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ORIGINAL ARTICLE

Volumetric bone mineral density and bone size in sleep-deprived individuals

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Abstract
Introduction Chronic sleep deprivation, which is associated with several age-related pathologies and altered endocrine function, may adversely affect bone. Our a priori hypothesis was that bone mineral density was lower in sleep-deprived (<6.5 h/night) vs. sleep-adequate (>6.5-10 h/night) individuals.
Methods Cross-sectional analysis of sleep and bone data on 1,146 individuals (652 women) was performed. Measurements were obtained at the distal radius by pQCT, and the spine and hip by DXA. Bone differences between sleep-deprived and sleep-adequate groups were compared after stratifying by sex and controlling for covariates.
Results Overall, 19% of the population was sleep deprived. Sleep-deprived women had lower cortical volumetric BMD ($1,208\pm4$ vs. $1,219\pm2$ mg/cm^3, P=0.03) than sleep-adequate women. Sleep-deprived men had lower pSSI, an estimate of torsional bending strength, than sleep-adequate men (358±10 vs. 382±5 mm^3, P=0.04), due to a slightly smaller periosteal circumference (43.9±0.4 vs. 44.8±0.2 mm, P=0.07) and cortical area (103±2 vs. 106±1±mm^2, P=0.06).
Conclusion Sleep deprivation is associated with some, but not all, bone outcomes. These findings may have important public health significance given the increasing prevalence of sleep deprivation.

Keywords Aging · Body composition · Bone density · Bone size · Sleep

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Introduction

Chronic sleep deprivation is an increasing problem, with approximately one-third of adults reporting less than 6.5 h of sleep per night [1]. Average sleep per night has decreased from approximately 9 h at the turn of the century to about 7.5 h in the early 1990s [2]. Several studies show adverse effects of sleep deprivation on metabolic and endocrine function [2–4]. In particular, Spiegel et al. [2] found that evening cortisol concentrations were greater during sleep deprivation (4 h/night) compared to a fully rested condition (12 h/night). These authors speculated that chronic sleep deprivation could increase the severity of age-related pathologies, such as diabetes and hypertension.

High cortisol levels seen during sleep deprivation may lead to decreased bone mineral density (BMD). Exposure to excess glucocorticoids results in decreased bone formation and BMD [5]. Cortisol profiles exhibit a period of low nocturnal concentrations, referred to as the quiescent period, followed by an abrupt increase after the first few hours of sleep and another sharp increase in the early morning. There is a progressive delay in the onset of the evening quiescent period with aging, and the early morning increase in cortisol concentrations takes place earlier [6]. These changes result in a modest elevation in nocturnal cortisol levels. Similar alterations are observed with sleep deprivation, even among young adults [6]. The effect of

sleep deprivation on bone has not been previously reported, although there is indirect evidence that there may be an association between sleep deprivation and decreased BMD.

Increased cortisol levels have been proposed as a possible explanation for the decreased BMD and increased fracture risk among individuals with depression [7–9], and abnormal sleeping patterns and decreased activity levels are often observed among these individuals. In a recent longitudinal study, decreased BMD and increased risk of non-vertebral fractures were observed among women who previously reported being under mental distress, defined in part as the presence of sleeping problems [10].

The present study was carried out to test the hypothesis that sleep-deprived individuals have lower BMD than sleep-normal individuals. This hypothesis was based on previous findings of increased cortisol levels among sleep-deprived individuals. However, sleep-deprived individuals also may have higher activity levels than normal-sleep people, and high activity levels are associated with increased bone size and BMD [11, 12]. We used baseline data from an ongoing longitudinal study on the effects of lifestyle on areal and volumetric BMD and bone size to test our hypothesis and to control for activity levels while awake.

Materials and methods

Subjects

The South Dakota Rural Bone Health Study (SDRBHS) is a study of 1,189 healthy adults aged 20 to 66 years. Of the 1,189 participants enrolled in 2001 and 2002, 504 were Hutterites, 349 were classified as rural non-Hutterites, and 336 were classified as non-rural non-Hutterites. The Hutterites are an isolated religious group of German descent that has resided in South Dakota since the late 1800s. To be classified as Hutterite, an individual had to be of Hutterite descent and currently residing on a Hutterite colony. Both rural (non-Hutterite) and non-rural populations were recruited from an eight-county area in eastern South Dakota that included at least one participating Hutterite colony. To be considered as rural, the subject had to have spent 75% or more of their life on a working farm or ranch while working less than 1,040 h/year off the farm. In order to be considered as non-rural, the subject could never have spent time living on a working farm or ranch. Details regarding subject recruitment are described in detail elsewhere [12]. Individuals with uncontrolled type I diabetes, parathyroid disease, or chronic regular use (>6 months) of oral steroids, anticonvulsants, or immunosuppressants were not eligible to participate. Since estrogen status is a potential covariate for females, we categorized women as either replete (n=581: post-menopausal and receiving HRT; pre-menopausal) or deplete (n=102: post-menopausal and no HRT) based on self-reported information. Written informed consent was obtained from all participants, and the study was approved by the South Dakota State University Institutional Review Board.

Materials and methods

Data collected at baseline included anthropometric and grip strength measurements, 24-h diet recalls, 7-day activity recall, including sleep information, and bone measurements by peripheral computed tomography (pQCT) at the 4% and 20% distal radius sites and total body, spine and hip bone measurements by dual energy X-ray absorptiometry (DXA).

Height without shoes and weight with light clothing were determined with a portable stadiometer (SECA) and digital scale (SECA, model 770). Height measurements, recorded to the nearest 0.5 cm, were taken in duplicate and repeated if different by more than 0.5 cm. Weight was recorded to the nearest 0.1 kg. Grip strength measurements, which have been shown to be significantly associated with pQCT bone measurements [12], were made as both a measure of arm strength and as an indicator of the overall fitness level. Measurements were made in triplicate, and the highest value recorded.

Twenty-four-hour dietary recall interviews were obtained. Nutrient intakes, including vitamin and mineral supplements, were determined using the Nutritionist V software (First Data Bank, San Bruno, CA). Physical activity was measured using a modified Seven-Day Physical Activity Recall [13], which requires the participant to determine the average amount of time spent per day sleeping, sitting, or in vigorous or moderate activity for both weekday and weekend days during the previous week. The remaining time was classified as light activity. The average daily percent time spent in moderate plus vigorous activity was then calculated. Average hours of sleep per night for both weekdays and weekend days were obtained from this questionnaire, and sleep-deprived individuals were defined as those individuals with less than an average of 6.5 h/night of sleep during the weekday [1]. Both dietary and activity recalls were completed during an interview by study personnel.

pQCT measurements of the left radius were obtained using a Norland-Stratec XCT2000 densitometer (Pforzheim, Germany). Arm length was measured from the elbow to the ulna styloid process, and a scout view was taken to identify the end of the radius. Slices were obtained at 4% and 20% of the measured arm length from the distal radius using a voxel size of 0.4 mm and scan speed of 30 mm/s with a 1-block rotation. Analysis algorithms and thresholds that were used

are reported elsewhere [12]. The polar stress strain index (pSSI) at 20% is based on structural and material properties obtained by pQCT and provides an estimate of torsional bending strength:

$$pSSI = \sum_{i=1,n} \frac{r_i^2 a(CD/ND)}{r_{max}}$$

where r_i is the voxel position from the center, a is the area of the pixel, r_{max} is the maximum distance of the voxel to the bone center, CD is the measured cortical density of the voxel, and ND is the normal physiological cortical density (1,200 mg/ccm) [14]. The coefficients of variation (CV) from duplicate scans obtained on nine adults following repositioning and with a scout view were 0.5%, 1.2% and 0.5% for cortical volumetric BMD (vBMD), cortical thickness and periosteal circumference at the 20% site and 2.6% and 2.4% for periosteal circumference and trabecular vBMD at the 4% distal site. Areal BMD (aBMD), bone mineral content (BMC) and bone area measurements of the total body, spine and hip were obtained using a Hologic QDR 4500A (Bedford, MA). CVs for total body, spine and hip aBMD measured by QDR4500A in adults are less than 1%.

Statistical methods

Statistical analyses were carried out using the JMP software package (version 5.0, SAS Institute, Inc., Cary, NC). Group differences between sleep-deprived and sleep-adequate groups in demographic, anthropometric, and bone characteristics after stratifying by sex were tested by Student's *t* test. Group differences in bone measurements also were assessed by general linear models, after including age, weight, height, percent body fat (by DXA), calcium and vitamin D intake, grip strength, percent time in moderate plus vigorous activity, and population group as covariates. Estrogen status was included in all models for women. These covariates are ones thought, or previously found, to affect bone. *P* values (two-sided) less than 0.10 are shown. Results are presented as the mean ± standard deviation (SD) or least square means ± standard error of the mean (LSM±SEM).

Results

Sleep data for 1,146 individuals of the 1,189 individuals were available. We excluded data from 10 individuals who had incomplete activity and sleep records and 33 individuals (28 Hutterites, 4 rural, and 1 non-rural) who had more than 10 h of sleep per night. Sleep greater than 10 h/night may be associated with other pathological conditions [15], and there were insufficient numbers to investigate this group separately. There were 469 (289 women) Hutterites, 342 (161 women) rural individuals, and 335 (202 women) non-rural individuals. Due to the very low percentage of Hutterites who were sleep deprived [approximately 3% of both men (5/180) and women (9/289)], and previous findings of increased bone size and BMD among this population [12, 16], all Hutterites were omitted from further analyses to simplify data analysis and interpretation. Later inclusion of the Hutterite group in the final statistical models did not alter the findings. An additional 15 non-Hutterite women were excluded due to possible effects of pregnancy and lactation on bone outcomes: 2 women who had given birth in the previous 6 months, 8 who were currently breast-feeding and 5 who had breast-fed in the previous 12 months. Population characteristics of those individuals included in the analyses are given in Table 1.

Overall, 19% of the population was sleep deprived. Fifteen percent of rural women and 22% of non-rural women were sleep deprived (P=0.09), whereas 20% of both rural and non-rural men were sleep deprived. There were no differences among sleep-deprived and sleep-adequate women, except for a slightly higher percent time in moderate plus vigorous activity among sleep-deprived women (P=0.09, Table 1). Sleep-deprived men were heavier than sleep-adequate men (P=0.02). As expected by definition, average hours of sleep per weekday and weekend night were lower in individuals who were sleep deprived compared to those who were sleep adequate.

There were no differences in any of the DXA bone measurements between sleep-deprived and sleep-adequate women or men before adjusting for covariates. After controlling for covariates, the only bone measures that were marginally different between women who were sleep deprived vs. sleep adequate were a higher bone area of the proximal hip (least square means: 34.3±0.3 vs. 33.4±0.2 cm^2, P=0.01) and trend toward a high bone area of the femoral neck (5.05±0.05 vs. 4.95±0.03 cm^2, P=0.056).

Bone measurements by pQCT at the 20% distal radius are shown in Figs. 1 and 2. Sleep-deprived women had lower cortical vBMD than sleep-adequate women both before (P=0.01) and after (P=0.03) inclusion of potential covariates (Fig. 1). This contrasts to men, who had greater vBMD if they were sleep deprived than if they were sleep adequate both before (P=0.09) and after (P=0.03) inclusion of potential covariates (Fig. 2). The slightly smaller periosteal circumference (P=0.07 with covariates) and cortical area (P=0.06 with covariates) among sleep-deprived compared to sleep-adequate men led to a lower polar SSI, an estimate of torsional bending strength, among sleep-deprived men than sleep-adequate men (P=0.04). There were no differences between sleep-deprived and

Table 1 Population characteristics and bone measurements of sleep-deprived (<6.5 h/night) and sleep-adequate (6.5–10 h/night) individuals

	Women		Men	
	Sleep-deprived (n=64)	Sleep-adequate (n=284)	Sleep-deprived (n=63)	Sleep-adequate (n=251)
Rural/non-rural	23/41[a]	135/149[a]	37/26	144/107
Estrogen replete/deplete	52/12	232/52	-	-
Age (years)	43±2	45±1	44±12	44±13
Weight (kg)	74.9±2.1	74.0±1.0	98.1±23.3[b]	92.0±16.4[b]
Height (cm)	163.7±0.8	164.2±0.4	178.4±7.1	178.9±7.7
%Fat	35±1	35±1	25±6	23±5
Calcium intake (mg/day)	933±88	1036±42	1,033±705	1,155±684
Vitamin D intake (IU/day)	284±34	275±16	240±245	273±250
Grip strength (kg)	29±1	30±1	50±8	51±9
% Time in moderate + vigorous activity	24±2[a]	21±1[a]	23±145	22±13
Hours sleep/weekday night	5.6±0.1[c]	7.6±0.1[c]	5.6±0.6[c]	7.4±0.7[c]
Hours sleep/weekend night	6.7±0.1[c]	7.9±0.1[c]	6.4±1.4[c]	7.7±1.0[c]
DXA Bone results				
Femoral neck				
BMC (g)	4.27±0.08	4.14±0.04	5.32±0.12	5.27±0.06
Bone area (cm^2)	5.04±0.05	4.98±0.02	5.88±0.05	5.85±0.03
aBMD (g/cm^2)	0.85±0.02	0.83±0.01	0.90±0.01	0.90±0.01
Proximal hip				
BMC(g)	32.6±0.7	32.1±0.3	48.9±1.1	48.0±0.5
Bone area (cm^2)	34.0±0.4	33.5±0.2[b]	45.0±0.6	45.3±0.3
aBMD (g/cm^2)	0.96±0.02	0.96±0.01	1.09±0.02	1.06±0.01
Lumbar spine				
BMC(g)	63.0±1.4	64.0±0.6	76.4±1.8	76.2±0.9
Bone area (cm^2)	60.2±0.6	60.0±0.3	70.5±0.8	70.5±0.4
aBMD (g/cm^2)	1.04±0.02	1.06±0.01	1.08±0.02	1.08±0.01
Total body				
BMC(g)	2,255±39	2,279±18	2,971±55	2,943±27
Bone area (cm^2)	2,005±20	2,009±9	2,405±24	2,410±12
pQCT Bone results				
4% radius				
Trabecular density (mg/ccm)	203±4	201±2	231±4	232±2
Periosteal circumference(mm)	58.5±0.5	58.7±0.3	67.8±0.7	68.8±0.3

Data are means ±SEM.
[a] P<0.10; [b] P<0.05; [c] P<0.001: superscripts note differences between groups within gender:

sleep-adequate women or men in trabecular vBMD or periosteal circumference at the 4% distal radius site (Table 1).

Discussion

We observed an associations between sleep deprivation and some bone parameters, but not others. Sleep deprivation was associated with decreased cortical vBMD in women and decreased polar SSI, an indicator of torsional bending strength, in men. The decreased pSSI, an estimate of torsional bending strength, in sleep-deprived men was a result of slightly smaller bones with thinner cortices when compared to sleep-adequate men. Bone size contributes significantly to bone strength, with a larger bone conferring greater strength than a smaller bone [17, 18]. A larger bone size has been associated with a decreased fracture risk [19, 20]. The differences in bone sites and parameters found to be associated with sleep deprivation may provide insight into the possible underlying mechanism for the observed associations, and although we are unaware of any studies that have reported adverse effects of sleep deprivation on bone, there is indirect evidence supporting such a relationship.

Abnormal sleeping patterns are often observed with depression, and several studies report decreased areal BMD and increased fracture risk among individuals with clinical depression [9, 21, 22]. In a recent longitudinal study, decreased areal BMD and increased risk of non-vertebral

Cortical vBMD (mg/ccm)	1208 ± 4 [a]	1219 ± 2 [a]
Cortical Thickness (mm)	2.56 ± 0.04	2.55 ± 0.02
Periosteal Circumference (mm)	36.7 ± 0.3	36.6 ± 0.2
Cortical Area (mm²)	73.0 ± 1.1	72.8 ± 0.5
Polar SSI (mm³)	226 ± 6	227 ± 3

Fig. 1 Schematic of pQCT measurements of the 20% distal radius among sleep-deprived and sleep-adequate women (not drawn to scale). Data are means ±SEM. Significance is based on a statistical model controlling for age, weight, height, % fat, calcium and vitamin D intake, grip strength, % time in moderate and vigorous activity, and population group. [a]$P<0.05$

fractures were observed among women who were under mental distress, defined in part as the presence of sleeping problems [10]. Although we observed lower volumetric BMD in sleep-deprived women than sleep-adequate women, we did not observe differences in areal BMD as previously reported. Bio-available testosterone is decreased in men with depression [23], and fragmented sleep has been shown to disrupt the circadian testosterone rhythm resulting in attenuation of the nocturnal rise in testosterone [24]. Testosterone is thought to play a role in periosteal expansion [25, 26], and our findings of a slightly smaller periosteal circumference and cortical area are consistent with decreased testosterone concentrations among sleep-deprived men. Increased cortisol levels, which are often observed in depression, also may influence bone.

We originally speculated that sleep deprivation would be associated with decreased BMD due to higher cortisol levels previously reported in sleep-deprived individuals [2].

Cortical vBMD (mg/ccm)	1197 ± 3 [a]	1191 ± 2 [a]
Cortical Thickness (mm)	3.01 ± 0.04	3.02 ± 0.02
Periosteal Circumference (mm)	43.9 ± 0.4 [b]	44.7 ± 0.2 [b]
Cortical Area (mm²)	103.3 ± 1.6 [b]	106.2 ± 0.8 [b]
Polar SSI (mm³)	358 ± 10 [a]	382 ± 5 [a]

Fig. 2 Schematic of pQCT measurements of the 20% distal radius among sleep-deprived and sleep-adequate men (not drawn to scale). Data are means ±SEM. Significance is based on a statistical model controlling for age, weight, height, % fat, calcium and vitamin D intake, grip strength, % time in moderate and vigorous activity, and population group. [a]$P<0.05$ [b]$P<0.07$

Exposure to excess glucocorticoids results in decreased bone formation and BMD, especially at trabecular bone sites [5]. However, our findings are not consistent with high cortisol levels since we did not observe any differences in trabecular vBMD or aBMD at predominantly trabecular bone sites (i.e., the lumbar spine).

Estrogen deficiency is known to disrupt sleep [27] and is associated with decreased cortical vBMD [28]. It is possible that women with low estrogen levels have less sleep and that the relationship we observed between low cortical vBMD and sleep deprivation is an indirect association that can be explained by low circulating estrogen concentrations. However, the relationship between low cortical vBMD and sleep deprivation remained significant when estrogen status was included in the statistical analysis as a covariate. We also did not find a difference in spine BMD or trabecular vBMD, which would be decreased with estrogen deficiency. It therefore seems unlikely that the explanation for decreased cortical vBMD among sleep-deprived women is a result of decreased estrogen levels.

There are circadian rhythms in many of the minerals, proteins, and hormones involved in bone metabolism, including serum calcium, osteocalcin, parathyroid hormone (PTH), growth hormone, and insulin-like-growth factor (IGF-I). Circadian rhythms in PTH and growth hormone profiles, both of which are important in bone health, are altered with sleep deprivation [3, 4, 29]. High PTH concentrations have adverse effects on cortical, but not trabecular, vBMD [30], a finding that would be consistent with our bone results among women, but not among men. However, effects of sleep deprivation on growth hormone and IGF-I also may explain the observed gender specificity of the bone effects we observed.

Growth hormone and IGF-I are important for periosteal expansion [31]. Decreased IGF-I and IGF-binding protein 3 (IGFBP-3) concentrations are found in children with obstructive sleep apnea, and these concentrations increase following corrective surgery (adenotonsillectomy) [32]. The periosteal circumference and cortical area are smaller among sleep-deprived men compared to those who were sleep adequate, leading to a lower polar SSI, an indicator of torsional bending strength. The bone effects we observed in the men are consistent with decreased GH secretion and lower IGF-I concentrations with sleep deprivation. The lack of a finding on bone size among women may be due to the lower absolute periosteal bone formation that occurs in women compared to men at this age [33].

There are several limitations to our study. First, this is a cross-sectional study, with recall of activity and sleep patterns being obtained for the previous week only. Whether the sleep patterns of the previous week are typical throughout the year is not known. Second, because of the cross-sectional nature of the data it is not possible to conclude

whether sleep deprivation per se caused the decreased BMD or whether some other confounding factor is responsible. It will be important to determine whether chronic sleep deprivation is shown to influence bone changes prospectively. In addition, it will be important to obtain hormonal measurements prospectively to help understand the possible mechanism(s) by which sleep deprivation may adversely affect bone. Third, we do not have information on the reason for the sleep deprivation. The underlying mechanism may differ if the sleep deficits are a result of insomnia vs. a lack of time to sleep due to increased work demands. We did not obtain specific information on whether or not individuals classified as sleep deprived actually had daytime fatigue or sleepiness, and we assumed that less than 6.5 h of sleep per night was insufficient, but there are individuals for whom this may be adequate.

The prevalence of sleep deprivation in this country parallels an increase in the incidence of osteoporosis and hip fractures [34]. Our findings of an association between sleep deprivation and reduced cortical vBMD in women and decreased torsional bending strength (pSSI) in men may explain, in part, some of these temporal trends. Additional studies in other populations are necessary to confirm these findings. Further confirmation may lead to simple public health recommendations for adequate sleep that may impact measures of bone health.

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