has been focused on the spine and the effects of alcohol on vertebral BMD and vertebral body height. Fifteen male and 15 female Sprague–Dawley rats (aged 30 days) were divided into three groups: an alcohol-fed group, matched to a pair-fed non-alcohol isocaloric–fed control group with animals of the same sex, and an ad libitum–fed control group. Alcohol-fed animals received a Lieber–DeCarli liquid diet containing 36% of caloric intake as alcohol; isocaloric pair-fed rats received the same diet without alcohol. After 45 days of feeding, the lumbar spine was removed. The fourth lumbar vertebra from each spine was dissected, and the vertebral body height was measured. Lumbar vertebral body height was significantly reduced by alcohol consumption in both male and female rats compared with findings for either control group. Cancellous and cortical BMD of the vertebral body was determined by peripheral quantitative computed tomography (pQCT). Male and female rats (aged 75 days) in the ad libitum–fed group had similar vertebral body cortical and cancellous BMD, with cortical BMD being greater than cancellous BMD. Lumbar vertebral body cancellous and cortical BMD declined for both male and female rats in response to alcohol consumption for 45 days compared with findings for either control group. More BMD loss occurred from cancellous than from cortical bone in both sexes after chronic alcohol consumption. Chronic alcohol consumption by growing rats results in vertebral growth reduction and vertebral osteopenia.

Keywords

Alcohol; Spine; Rat; Bone mineral density

1. Introduction

The long bones of the rat have been studied extensively to determine the effect of alcohol on bone growth and strength (Hogan et al., 1997, 1999; Peng et al., 1988; Sampson, 1998; Sampson et al., 1996, 1998; Turner et al., 1998; Wezeman et al., 1999) and fracture healing (Elmali et al., 2002). It is well known that alcohol-fed growing male and female rats weigh less, are shorter in total body length, and have shorter long bones than their non–alcohol-fed counterparts. Irreversible damage to the rat skeleton occurs after extended periods of alcohol

consumption. Although alcohol withdrawal is accompanied by a return to normal for many measured functions, some long bone growth parameters are permanently limited (Sampson, 1998; Sampson et al., 1998; Sampson & Spears, 1999; Wezeman et al., 1999). Vertebral bone mineral density and vertebral body height may also be significantly altered in the growing rat fed alcohol chronically. By comparison, the question regarding an effect of chronic alcohol consumption on spine growth may have clinical implications for human beings. It is known that individuals born of alcoholic mothers (fetal alcohol syndrome) have reduced bone age and stature that persists throughout the lifetime (Habbick et al., 1998).

Although little is known about bone-specific differences in the skeletal response to acute or chronic alcohol intake, it may be presumed that a negative effect of alcohol on both long bone and vertebral growth makes a collective contribution to reduced stature. Only a few investigators have reported the use of rat vertebrae in studies on the effects of alcohol on bone. Diez et al. (1997) found early and somewhat irreversible striking changes in rat fourth lumbar vertebral trabecular histomorphometry after a single intraperitoneal injection of alcohol (2 g/kg). Turner et al. (1998) demonstrated that a single intraperitoneal injection of a moderate amount of alcohol (1.2 g/kg) transiently increased rat lumbar vertebral gene expression for bone matrix proteins. Using dual-energy x-ray absorptiometry, Nishiguchi et al. (2000) reported the loss of bone mineral density from the L2 through L4 spinal segment in male and female rats after alcohol intake without determining whether the loss was from cortical or cancellous vertebral bone. In chronic alcohol-feeding protocols, with the use of the Lieber–DeCarli diet containing 36% of caloric value as ethanol, serum alcohol levels are maintained at 110–250 mg/dl (Hogan et al., 1997, 1999; Wezeman et al., 1999, 2000). In adult rats, moderate consumption levels [3% caloric intake (Turner et al., 2001)] result in decreased bone turnover, supporting the suggestion that even moderate levels of alcohol have an adverse effect on cancellous bone.

Whereas a reduction in vertebral height due to alcohol impairment of osteogenesis would contribute to diminished spine length in experimental animals and stature in human beings, alcohol-induced changes in vertebral bone mass and quality could also predispose regions of the human spine to compressive failure, similar to the effects of estrogen depletion or aging. Experimentally weakened bone quality and mass of rat lumbar vertebrae leads to lowered compressive strength (Jiang et al., 1997). Bone mineral density measurements provide partial information about the integrity of bone. Peripheral quantitative computed tomography (pQCT) determines true volumetric bone mineral, and this technology has been applied to the measurement of cortical and cancellous bone mineral density in rodents (Breen et al., 1996; Ferretti et al., 1995, 1996; Gasser, 1995; Jamsa et al., 1998; Rosen et al., 1995; Wezeman et al., 1999). The accuracy and precision of bone mineral density measurements by pQCT are highly significant, approaching 98%–99% (Cann & Genant, 1980; Genant et al., 1982).

In addition, alcohol-induced reductions in bone density and strength are accompanied by changes in tissue material properties (Hogan et al., 1999). Some, but not all, bone structural properties associated with tissue deformability correlate with bone mineral density, and no correlation exists in rats between bone mineral density and femur strength and stiffness (Ferretti et al., 1993). A great part of bone strength or fracture risk variance remains unexplained by bone mineral density alone; bone strength is determined almost equally by bone mass and bone quality (Ferretti et al., 1996; Jones & Boyde, 1994). Changes in parameters, such as matrix mineralization, crystal characteristics, collagen disposition, and tissue porosity, all potentially account for altered bone material properties (Ferretti, 1995) that are possibly related to the effects of chronic and excessive alcohol consumption. Bone material and geometric properties account for a significant part of bone strength variance (Hogan et al., 1999), and geometric variables themselves have been proposed as better

descriptors of bone strength than bone mineral density (Ferretti, 1995; Ferretti et al., 1993; Jamsa et al., 1998).

In this investigation, we hypothesized that chronic alcohol consumption by growing male and female rats would lead to a reduction in the height of lumbar vertebrae, specifically measured at the fourth lumbar level, and that alcohol consumed for the extended period would also reduce cancellous bone mineral density at this vertebral level. Evidence to these effects would document an additional skeletal site of action for alcohol in support of the influence of alcohol on osteogenesis resulting in reduced length (rat) and stature (human being) and vertebral bone mineral density.

2. Materials and methods

This protocol received Loyola University Medical Center institutional IACUC unconditional approval. A total of 15 male and 15 female rats (Sprague–Dawley; aged 30 days) were allowed to acclimate to their environment for 4 days before the beginning of the research protocol. The well-established Lieber–DeCarli liquid diet without alcohol was administered 4 days before the study was begun to allow the animals to become accustomed to the new diet. Control and experimental diets were freshly made each day. Rats were weighed and individually caged, with a 12 h–12 h light–dark cycle. Three age- and weight-matched groups were maintained on the dietary regimen for 45 days. The alcohol-fed group ($n = 5$) received the alcohol diet containing 36% of the calories as alcohol. The second, pair-fed, group ($n = 5$) received an equal number of calories as their alcohol-fed mate, with dextran–maltose substituted for alcohol. The third, ad libitum–fed, group ($n = 5$) was allowed to consume an unlimited amount of rat chow. All animals had free access to fresh water throughout the feeding period. Animals were weighed on a weekly basis, and measurements of daily food consumption were recorded. After 4 weeks of feeding, the rats from each group were killed by decapitation, and the lumbar spine was removed en bloc. At the time animals were killed, blood was recovered and serum was separated. Serum levels of alcohol were determined by using a commercial kit (Sigma, St. Louis, MO), following the protocol for serum samples.

The spine was placed in 70% ethanol for fixation, after which the soft tissues were removed by dissection under a stereomicroscope. The cleaned spines were placed in fresh 70% ethanol before pQCT was performed and length measurements were taken. Posterior vertebral elements were excluded from the region of analysis. The fourth lumbar vertebra was dissected from each spine, and its length was measured by using a caliper. Lengths of the whole vertebral body, including the end plates, were measured in the longitudinal axis.

Cancellous and cortical bone mineral density of each fourth lumbar vertebra was determined by using pQCT. The vertebral body was positioned in a Nordland Stratec bone densitometer (Stratec Medizintechnik, Mannheim, Germany). The bones were positioned uniformly on a support, so that the instrument-scanning plane was perpendicular to the longitudinal axis of the vertebra. Scout views were obtained to determine the midpoint of the vertebral body. Two density measurements were performed 1 mm apart at the midpoint of the vertebral body. The cancellous area of the bone was defined as 45% of the total bone cross-sectional area at the midpoint of each vertebra. The instrument was set to use threshold contour mode (soft tissue threshold set at 220 mg/cm^3) and concentric peel algorithm (55% peel-off). Scans, with the use of a voxel size of 0.09 mm, were made at 50 kV and 0.3 mA.

Data were stored electronically and analyzed by using SPSS software. The percent difference between control and experimental groups was determined. One-way analysis of variance (ANOVA) and Tukey post hoc procedure were used to determine significant

differences among experimental groups and percent differences. Probability values less than .05 were considered significant.

3. Results

All male and female rats gained weight during the 45-day feeding period. There were no significant differences between initial weights of male and female rats in the alcohol-fed group compared with findings for their pair-fed or ad libitum-fed controls. Weight for female rats fed alcohol increased from an average of 63.2 ± 2.8 g at the beginning of the study to 186.8 ± 18.2 g at the time animals were killed. Weight for female rats paired with alcohol-fed rats increased from 63.3 ± 2.8 g to 200.8 ± 9.0 g, and weight for female rats fed chow ad libitum increased from 77.2 ± 9.1 g to 222.5 ± 7.0 g at the time animals were killed. Weight for male rats fed alcohol increased from an average of 75.0 ± 3.1 g at the beginning of the study to 261.0 ± 14.7 g at the time animals were killed. Weight of male rats paired with rats fed alcohol increased from 76.1 ± 4.3 g to 277.3 ± 25.5 g, and weight for male rats fed chow ad libitum increased from 78.3 ± 10.4 g to 371.3 ± 22.9 g at the time animals were killed. The final weights of male and female rats fed alcohol were significantly different compared with weights for control animals of the same sex ($P < .001$).

At the time animals were killed, the serum alcohol concentration for male rats fed alcohol averaged 189 ± 9.8 mg/dl, and the concentration for female rats fed alcohol averaged 175 ± 6.2 mg/dl. No detectable levels of alcohol were present in serum samples for male or female rats in either control group.

The lumbar vertebral body height in male rats fed rat chow ad libitum was greater than that of female rats fed rat chow ad libitum [male rats: 8.22 ± 0.28 mm; female rats: 7.19 ± 0.56 mm ($P < .01$)]. The average height of the fourth lumbar vertebral body for male rats fed alcohol was significantly less than that for either male control group (Table 1). There were no significant differences between the male pairfed and ad libitum-fed groups. Similarly, the average height of the fourth lumbar vertebral body for female rats fed alcohol was significantly less than that for either female control group. There were no significant differences between female pair-fed and ad libitum-fed groups. The percent vertebral body height loss after consumption of the alcohol diet did not differ between male and female rats [5.5% reduction in height for male rats fed alcohol compared with findings for the pair-fed controls vs. 5.0% reduction in height for female rats fed alcohol compared with findings for the pair-fed controls ($P = .85$) (Table 1)].

Cancellous bone mineral density of the fourth lumbar vertebral body was similar between male and female rats at 75 days of age. The same was true for cortical bone mineral density (Table 2). No significant difference was found for vertebral cancellous or cortical bone mineral density between ad libitum-fed male and female rats (cancellous, $P = .83$; cortical, $P = .68$). Peripheral quantitative computed tomography measurement of vertebral cancellous bone mineral density in male and female rats fed alcohol revealed a significant reduction compared with findings for either control group. Vertebral body cortical bone mineral density in male and female rats was also significantly reduced by alcohol consumption only compared with findings for the ad libitum-fed control group (Table 2). Male rats did not differ from female rats in the percent loss of either cortical or cancellous bone mineral density from the vertebral body [cancellous: alcohol-fed vs. pair-fed female rats = 27.3% decrease, and alcohol-fed vs. pair-fed male rats = 35.9% decrease ($P = .79$); cortical: alcohol-fed vs. pair-fed female rats = 10.5% decrease, and alcohol-fed vs. pair-fed male rats = 2.8% decrease ($P = .44$)]. Cortical bone mineral density was greater than cancellous bone mineral density for both male and female rats in all groups. More bone mineral density loss occurred from cancellous bone than from cortical bone in both sexes (female rats: 27.3%

cancellous bone loss, alcohol-fed vs. pair-fed groups, compared with 10.5% cortical bone loss, alcohol-fed vs. pair-fed groups; male rats: 35.9% cancellous bone loss, alcohol-fed vs. pair-fed groups, compared with 2.8% cortical bone loss, alcohol-fed vs. pair-fed groups) (Table 2).

4. Discussion

Vertebral body height is directly related to stature in bipeds and body length in quadrupeds. Total vertebral height (i.e., the sum of the heights of the individual vertebral bodies) is different from total spine length, which includes the thickness of the intervertebral discs. In mammals, the cancellous bone of the vertebral body is enclosed by encircling cortical bone and the superior and inferior cortical end plates. Approximately 60%–70% of the vertebral body is cancellous bone (Riggs et al., 1981). Growth in vertebral height occurs by endochondral ossification at the end plate region, whereas circumferential enlargement of the vertebral body is the result of periosteal intramembranous ossification. Reductions in spine length can result from reduced vertebral growth, reduced vertebral growth combined with reduced intervertebral disc formation, or pathologic changes in either structure. Vertebral fracture risk is related to both bone size and bone mass (Rehman et al., 2003).

Although insults to bone growth from continuously high serum alcohol levels have been extensively studied in rat long bones, there is insufficient information concerning alcohol-induced growth insults to the spine. Only a few investigators have reported the use of vertebrae in studies on the effects of alcohol on bone. Diez et al. (1997) found early and somewhat irreversible striking changes in rat fourth lumbar vertebral trabecular histomorphometry after a single intraperitoneal injection of alcohol (2 g/kg). Turner et al. (1998) demonstrated that a single intraperitoneal injection of a moderate amount of alcohol (1.2 g/kg) transiently increased rat lumbar vertebral gene expression for bone matrix proteins. Using dual-energy x-ray absorptiometry, Nishiguchi et al. (2000) reported a loss of bone mineral density from the L2 through L4 spinal segment in male and female rats after alcohol intake without determining whether the loss was from cortical or cancellous vertebral bone. This investigation was therefore designed to test the hypothesis that chronic alcohol consumption by growing male and female rats reduces two major indices of vertebral integrity at the organ level: vertebral body height and bone mineral density.

Results from histomorphometric and biomechanical studies have clearly demonstrated that alcohol consumption alters bone mechanical characteristics and architectural properties that confer bone fragility. Alcohol-induced reductions in bone volume and mineral content combine with alterations in tissue architecture, resulting in reduced bone strength. In the spine, these events would be reflected in changes of individual anatomic units, the vertebrae, in which individual unit height would be reduced, accompanied by lowered bone mineral density. In the current study, however, we did not examine the accompanying intrinsic or material properties of the vertebrae. In the current investigation, vertebral body height for both male and female rats was reduced after the period of alcohol consumption, with no significant differences noted between alcohol-fed animals of either sex and both control groups. The effect of alcohol was not due to caloric restriction in either male or female rats, as demonstrated by the lack of difference between pair-fed and ad libitum-fed groups.

As expected, the average height of the fourth lumbar vertebral body for male rats in the ad libitum-fed group was significantly greater than that for female rats in the ad libitum-fed group. After both male and female rats consumed alcohol for the experimental period, their vertebral body heights were significantly reduced compared with findings for either control group. However, when the percent changes in size were calculated no significant differences were observed between male and female rats. Male rats had 5.5% less vertebral body height;

female rats had 5.0% less ($P = .85$). The equivalence in this proportionate change strongly supports the suggestion that the alcohol-induced failure in vertebral osteogenesis is similar in male and female rats, as it is in long bones such as the femur.

The alcohol-induced reduction in osteogenesis resulted in lowered bone mineral density in both cancellous and cortical bone compared with findings for control groups fed either a normal diet or an isocaloric diet without alcohol. Findings obtained from previous studies, with the use of different bone mass–determination techniques and femurs, have shown that bone mass in the rat increases with age (Sampson et al., 1998). As expected, cortical values in all groups in the current study exceeded cancellous values in both male and female rats. At 75 days of age, cancellous bone mineral density values for male and female rats in the ad libitum–fed control groups did not differ significantly; similarly, cortical bone mineral density values for male and female rats did not differ significantly. After 45 days of alcohol consumption (rat age, 75 days), pQCT at the midpoint of the length of the vertebral body at the fourth lumbar level revealed significantly lower cancellous and cortical mineral contents in both male and female rats. Interestingly, the comparison of the percent change of either cortical or cancellous bone mineral density between male and female rats was without significant difference. However, chronic alcohol consumption resulted in a significantly greater percent change in cancellous bone mineral density than in cortical bone mineral density for both male and female rats.

One speculative notion is that the microarchitecture of cancellous bone exposes a vast trabecular surface density, with its adherent osteoblast population, to the prevailing serum alcohol concentration, which diffuses from the marrow capillary networks and sinusoids to osteoblasts. Trabecular surfaces are extensively covered by osteoblasts and bone lining cells, which lie adjacent to marrow sinusoids. However, microanatomic features have not been studied relative to the perfusion of alcohol from the vasculature to bone cells. On the contrary, bone turnover rates, which are higher in trabecular bone, rather than histologic organization, may more importantly account for differences between skeletal sites in the various alcohol-fed rat models.

In conclusion, two indices of the effect of alcohol on the growing spine of male and female rats are a reduction in vertebral body height and in bone mineral density in both cancellous and cortical compartments. Chronic alcohol consumption during skeletal growth may contribute significantly to developmental abnormalities of the spine and vertebral fragility accompanying osteopenia.

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Table 1

Comparison, in male and female rats, of fourth lumbar vertebral body height, measured from the superior cortical end plate to the inferior cortical end plate

Treatment group	Vertebral body height (mm)
Male rats	
Alcohol-fed	7.27 ± 0.20*
Pair-fed	7.69 ± 0.06
Ad libitum-fed	8.22 ± 0.28
Female rats	
Alcohol-fed	6.49 ± 0.15*
Pair-fed	6.83 ± 0.21
Ad libitum-fed	7.19 ± 0.56

Values are expressed as the mean ($n = 5$) ± S.D.

* $P < .01$ compared with values for either control group.

Table 2

Comparison, in male and female rats, of fourth lumbar vertebral body cancellous and cortical bone mineral density (BMD), as determined by peripheral quantitative computed tomography

Treatment group	Cancellous BMD (mg/cm ³)	Cortical BMD (mg/cm ³)
Male rats		
Alcohol-fed	203.00 ± 28.14 [*]	612.85 ± 62.40 ^{**}
Pair-fed	316.61 ± 22.15	630.20 ± 38.65
Ad libitum-fed	391.42 ± 101.50	767.82 ± 21.48
Female rats		
Alcohol-fed	224.60 ± 64.14 [*]	593.88 ± 28.40 ^{**}
Pair-fed	308.74 ± 60.17	663.21 ± 97.98
Ad libitum-fed	375.31 ± 29.96	733.14 ± 40.78

Values are expressed as the mean ($n = 5$) ± S.D.

^{*} $P < .05$ compared with values for either control group.

^{**} $P < .01$ compared with values for ad libitum-fed control group.