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AIM AND SCOPE

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INDEXING/ABSTRACTING

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ORIGINAL ARTICLE

Case Control Study

Abdominal obesity adversely affects bone mass in children

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Abstract

AIM
To determine the effect of childhood obesity and insulin resistance on bone health.

METHODS
We conducted a cross sectional study in pubertal adolescents and young adults 13-20 years old who were either overweight/obese or normal weight. Participants were Tanner 3 or above for pubertal stage, and had fasting blood work done to measure glucose, insulin, C-reactive protein and lipid levels. Homeostatic model of insulin resistance (HOMA-IR) was calculated using the formula (Fasting Blood Glucose *Insulin/405). Body composition and bone mineral density were measured using dual energy X-ray absorptiometry (DXA; Hologic QDR 4500, Waltham, MA, United Kingdom).

RESULTS
Percent trunk fat was associated inversely with whole

body bone mineral content (BMC), whereas HOMA-IR was associated positively with whole body BMC.

CONCLUSION

Our results suggest that abdominal adiposity may have an adverse effect on whole body bone parameters and that this effect is not mediated by insulin resistance.

Key words: Obesity; Bone mineral density; Insulin resistance

Core tip: Abdominal adiposity has an adverse impact on whole body bone mineral content in adolescents. This effect does not seem to be mediated by the increased insulin resistance associated with increased abdominal adiposity. Attention to body composition rather than just body weight is needed to counsel adolescents regarding optimal bone health.

INTRODUCTION

The antecedents of adult onset osteoporosis start in childhood, and while the effect of several childhood systemic diseases on bone health[1] has been recognized, the effect of childhood obesity on bone health remains unclear. Historically in adults, higher body mass index (BMI) was believed to be bone protective with increased bone mineral density (BMD) reported with higher BMI[2]. Further studies have revealed this to be proportional to total lean mass rather than total fat mass. However, the relative distribution of fat in the body may also play a role, and visceral adiposity in particular has been demonstrated to have an adverse impact on bone[3,4]. Visceral adiposity is directly associated with insulin resistance, and the link between obesity and bone health may be mediated by the underlying insulin resistance. Insulin is a bone anabolic hormone[5] and higher insulin levels may result in increased bone formation. However, a state of insulin resistance may negate the beneficial effects of insulin on bone. This in fact has been suggested in recent studies in adults[6,7]. However, data in children remain inconclusive.

Data regarding the relationship between insulin resistance, BMD and fracture risk are conflicting. While adults with long standing type 2 diabetes tend to have more fractures[8-10], their BMD has been reported to be high or normal in various studies. Potential conflicting factors include the duration of type 2 diabetes (as type 2 diabetes can go unrecognized for a long time), and

degree of hyperglycemia. While obese boys tend to have more fractures than their lean counterparts[11], the pathophysiology behind this association remains to be delineated, and the effect of insulin resistance without overt type 2 diabetes on bone health in adolescents remains unclear. In this study, we examined the association of body composition and insulin resistance with whole body BMD and bone mineral content (BMC) in a group of overweight and normal weight pubertal adolescents, none of whom had type 2 diabetes. We hypothesized that overweight children with greater visceral adiposity (as assessed by percent trunk fat) would have lower BMD and BMC compared to their normal weight counterparts, which would be associated with the degree of insulin resistance.

MATERIALS AND METHODS

This was a cross-sectional study of children 13-20 years who were either normal weight or overweight. Subjects were recruited from our clinics and through recruitment fliers and campus wide e-mail notifications between 2006-2008. A total of 37 children were enrolled. Study subjects were defined as being overweight if their BMI was above the 85th percentile for age and gender (Group 1) and normal weight if their BMI was between the 3rd to 85th percentiles for age and gender (Group 2). The research protocol was approved by the Institutional Review Board at the University of Oklahoma Health Sciences Center. All subjects < 18 years old provided assent for study participation. Participants 18 years or older and parents of participants < 18 years old provided consent for study participation.

Children were excluded from the study if: (1) They had any coexisting endocrine, genetic or metabolic disease that may affect bone metabolism; or (2) if they were on any medications that may affect bone, including those that could affect substrate metabolism, psychotropic medications, weight loss medications, and oral contraceptives for female subjects. To control for the well-described increase in bone mineral acquisition during early stages of puberty, children who were prepubertal or early pubertal (Tanner 1 and 2) were excluded. Children were also excluded if they had impaired fasting glucose or diabetes based on fasting glucose values[12].

After obtaining appropriate consent and assent, each child underwent a history and physical examination by a board certified pediatrician. Height and weight were used to calculate BMI, waist and hip circumference were obtained on each subject, and the presence and degree of acanthosis nigricans noted if present. Study participants then underwent a fasting blood draw for glucose and insulin levels, lipid profile and apolipoprotein C-Ⅲ levels. Homeostatic model of insulin resistance (HOMA-IR) was calculated using the formula: (Fasting Blood Glucose *Insulin)/405. Studies have shown that HOMA-IR correlates well with insulin resistance as measured by insulin clamp studies[13]. All testing was

Table 1 Descriptive data of the overweight and normal weight groups

Covariates	Overweight *n* = 23	Normal weight *n* = 14	*P* value
	mean (SD)	mean (SD)	
Age (mo)	187 (25.4)	198 (31.1)	0.40[b]
Gender (% age females)	43.48%	57.14%	0.42
Birth weight (g)	3385 (644)	3179 (908)	0.42[b]
Weight (kg)	93.7 (19.9)	57.4 (7.51)	< 0.0001[a]
Weight %ile	95.1 (6.35)	52.5 (20.8)	< 0.0001[b]
Height (cm)	168 (9.90)	167 (6.92)	0.72[a]
Height %ile	59.3 (30.5)	60.1 (31.2)	0.88[b]
BMI kg/m^2	32.9 (5.60)	20.5 (1.51)	< 0.0001[a]
BMI %ile	96.6 (3.17)	47.3 (17.1)	< 0.0001[b]
Total activity time/d (min)	303 (125)	307 (109)	0.93
Apolipoprotein C III (mg/dL)	6.71 (1.53)	6.56 (140)	0.75[a]
C-reactive protein	2.81 (2.85)[c]	2.61(2.41)[d]	0.86
HOMA-IR	3.23 (1.78)	2.49 (3.49)	0.02
Waist circumference (cm)	98.5 (13.7)	69.2 (5.79)	< 0.0001[a]
Hip circumference (cm)	118 (11.4)	94.8 (5.72)	< 0.0001[a]
Waist to hip ratio	0.84 (0.06)	0.73 (0.05)	< 0.0001[a]
Total lean mass (kg) (DXA)	50.58 (10.78)	55.40 (12.68)	0.23[a]
Percent trunk fat (DXA)	36.4 (9.3)	17.1 (6.49)	< 0.0001
Spine BMD (g/cm^2)	1.06 (0.14)	1.06 (0.13)	0.95[a]
BMD L-spine Z-score	1.32 (1.24)	1.36 (1.00)	0.92
Whole body BMD (g/cm^2)	1.10 (0.09)	1.06 (0.07)	0.21[a]
Whole body BMC (g)	2417 (408)	2116 (281)	0.02[a]

[a]Student's *t*-test; [b]Wilcoxon-Mann-Whitney test; [c]*n* = 16; [d]*n* = 9. SD: Standard deviation; HOMA-IR: Homeostatic model assessment-estimated insulin resistance; BMD: Bone mineral density; BMC: Bone mineral content; BMI: Body mass index.

done by an experienced nurse assigned to the study at the General Clinical Research Center at the University of Oklahoma.

Whole body (WB) BMC and BMD, lumbar spine BMD, and body composition were measured using dual energy X-ray absorptiometry (DXA; Hologic QDR 4500, Waltham, MA, United Kingdom). Percent trunk fat [(trunk fat/total fat) × 100] was used as a surrogate for visceral fat[14]. Similarly, the waist to hip ratio was used as a surrogate for visceral fat[14]. Daily physical activity was assessed using a step activity monitor (Step Watch 3, Orthocare Innovations, Oklahoma City, OK, United States)[15]. Subjects were asked to wear the step activity monitor on their right ankle during the day time when they were awake for 5 to 7 consecutive days. The monitor records the number of strides taken on a minute to minute basis. Data from the monitor is downloaded to a computer software program which calculates the activity time in a day (any minute in which a stride was taken is considered an active time) and the total amount of strides taken each day averaged over the days the monitor was worn. The accuracy of the step activity monitor exceeds 99% ± 1% in older adults[15], as well as in children[16]. Test-retest intraclass reliability coefficient for the measurement of total daily strides and total daily minutes of activity are R = 0.94 and R = 0.91, respectively[15].

Statistical analysis

Statistical analysis for this study was performed and reviewed by Michael A Anderson (co-author), a bio-statistician at Department of public health, University of Oklahoma Health Sciences Center. Descriptive statistics

were computed for age, gender, smoking, birth weight, current weight, height, BMI, waist circumference, hip circumference, waist to hip ratio, BMC and BMD, trunk % fat, and HOMA-IR. All continuous variables were assessed for normality using the Shapiro-Wilk test for normality and comparisons between overweight and normal weight groups were made using the Student *t*-test or the Wilcoxon-Mann-Whitney test, as appropriate. One outlier was identified (HOMA-IR > 13) and after checking for data entry error, this subject was excluded from data analysis. Pearson's correlation coefficient was used to test the strength of the linear association. Robust regression was used to fit a multiple linear regression model to test the effect of HOMA-IR and percent trunk fat on WB-BMC and all BMD variables while controlling for gender and physical activity (total activity time % of day), which are potential confounders of the association. The effect of percent trunk fat on HOMA-IR while controlling for gender and physical activity was similarly tested.

RESULTS

Demographic data revealed no significant difference in age, gender, birth weight or current height between the two groups (Table 1). Per study design, group 1 consisting of overweight participants had a significantly higher mean body weight, BMI, waist circumference, hip circumference, waist to hip ratio and percent trunk fat (Table 1). Total activity time per day and sedentary time per day did not differ between the two groups.

WB-BMC was significantly higher in the overweight

Variable	Whole body BMC		Spine BMD	
	β	*P* value	β	*P* value
Gender	-704.28	< 0.0001	0.0876	0.18
Activity time % of day	-0.55	0.79	-0.0003	0.86
Waist to hip ratio	-111.619	0.86	0.4707	0.27
Percent trunk fat	-2112.67	< 0.0001	-0.3706	0.18
Total lean mass	-0.0022	0.59	0.00	0.98
HOMA IR	123.3	< 0.0001	-0.1295	0.29

Table 2 Robust regression with whole body bone mineral content or spine bone mineral density as the dependent variable after

Other covariates in the model include waist to hip ratio, truck to total fat ratio, total lean mass, CRP, total activity time, apo CⅢ ratio, gender, HOMA-IR. BMC: Bone mineral content; BMD: Bone mineral density; HOMA-IR: Homeostatic model assessment-estimated insulin resistance.

group as was HOMA-IR (Table 1). BMD in both lower extremities was also significantly higher in the overweight group compared to the normal weight group (Table 1). In contrast, WB BMD, and spine BMD did not differ across groups. Similarly Lumbar spine BMD Z-score and total body less head (TBLH) BMD Z-score did not significantly differ between the two groups.

Robust regression with HOMA-IR as the dependent variable revealed that waist to hip ratio [β = 12.72 (3.88); *P* < 0.01], and activity time % of day [β = -0.03 (0.04); *P* = 0.05], but not percent trunk fat, were significantly related to HOMA-IR. Robust regression with WB-BMC as the dependent variable revealed a significant inverse association with percent trunk fat [β = -2112.67 (338.13); *P* < 0.01] (Table 2), and a positive association with HOMA-IR (*P* = 0.03) (Table 2) after controlling for potential confounders, gender and physical activity. BMD variables (WB BMD, and spine BMD) had inverse associations with percent trunk fat, but did not reach statistical significance. Apolipoprotein C-Ⅲ which is considered to be a marker of insulin resistance[17] did not differ significantly between the two groups and had no significant association with any BMD/BMC variables. Insulin values did not have a significant correlation with either WB-BMC (-0.12, *P* = 0.46) or subtotal BMC (-0.16, *P* = 0.36).

DISCUSSION

In this cross sectional study of bone parameters in normal-weight and overweight adolescents in the later stages of puberty, we show that higher trunk fat is associated with lower WB-BMC, whereas higher HOMA-IR is associated with higher WB-BMC after controlling for potential confounders. Both our groups were well matched for age and gender.

As expected, overweight subjects (Group 1) had a higher waist to hip ratio, percent trunk fat and HOMA-IR than normal-weight participants (Group 2). Waist to hip ratio is a reasonable surrogate for visceral adiposity, as is percent trunk fat[14]. The positive relationship between HOMA-IR and waist to hip ratio observed in our study has been documented by others[18,19]. Similarly higher BMC in obese and overweight subjects as observed in our study has been reported by others[20,21].

However, data are lacking regarding associations of insulin resistance parameters with bone variables in adolescents. Overweight subjects had higher BMD than normal-weight subjects in the lower extremities, consistent with the impact of greater loading (from greater body size) in overweight adolescents at this weight bearing region. This has been previously shown in the Framingham study in adults[22].

In our study, WB BMC was positively associated with HOMA-IR and negatively with the percent trunk fat, a good surrogate measure of visceral fat[14]. In adults, insulin resistance has been shown to have an adverse impact on bone mass[23]. In the MIDUS 11 study by Srikanthan *et al*[6] with approximately 717 adult participants, higher HOMA-IR levels were associated with higher BMD in the femoral neck but with decreased femoral neck strength. The femoral neck is not a site recommended for measurement of BMD in adolescents as landmarks are not well defined at this age making repeat measurements difficult. While the study by Srikanthan *et al*[6] included subjects with impaired glucose tolerance and diabetes, we excluded subjects with either of these conditions. Thus a higher HOMA IR value in our study would primarily be driven by higher insulin levels. A very elegant review by Fulzele *et al*[24] details the effects of insulin on bone acquisition, acting *via* insulin receptors expressed on osteoblasts. Given the multitude of anabolic actions of insulin on bone, it is not surprising that higher insulin levels would be associated with higher bone mass, despite associated insulin resistance. Also, HOMA-IR is a very crude measure of insulin resistance, and additionally, in any particular individual, there can be differential/partial insulin resistance in different organ/tissues[25,26]. Higher bone mass associated with higher HOMA-IR in overweight adolescents may mean that their osteoblasts are still sensitive to insulin signaling and its bone anabolic effects.

In contrast, recent literature suggests that visceral adiposity affects bone health adversely[3,27]. In our study, there was no association between WB BMD and waist to hip ratio, however, there was a significant inverse association between WB BMC and percent trunk fat, a good indicator of abdominal adiposity relative to total fat mass and visceral adiposity[14], consistent with other studies[3,28]. While it is not surprising that we

observed this inverse relationship of percent trunk fat with WB BMC, the pathogenic mechanism underlying this relationship remains unclear. Our initial postulate that the adverse effect of abdominal adiposity on bone mass in overweight children may be mediated by insulin resistance secondary to higher abdominal adiposity did not hold true. Another possible pathogenic mechanism in overweight adults may be an atherogenic lipid profile[29]. An elegant review by Tintut *et al*[29] discusses the relationship of poor bone mineralization with an adverse lipid profile, which may be mediated by vascular ischemia secondary to atherosclerosis. However, this is unlikely to be the mechanism linking low bone mass and abdominal adiposity in adolescents, in whom frank atherosclerosis is unusual despite an adverse lipid profile. In addition, we found no associations of lipids including apolipoprotein C Ⅲ with bone variables. The possibility that certain adipokines secreted preferentially by visceral fat may mediate this effect needs to be further explored.

Higher cortisol and decreased growth hormone secretion is well reported in obese subjects. A higher fracture rate has been reported in obese adolescents[11], however, our sample size was not large enough to draw any conclusions regarding fracture prevalence. It is interesting that physical activity did not differ significantly between our two groups, and may reflect low levels of activity in both groups. We do not have vitamin D levels on the subjects, however, the impact of vitamin D supplementation on bone mass in subjects who are vitamin D sufficient remains controversial[30]. Finally, this is a cross sectional study and thus the results do not imply causation.

In conclusion, our data add to existing literature that suggests that abdominal adiposity has an adverse impact on WB BMC in adolescents. In addition, our study shows that this effect is not mediated by the increased insulin resistance associated with increased abdominal adiposity. Attention to body composition rather than just body weight is needed to counsel adolescents regarding optimal bone health. Further studies are needed to delineate the mechanisms by which visceral adiposity adversely affects bone health.

ARTICLE HIGHLIGHTS

Research background
Adult onset osteoporosis has its antecedent in childhood. With the rise in obesity epidemic, the effect of childhood obesity on bone health needs to be delineated. Historically in adults, higher body mass index (BMI) was believed to be bone protective with increased bone mineral density reported with higher BMI. Further studies have revealed this to be proportional to total lean mass rather than total fat mass. However, the relative distribution of fat in the body may also play a role, and visceral adiposity in particular has been demonstrated to have an adverse impact on bone. Visceral adiposity is directly associated with insulin resistance, and the link between obesity and bone health may be mediated by the underlying insulin resistance. Insulin is a bone anabolic hormone and higher insulin levels may result in increased bone formation. However, a state of insulin resistance may negate the beneficial effects of insulin on bone. This in fact has been suggested in recent studies in adults. However, data in children remain inconclusive.

Research motivation
The main motivation for this research study was to understand the effect of body composition and insulin resistance on bone health in children.

Research methods
The study showed that percent trunk fat was associated inversely with whole body bone mineral content (BMC), whereas homeostatic model of insulin resistance was associated positively with whole body BMC.

Research results
These results suggest that abdominal adiposity may have an adverse effect on whole body bone parameters and that this effect is not mediated by insulin resistance.

Research perspectives
Future research should look at other possible connection between adipose tissue and bone health.

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