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ORIGINAL ARTICLE

Association of body mass index and waist circumference with osteocalcin and C-terminal telopeptide in Iranian elderly: results from a cross-sectional study

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Abstract
There is no agreement on the role of obesity as a protection or unfavorable factor on bone. In the present study, the association of body mass index (BMI) and waist circumference (WC) with osteocalcin, C-terminal telopeptide of type 1 collagen (CTX-I), highly sensitive C-reactive protein (hs-CRP), parathormon (PTH) and 25-hydroxyvitamin D (25(OH)D) in elderly people was investigated. This cross-sectional study was conducted on 178 elderly residents in Tehran, with a mean age of 67.04 (60–83). Serum osteocalcin, hs-CRP, 25(OH) D, PTH and urine CTX-I were measured for all participants. Waist circumference, weight and height were measured and BMI was calculated. Linear regression and Pearson correlation were performed to evaluate the relation of BMI and waist circumference with other variables. A significant inverse association was found between BMI with osteocalcin ($\beta = -0.171$, $p = 0.027$) after control for covariates. In addition, there were a significant relation of BMI and WC with hs-CRP ($\beta = 0.246$, $p = 0.002$ and $\beta = 0.219$, $p = 0.006$, respectively) and PTH ($\beta = 0.1169$, $p = 0.040$ and $\beta = 0.200$, $p = 0.018$), respectively. The present study did not show a significant relation of BMI and WC with urine CTX-I even after adjustment for potential confounders ($\beta = -0.143$, $p = 0.065$ and $\beta = -0.104$, $p = 0.183$, respectively). The present study has concluded that obesity is an undesirable factor for bone metabolism by reducing serum osteocalcin and by increasing hs-CRP and PTH which contribute to bone resorption.

Keywords Obesity · Bone marker · Elderly · Osteocalcin · CTX-I

Introduction

Fracture is one of the most important public health concerns that rise with increasing in elderly population. Falling and fracture in the elderly occurs due to decrease in performance and disability which leads to increased high medical costs and mortality [1]. Recent studies have shown that there is an indirect association between adipose tissue and osteoclast bone activity in the body [2, 3]. Traditionally, weight loss and obesity have been recognized as a risk factor and protection factor for bone, receptively [4]. Recently, this viewpoint has been challenged by new studies with increasing the incidence of vertebral and non-vertebral fractures in postmenopausal women and older men compared with matched individuals [5–8]. It is believed that high weight with increasing mechanical load has a positive effect on the body skeleton [9]. However, recent researches suggest that fat tissue has an adverse effect on bone and reduce bone formation [8, 10]. Several mechanisms for the relationship between bone mineral content and adipose and muscle tissues have been proposed [9]. To assess the relationship between body weight and bone mass, it is necessary to distinguish the body fat mass and lean mass [11]. Weight gain in post-menopausal period increases the number of adipocytes which is an important source of estrogen derivatives and then increases bone mineral density (BMD) in these women [12, 13]. Moreover, insulin resistance in fat cells may increase the circulating levels of sex hormones such as androgens and steroids, thereby increasing bone mass [14]. Also, several studies have suggested that obesity and bone

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metabolism have been linked together and both osteoblasts and adipocytes originate from mesenchyme cells [15–17]. With aging, osteoblasts are changed by fat cells in bone marrow and increase bone marrow fat leads to decrease in the volume of trabecular bone [18, 19]. Osteocalcin is a vitamin K-linked protein which is mainly made by osteoblasts and known as a biomarker for bone remodeling [20]. Carboxylated osteocalcin by vitamin K has a high affinity for calcium and hydroxyapatite in bone matrix, while uncarboxylated osteocalcin plays a hormonal role in body [6, 21]. Recent studies have suggested inverse relationship between circulating osteocalcin and glucose homeostasis, energy expenditure and fat cells in people [22–26]. C-telopeptide of type I collagen (CTX-I) represents a part of bone collagen that is released during the breakdown of bone into serum and urine and, therefore, it is evaluated as an indicator of bone loss [27]. Some studies have shown an inverse correlation between CTX-I and body mass index (BMI) and waist circumference [28, 29]. On the other hand, there are some other studies that did not find any significant relationship [30, 31]. In another study, it was observed that CTX-I has a positive correlation with BMI [32, 33]. Regarding the contradictory results of studies that investigated relation of BMI with bone [12–14, 18, 19] and scarcity of research on the role of osteocalcin and CTX-I in bone strength [31–35], this study was conducted to assess the relationship of BMI and waist circumference (WC) with osteocalcin, CTX-I, hs-CRP, PTH and 25(OH)D in elderly people.

Materials and methods

Participants

This cross-sectional study was conducted on 178 elderly subjects (51 men and 127 women) with a mean age of 67.04 (60–83), referred to health centers in Tehran. Participants were selected using two-stage cluster sampling of 25 health centers in Tehran. Health centers in Tehran were divided into five regions: North, South, East, West and Central and then prepared a list of health centers in each area, and 25 health centers were selected randomly (in attention to constraints budget and time) based on the number of health centers in each region proration. Then, the total number of samples (178) divided by the number of health centers (25) and obtained the number of samples in each home centers.

Anthropometric measurement

Patient's height was measured without shoes by a wall stadiometer with a sensitivity of 0.1 cm (Seca, Germany) and weight by digital scale (Seca 808, Germany) with an accuracy of 0.1 kg with light clothes (without a coat and rain coat). BMI was calculated by dividing weight in kilograms by the square of height in meters. Waist circumference was measured with a tape measure between the iliac crest and the lowest rib on the exhale.

Laboratory investigation

10 mL of blood and 3 mL urine samples were obtained between 7 and 10 am from all of fasted participants in acid-washed test tubes without anticoagulant. After storing at room temperature for 30 min and clot formation, blood samples were centrifuged at 1500*g* for 20 min. Serums were stored in – 80 °C until future testing. Serum human N-MID osteocalcin was measured by ELISA kit (Bioassay Technology Laboratory, Shanghai Crystal Day Biotech Co., Ltd., Shanghai, China), with CV < 10% and sensitivity of 0.22 ng/mL. The human CTX-I ELISA kit (Bioassay Technology Laboratory, Shanghai Crystal Day Biotech Co., Ltd., Shanghai, China), with intra-Assay: CV < 10% and sensitivity of 0.24 ng/mL was used for the quantitative measurement of CTX-I in urine. The measurement of hs-CRP was performed by immunoturbidimetric assay based on the kit instructions (Pars Azmoon, Iran, Tehran). The 25(OH) D and PTH were measured using an enzymatic method, using commercial kits (with Pars Azmoon, Iran, Tehran and DRG, Marburg, Germany, respectively).

Statistical methods

People were grouped based on the tertiles of BMI and waist circumference. For comparison general characteristics among tertiles, we used one-way ANOVA and Chi-square tests for quantitative and qualitative variables, respectively. The Kolmogorov and Smirnov test was used for evaluating the normality of data, and non-normally distributed variables were log-transformed. Linear multiple-regression and Pearson correlation were performed to evaluate the relation of BMI and waist circumference with other variables including osteocalcin, CTX-I, hs-CRP, 25(OH) D and PTH. All statistical calculations were performed with the SPSS (Statistical Package for Social Sciences) for Windows 15.0 software package (SPSS, Chicago, IL, USA). The level of statistical significance was pre-set at $p < 0.05$.

Results

General characteristics of the participants were reported in Table 1. Data were provided for participants divided into normal ($n = 25$), overweight ($n = 77$) and obese ($n = 76$). Among all variables only the weight ($p < 0.001$), BMI ($p < 0.001$) and WC ($p < 0.001$) were significantly higher in obese individual than others. The mean (SD) concentration

Table 1 General characteristics of participants based on tertiles of BMI

	Tertiles of BMI			*p* value*
	Normal (25)	Overweight (77)	Obese (76)	
Age	66.64 ± 6.87	67.55 ± 5.59	66.72 ± 6.13	0.609
Sex (M/F) (%)				
Male	35.7	31.8	19.3	0.093
Female	64.3	68.2	80.7	
Weight (kg)	61.58 ± 12.22	68.49 ± 7.79	80.21 ± 12.59	< 0.001
BMI (kg/m^2)	23.21 ± 1.84	27.56 ± 1.40	34.22 ± 3.55	< 0.001
WC (cm^2)	89.30 ± 10.45	96.93 ± 6.53	105.52 ± 10.19	< 0.001
25(OH)D (nmol/L)	121.25 ± 71.49	101.84 ± 64.72	114.39 ± 73.72	0.428
PTH (pg/mL)	43.50 ± 16.21	48.52 ± 22.35	52.74 ± 32.57	0.359
Urine CTX-I (ng/mL)	32.32 ± 7.63	33.05 ± 8.10	31.64 ± 7.20	0.536
Osteocalcin (ng/mL)	24.75 ± 21	21.69 ± 14.76	17.91 ± 11.17	0.080
hs-CRP (mg/dL)	5.01 ± 13.03	4.97 ± 18.97	4.37 ± 5.33	0.958
Calcium supplement intake (%)				
Yes	36	35.1	32	0.897
Vitamin D supplement intake (%)				
Yes	44	43.4	44.7	0.987
Physical activity (%)				
Very low	11.9	39.3	48.8	0.645
Low	16.1	46.8	37.1	
Moderate and high	14	43.3	42.7	

BMI body mass index, *WC* waist circumference

*Obtained from ANOVA for continuous variables and χ^2 test for categorical variables

Table 2 Correlation of BMI and WC with bone biomarkers

Variable	BMI (kg/m^2)		WC (cm^2)	
	r	*p*	*r*	*p*
Osteocalcin (ng/mL)	− 0.158	0.035	−0.021	0.776
Urine CTX-I (ng/mL)	− 0.153	0.043	0.050	0.506
hs-CRP (mg/dL)	0.275	0.001	0.187	0.014
25(OH)D(nmol/L)	− 0.054	0.506	− 0.002	0.980
PTH(pg/mL)	0.184	0.023	0.182	0.025

Data are Pearson correlation coefficients. All biochemistry data were log-transformed prior to analysis

Table 3 Multiple linear regression analysis of association between BMI and WC with bone biomarkers

	BMI(kg/m^2)		WC (cm^2)	
	β	*p**	*β*	*p**
Osteocalcin (ng/mL)	− 0.171	0.027	− 0.062	0.427
Urine CTX-I (ng/mL)	− 0.143	0.065	− 0.104	0.183
hs-CRP (mg/dL)	0.246	0.002	0.219	0.006
25(OH)D (nmol/L)	− 0.014	0.887	0.051	0.623
PTH (pg/mL)	0.169	0.040	0.200	0.018

*All variables were adjusted for age, sex, income, physical activity, job, age, sex, income, physical activity, job, smoking, marital status, vitamin D and calcium supplement intake

of serum osteocalcin and urine CTX-I for all participants were 20.51 (14.57) ng/mL and 32.34 (7.64) ng/mL, respectively. A non-significant reduction in serum osteocalcin associated with BMI was shown ($p = 0.080$), as evidenced by the serum osteocalcin level that was 24.75 ng/mL in normal weight people, 21.69 ng/mL in overweight people, and 17.91 ng/mL in obese people. The concentration of urine CTX-I was statistically significant ($p = 0.536$) higher in overweight people (33.05 ng/mL) than that of normal weight people (32.32 ng/mL) and obese subjects (31.64 ng/mL). Correlation of BMI and WC with osteocalcin, CTX-I, hs-CRP, 25(OH) D and PTH were presented in Table 2. A significant inverse association between BMI with osteocalcin ($r = -0.158$, $p = 0.035$) and CTX-I ($r = -0.153$, $p = 0.043$) was observed. In addition, a significant relation between BMI and hs-CRP ($r = 0.275$, $p = 0.001$), and PTH ($r = 0.184$, $p = 0.023$) was indicated. Moreover, we found a significant relation between WC, hs-CRP ($r = 0.187$, $p = 0.014$), and PTH ($r = 0.182$, $p = 0.025$). These relationships in β estimates after adjusted for confounders such as age, sex, income, physical activity, job, smoking, marital status, vitamin D and calcium supplement intake were shown in Table 3. BMI had a significant relationship with osteocalcin ($\beta = -0.171$, $p = 0.027$), hs-CRP ($\beta = 0.246$, $p = 0.002$) and

PTH ($\beta = 0.169$, $p = 0.040$). Moreover, we found WC had a significant association with hs-CRP ($\beta = 0.219$, $p = 0.006$) and PTH ($\beta = 0.200$, $p = 0.018$). However, in multiple linear regression analysis, there was no statistically significant relation of BMI and WC with CTX-I ($\beta = -0.143$, $p = 0.065$ and $\beta = -0.104$, $p = 0.183$, respectively) after adjustment for potential confounders.

Discussion

In the present study, we investigated the relationship of BMI and WC with osteocalcin, CTX-I, hs-CRP, PTH, and 25(OH) D in elderly. Our findings showed a significant inverse association between BMI and osteocalcin in elderly. Moreover, there were significant association between BMI and WC with hs-CRP and PTH. However, there was no significant association between other variables in elderly people such as WC with osteocalcin, CTX-I and 25(OH) D, and BMI with 25(OH) D and CTX-I.

The relationship of serum bone biomarkers and BMI and also body metabolism have been examined in several studies, which most of them have investigated the role of osteocalcin as a known factor [36–38]. In middle aged and elderly people, the total osteocalcin concentration has the inverse relationship with BMI, waist circumference, fasting plasma glucose (FPG), insulin resistance, higher level TG, and leptin and positively correlated with adiponectin concentration [39, 40]. In this study, the increase in BMI as an indicator of obesity was associated with reduction in bone turnover markers in elderly people. Reduction of osteocalcin as a recovery marker resulted in increasing in bone loss and body fat accretion. In accord with these results, a recent meta-analysis has shown that there is a significant inverse association between serum osteocalcin levels and BMI [41]. Based on epidemiological assumptions, it is generally accepted that higher BMI increases and improves the differentiation of bone osteoblasts [11]. Traditionally, weight loss as a risk factor for bone fractures and obesity has been recognized as a protection factor in bone [4]. It is believed that high weight with increasing mechanical load has a positive effect on body skeleton [9].

Another finding of this study was a significant correlation between BMI and CTX-I, but this association did not remain significant after adjusted for covariates. Few studies have examined the role of CTX-I with BMI and body metabolism. However, Movahed et al. reported an inverse association between serum CTX-I and BMI and WC [28] and Holecki et al. in a cohort study found that weight loss reduces the concentration of serum CTX-I [32]. In another study, Weiler et al. observed that serum CTX-I has a positive relation with BMI and is negatively associated with vitamin D concentration [33]. In accord with our study, Bezerra et al. did not reveal any significant relationships between serum CTX-I and BMI and waist circumference [30]. In addition, Liu et al. observed that BMI and vitamin D had no significant difference among the tertiles of serum CTX-I [31]. The results of WC and vitamin D association with CTX-I in these studies were similar with the present study, in which we did not show a significant association between the urine CTX-I and WC and 25(OH) D. There are many discrepancies in the results of the studies which may due to differences in age, gender, country, type of study population and known or unknown potential confounders. However, the results of the Holecki et al. in a cohort study is much stronger than others cross-sectional studies.

In the present study, increasing BMI and WC was associated with increasing the hs-CRP and PTH as two risk factors of bone resorption. C-reactive protein is primarily synthesized in the liver by interleukin (IL)-6, IL-1-beta, and tumor necrosis factor (TNF)-alpha stimulants [42]. Adipose tissue secretes IL-1-beta and IL-6 which are responsible for the production of CRP [43, 44]. There are studies that have shown that there is a positive and significant correlation between BMI and WC with hs-CRP [45, 46]. Choi et al., in a meta-analysis study on 51 cross-sectional studies showed that there is a positive and significant correlation between BMI and waist circumference with hs-CRP concentration [47]. Reserves of adipose tissue with the increase in BMI and WC as an active endocrine organ, secretes different cytokines and hormones in blood which enhance the levels of hs-CRP in the body [48, 49]. Studies have shown that higher hs-CRP concentration in elderly people is an independent risk factor of osteoporosis [50, 51].

PTH is a calcium-regulating hormone that increases blood calcium levels by bone breakdown [52]. In a meta-analysis study, participants with high levels of PTH had more BMI and weight than control people [53]. The exact underlying mechanism of the association between obesity and PTH is unknown. But it may be related to increasing PTH through vitamin D deficiency, increasing sex hormones, and increment insulin [54–57]. In the same line with the current study, several studies found that higher BMI increases levels of PTH which leads to bone resorption [58–60]. With regard to the previous research, the conclusion is that obesity may be an undesirable factor in bone metabolism by increasing the number of factors that contribute to bone resorption compared with the factors lead to bone remodeling.

The strengths of this study can be noted to special evaluation of the association of bone factors with BMI and waist circumference. Moreover, in this study we tried to adjust all known potential confounders. However, the major limitation of this study is the cross-sectional study design, because it is not recognized causal relationships and require to be examined this relationship in a large prospective cohort studies. In addition, it is suggested using the bioelectric impedance

analysis (BIA) devices in future studies to measure the anthropometric data and body composition accurately.

In conclusion, our study indicated a significant inverse association between BMI with osteocalcin and a statistically significant relation of BMI and WC with hs-CRP and PTH. This study suggests that obesity has a negative effect on bone regeneration.

Compliance with ethical standards

Conflict of interest None of the authors had any personal or financial conflicts of interest.

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