

## Case Control Study

**Abdominal obesity adversely affects bone mass in children**

Sowmya Krishnan, Michael P Anderson, David A Fields, Madhusmita Misra

Sowmya Krishnan, David A Fields, Department of Pediatrics, University of Oklahoma Health Sciences Center, Harold Hamm Diabetes Center, Oklahoma City, OK 73104, United States

Michael P Anderson, College of Public Health, University of Oklahoma Health Science Center, Oklahoma City, OK 73104, United States

Madhusmita Misra, Massachusetts General Hospital for Children and Harvard Medical School, Boston, MA 02114, United States

ORCID number: Sowmya Krishnan (0000-0001-5600-0753); Michael P Anderson (0000-0002-2319-2282); David A Fields (0000-0002-6845-1196); Madhusmita Misra (0000-0002-9405-2981).

**Author contributions:** Krishnan S collected data; Anderson MP helped in statistical analysis; Fields DA and Misra M helped in writing the paper.

Supported by Novo-Nordisk, No. C7042301.

**Institutional review board statement:** The study has been approved by the University of Oklahoma Health sciences Center Institutional review board research ethics committee and has been performed in accordance with the ethical standards as laid down in the 1964 declaration of Helsinki and its later amendments.

**Informed consent statement:** All study participants or their legal guardians provided informed consent prior to enrollment in the study.

**Conflict-of-interest statement:** David A Fields has received grant funding from Nestle and Mead Johnson.

**Data sharing statement:** Consent was not obtained from participants for sharing data but presented data is anonymized and risk of identification is low.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and

the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Sowmya Krishnan, MD, Associate Professor, Department of Pediatrics, University of Oklahoma Health Sciences Center, Harold Hamm Diabetes Center, 1200, N Children's Avenue, Suite 4500, Oklahoma City, OK 73104, United States. [sowmya-krishnan@ouhsc.edu](mailto:sowmya-krishnan@ouhsc.edu)  
Telephone: +1-405-2718000-43091  
Fax: +1-405-2713093

Received: August 25, 2017

Peer-review started: September 17, 2017

First decision: October 23, 2017

Revised: November 8, 2017

Accepted: November 27, 2017

Article in press: November 27, 2017

Published online: February 8, 2018

**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

© **The Author(s) 2018.** Published by Baishideng Publishing Group Inc. All rights reserved.

**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.

Krishnan S, Anderson MP, Fields DA, Misra M. Abdominal obesity adversely affects bone mass in children. *World J Clin Pediatr* 2018; 7(1): 43-48 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v7/i1/43.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v7.i1.43>

## INTRODUCTION

The antecedents of adult onset osteoporosis start in childhood, and while the effect of several childhood systemic diseases on bone health<sup>[1]</sup> 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<sup>[2]</sup>. 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<sup>[3,4]</sup>. 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<sup>[5]</sup> 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<sup>[6,7]</sup>. 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<sup>[8-10]</sup>, 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<sup>[11]</sup>, 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 85<sup>th</sup> percentile for age and gender (Group 1) and normal weight if their BMI was between the 3<sup>rd</sup> to 85<sup>th</sup> 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<sup>[12]</sup>.

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<sup>[13]</sup>. All testing was

**Table 1** Descriptive data of the overweight and normal weight groups

Covariates	Overweight <i>n</i> = 23	Normal weight <i>n</i> = 14	<i>P</i> value
	mean (SD)	mean (SD)	
Age (mo)	187 (25.4)	198 (31.1)	0.40 <sup>b</sup>
Gender (% age females)	43.48%	57.14%	0.42
Birth weight (g)	3385 (644)	3179 (908)	0.42 <sup>b</sup>
Weight (kg)	93.7 (19.9)	57.4 (7.51)	< 0.0001 <sup>a</sup>
Weight %ile	95.1 (6.35)	52.5 (20.8)	< 0.0001 <sup>b</sup>
Height (cm)	168 (9.90)	167 (6.92)	0.72 <sup>a</sup>
Height %ile	59.3 (30.5)	60.1 (31.2)	0.88 <sup>b</sup>
BMI kg/m <sup>2</sup>	32.9 (5.60)	20.5 (1.51)	< 0.0001 <sup>a</sup>
BMI %ile	96.6 (3.17)	47.3 (17.1)	< 0.0001 <sup>b</sup>
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 <sup>a</sup>
C-reactive protein	2.81 (2.85) <sup>c</sup>	2.61(2.41) <sup>d</sup>	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 <sup>a</sup>
Hip circumference (cm)	118 (11.4)	94.8 (5.72)	< 0.0001 <sup>a</sup>
Waist to hip ratio	0.84 (0.06)	0.73 (0.05)	< 0.0001 <sup>a</sup>
Total lean mass (kg) (DXA)	50.58 (10.78)	55.40 (12.68)	0.23 <sup>a</sup>
Percent trunk fat (DXA)	36.4 (9.3)	17.1 (6.49)	< 0.0001
Spine BMD (g/cm <sup>3</sup> )	1.06 (0.14)	1.06 (0.13)	0.95 <sup>a</sup>
BMD L-spine Z-score	1.32 (1.24)	1.36 (1.00)	0.92
Whole body BMD (g/cm <sup>3</sup> )	1.10 (0.09)	1.06 (0.07)	0.21 <sup>a</sup>
Whole body BMC (g)	2417 (408)	2116 (281)	0.02 <sup>a</sup>

<sup>a</sup>Student's *t*-test; <sup>b</sup>Wilcoxon-Mann-Whitney test; <sup>c</sup>*n* = 16; <sup>d</sup>*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<sup>[14]</sup>. Similarly, the waist to hip ratio was used as a surrogate for visceral fat<sup>[14]</sup>. Daily physical activity was assessed using a step activity monitor (Step Watch 3, Orthocare Innovations, Oklahoma City, OK, United States)<sup>[15]</sup>. 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<sup>[15]</sup>, as well as in children<sup>[16]</sup>. 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<sup>[15]</sup>.

### Statistical analysis

Statistical analysis for this study was performed and reviewed by Michael A Anderson (co-author), a biostatistician 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

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

Variable	Whole body BMC		Spine BMD	
	$\beta$	P value	$\beta$	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

Other covariates in the model include waist to hip ratio, trunk 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 [ $\beta = 12.72$  (3.88);  $P < 0.01$ ], and activity time % of day [ $\beta = -0.03$  (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 [ $\beta = -2112.67$  (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<sup>[17]</sup> 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<sup>[14]</sup>. The positive relationship between HOMA-IR and waist to hip ratio observed in our study has been documented by others<sup>[18,19]</sup>. Similarly higher BMC in obese and overweight subjects as observed in our study has been reported by others<sup>[20,21]</sup>.

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<sup>[22]</sup>.

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<sup>[14]</sup>. In adults, insulin resistance has been shown to have an adverse impact on bone mass<sup>[23]</sup>. In the MIDUS 11 study by Srikanthan *et al*<sup>[6]</sup> 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*<sup>[6]</sup> 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*<sup>[24]</sup> 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<sup>[25,26]</sup>. 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<sup>[3,27]</sup>. In our study, there was no association between WB BMC 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<sup>[14]</sup>, consistent with other studies<sup>[3,28]</sup>. 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<sup>[29]</sup>. An elegant review by Tintut *et al.*<sup>[29]</sup> 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<sup>[11]</sup>, 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<sup>[30]</sup>. 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.

## REFERENCES

- 1 **Baim S**, Binkley N, Bilezikian JP, Kendler DL, Hans DB, Lewiecki EM, Silverman S. Official Positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD Position Development Conference. *J Clin Densitom* 2008; **11**: 75-91 [PMID: 18442754 DOI: 10.1016/j.jocd.2007.12.007]
- 2 **Beck TJ**, Petit MA, Wu G, LeBoff MS, Cauley JA, Chen Z. Does obesity really make the femur stronger? BMD, geometry, and fracture incidence in the women's health initiative-observational study. *J Bone Miner Res* 2009; **24**: 1369-1379 [PMID: 19292617 DOI: 10.1359/jbmr.090307]
- 3 **Gilsanz V**, Chalfant J, Mo AO, Lee DC, Dorey FJ, Mittelman SD. Reciprocal relations of subcutaneous and visceral fat to bone structure and strength. *J Clin Endocrinol Metab* 2009; **94**: 3387-3393 [PMID: 19531595 DOI: 10.1210/jc.2008-2422]
- 4 **Cohen A**, Dempster DW, Recker RR, Lappe JM, Zhou H, Zwahlen A, Müller R, Zhao B, Guo X, Lang T, Saeed I, Liu XS, Guo XE, Cremers S, Rosen CJ, Stein EM, Nickolas TL, McMahon DJ, Young P, Shane E. Abdominal fat is associated with lower bone formation and inferior bone quality in healthy premenopausal women: a transiliac bone biopsy study. *J Clin Endocrinol Metab* 2013; **98**: 2562-2572 [PMID: 23515452 DOI: 10.1210/jc.2013-1047]
- 5 **Fulzele K**, Riddle RC, DiGirolamo DJ, Cao X, Wan C, Chen D, Faugere MC, Aja S, Hussain MA, Brüning JC, Clemens TL. Insulin receptor signaling in osteoblasts regulates postnatal bone acquisition and body composition. *Cell* 2010; **142**: 309-319 [PMID: 20655471 DOI: 10.1016/j.cell.2010.06.002]
- 6 **Srikanthan P**, Crandall CJ, Miller-Martinez D, Seeman TE, Greendale GA, Binkley N, Karlamangla AS. Insulin resistance and bone strength: findings from the study of midlife in the United States. *J Bone Miner Res* 2014; **29**: 796-803 [PMID: 23983216 DOI: 10.1002/jbmr.2083]
- 7 **Shin D**, Kim S, Kim KH, Lee K, Park SM. Association between insulin resistance and bone mass in men. *J Clin Endocrinol Metab* 2014; **99**: 988-995 [PMID: 24423302 DOI: 10.1210/jc.2013-3338]
- 8 **de Liefde II**, van der Klift M, de Laet CE, van Daele PL, Hofman A, Pols HA. Bone mineral density and fracture risk in type-2 diabetes mellitus: the Rotterdam Study. *Osteoporos Int* 2005; **16**: 1713-1720 [PMID: 15940395 DOI: 10.1007/s00198-005-1909-1]
- 9 **Schwartz AV**, Sellmeyer DE, Ensrud KE, Cauley JA, Tabor HK, Schreiner PJ, Jamal SA, Black DM, Cummings SR; Study of Osteoporotic Features Research Group. Older women with diabetes have an increased risk of fracture: a prospective study. *J Clin Endocrinol Metab* 2001; **86**: 32-38 [PMID: 11231974 DOI: 10.1210/jcem.86.1.7139]
- 10 **Janghorbani M**, Feskanich D, Willett WC, Hu F. Prospective study of diabetes and risk of hip fracture: the Nurses' Health Study. *Diabetes Care* 2006; **29**: 1573-1578 [PMID: 16801581 DOI: 10.2337/dc06-0440]

- 11 **Goulding A**, Jones IE, Taylor RW, Williams SM, Manning PJ. Bone mineral density and body composition in boys with distal forearm fractures: a dual-energy x-ray absorptiometry study. *J Pediatr* 2001; **139**: 509-515 [PMID: 11598596 DOI: 10.1067/mpd.2001.116297]
- 12 **American Diabetes Association.** (2) Classification and diagnosis of diabetes. *Diabetes Care* 2015; **38** Suppl: S8-S16 [PMID: 25537714 DOI: 10.2337/dc15-S005]
- 13 **Matthews DR**, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412-419 [PMID: 3899825 DOI: 10.1007/BF00280883]
- 14 **Savgan-Gurol E**, Bredella M, Russell M, Mendes N, Klibanski A, Misra M. Waist to hip ratio and trunk to extremity fat (DXA) are better surrogates for IMCL and for visceral fat respectively than for subcutaneous fat in adolescent girls. *Nutr Metab (Lond)* 2010; **7**: 86 [PMID: 21143876 DOI: 10.1186/1743-7075-7-86]
- 15 **Gardner AW**, Montgomery PS, Scott KJ, Afaq A, Blevins SM. Patterns of ambulatory activity in subjects with and without intermittent claudication. *J Vasc Surg* 2007; **46**: 1208-1214 [PMID: 17919876 DOI: 10.1016/j.jvs.2007.07.038]
- 16 **McDonald CM**, Widman L, Abresch RT, Walsh SA, Walsh DD. Utility of a step activity monitor for the measurement of daily ambulatory activity in children. *Arch Phys Med Rehabil* 2005; **86**: 793-801 [PMID: 15827934 DOI: 10.1016/j.apmr.2004.10.011]
- 17 **Lee HY**, Birkenfeld AL, Jornayvaz FR, Jurczak MJ, Kanda S, Popov V, Frederick DW, Zhang D, Guigni B, Bharadwaj KG, Choi CS, Goldberg IJ, Park JH, Petersen KF, Samuel VT, Shulman GI. Apolipoprotein CIII overexpressing mice are predisposed to diet-induced hepatic steatosis and hepatic insulin resistance. *Hepatology* 2011; **54**: 1650-1660 [PMID: 21793029 DOI: 10.1002/hep.24571]
- 18 **Stepien M**, Stepien A, Wlazel RN, Paradowski M, Rizzo M, Banach M, Rysz J. Predictors of insulin resistance in patients with obesity: a pilot study. *Angiology* 2014; **65**: 22-30 [PMID: 23267236 DOI: 10.1177/0003319712468291]
- 19 **Du T**, Yuan G, Zhang M, Zhou X, Sun X, Yu X. Clinical usefulness of lipid ratios, visceral adiposity indicators, and the triglycerides and glucose index as risk markers of insulin resistance. *Cardiovasc Diabetol* 2014; **13**: 146 [PMID: 25326814 DOI: 10.1186/s12933-014-0146-3]
- 20 **Maggio AB**, Belli DC, Puigdefabregas JW, Rizzoli R, Farpour-Lambert NJ, Beghetti M, McLin VA. High bone density in adolescents with obesity is related to fat mass and serum leptin concentrations. *J Pediatr Gastroenterol Nutr* 2014; **58**: 723-728 [PMID: 24399210 DOI: 10.1097/MPG.0000000000000297]
- 21 **Leonard MB**, Shults J, Wilson BA, Tershakovec AM, Zemel BS. Obesity during childhood and adolescence augments bone mass and bone dimensions. *Am J Clin Nutr* 2004; **80**: 514-523 [PMID: 15277178]
- 22 **Felson DT**, Zhang Y, Hannan MT, Anderson JJ. Effects of weight and body mass index on bone mineral density in men and women: the Framingham study. *J Bone Miner Res* 1993; **8**: 567-573 [PMID: 8511983 DOI: 10.1002/jbmr.5650080507]
- 23 **Shin D.** Association between metabolic syndrome, radiographic knee osteoarthritis, and intensity of knee pain: results of a national survey. *J Clin Endocrinol Metab* 2014; **99**: 3177-3183 [PMID: 24780047 DOI: 10.1210/jc.2014-1043]
- 24 **Fulzele K**, Clemens TL. Novel functions for insulin in bone. *Bone* 2012; **50**: 452-456 [PMID: 21723973 DOI: 10.1016/j.bone.2011.06.018]
- 25 **Parker VE**, Savage DB, O'Rahilly S, Semple RK. Mechanistic insights into insulin resistance in the genetic era. *Diabet Med* 2011; **28**: 1476-1486 [PMID: 21992440 DOI: 10.1111/j.1464-5491.2011.03463.x]
- 26 **Brown MS**, Goldstein JL. Selective versus total insulin resistance: a pathogenic paradox. *Cell Metab* 2008; **7**: 95-96 [PMID: 18249166 DOI: 10.1016/j.cmet.2007.12.009]
- 27 **Júnior IF**, Cardoso JR, Christofaro DG, Codogno JS, de Moraes AC, Fernandes RA. The relationship between visceral fat thickness and bone mineral density in sedentary obese children and adolescents. *BMC Pediatr* 2013; **13**: 37 [PMID: 23510224 DOI: 10.1186/1471-2431-13-37]
- 28 **Russell M**, Mendes N, Miller KK, Rosen CJ, Lee H, Klibanski A, Misra M. Visceral fat is a negative predictor of bone density measures in obese adolescent girls. *J Clin Endocrinol Metab* 2010; **95**: 1247-1255 [PMID: 20080853 DOI: 10.1210/jc.2009-1475]
- 29 **Tintut Y**, Demer LL. Effects of bioactive lipids and lipoproteins on bone. *Trends Endocrinol Metab* 2014; **25**: 53-59 [PMID: 24183940 DOI: 10.1016/j.tem.2013.10.001]
- 30 **Winzenberg T**, Powell S, Shaw KA, Jones G. Effects of vitamin D supplementation on bone density in healthy children: systematic review and meta-analysis. *BMJ* 2011; **342**: c7254 [PMID: 21266418 DOI: 10.1136/bmj.c7254]

**P- Reviewer:** Arslan N, Urganci N, Wang R, Watanabe T  
**S- Editor:** Ji FF **L- Editor:** A **E- Editor:** Li RF

