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Original Article

Relationships among Bone Metabolic Markers, Body Fat Composition and Carotid Intima–Media Thickness in Premenopausal Obese Women

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Osteocalcin (OC) is inversely related to body fat distribution and fasting glucose levels. We sought to observe the effect of OC on fat distribution and subclinical atherosclerosis as measured by carotid intima-media thickness (CIMT) in premenopausal obese women. In this prospective observational study, totally, 73 premenopausal obese women (aged 17-55 years) and 53 healthy women (aged 20-50 years) with normal weight were included as controls. Anthropometric measurements, total fat and fat ratio, insulin, fasting blood glucose, and OC levels were estimated. Ultrasonography was used to assess fat distribution, and fat thickness was measured in 4 regions. Subcutaneous fat (SCF), visceral fat (VF), and preperitoneal fat (PPF) thicknesses were considerably higher in obese subjects ($p < 0.01$) than healthy controls, while OC levels were significantly lower. No correlation was observed between OC levels and SCF, VF, or PPF. In a multiple regression analysis, OC was significantly positively associated with SCF ($p = 0.04$, Beta = 0.284). No associations were observed between OC levels and VF, PPF, or CIMT. A significant association was observed between parathyroid hormone (PTH) and VF ($p = 0.021$, Beta = 0.284), and vitamin D levels were inversely associated with VF ($p = 0.002$, r = −0.366). OC levels were lower in premenopausal obese women than normal-weight healthy controls, but OC exhibited no correlation with VF or PPF, and only a weak positive association with SCF. Additionally, VF was positively correlated with PTH and inversely correlated with vitamin D. These results suggest that OC may be an early indicator of lipid accumulation in te subcutaneous area and development of atherosclerosis.

Key words: body fat composition, carotid intima-media thickness, obesity, osteocalcin, premenopausal women

Several studies support a link between energy metabolism and bone [1, 2]. Osteocalcin (OC) is produced by osteoblastic cells as a marker of bone formation, and it additionally appears to be involved in fat and glucose metabolism [3].

Lee *et al.* reported that knockout mice with both OC alleles eliminated exhibited expanded fat mass, diminished insulin secretion, and β-cell proliferation [4]. On the other hand, when OC levels were higher, fat pads were small, β-cell proliferation was higher, and the mice showed higher insulin sensitivity. When recombinant uncarboxylated OC was administered to wild-type mice, increased adiponectin expression, reduction of fat mass, better handling of glucose, and decreased weight gain in the presence of a high-fat diet were observed [5].

Emerging evidence from human studies has shown that OC regulates glucose metabolism and fat mass [6-11]. OC has been shown to have an inverse association with fat mass [7, 8], percentage body fat [6-8, 10], and waist

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circumference (WC) in men [9]. On the other hand, regional variations in OC production in fat tissue are still unresolved, and there are only a few studies that have reported OC levels in premenopausal women.

Although recent studies have proposed an association between serum OC and cardiovascular events, the findings are contradictory. Particular uncertainty remains regarding the independent association between OC and atherosclerosis. Pennisi *et al.* showed that patients with severe atherosclerotic lesions of the carotid and/or femoral artery had lower OC levels [12]. Kanazawa *et al.* stated that OC levels correlated inversely with carotid intima-media thickness (CIMT) in men [6]. Serum OC levels were also linked to lower risks of coronary heart disease and metabolic disorders in Chinese adults [13, 14]. Finally, serum OC levels have been shown to be independently and inversely related to carotid atherosclerosis in type 2 diabetics [15]. It is possible that the effects of confounding factors were responsible for these varying results.

In the present study, therefore, we examined the potential correlation between serum OC levels and each of body fat composition and CIMT in premenopausal obese women.

Methods

Study population. In this prospective observational study, totally, 73 obese premenopausal women (aged 17-55 years) and 53 healthy women (aged 20-50 years) with normal weight were included in this prospective observational study. Patients with any of the following were excluded: irregular menstrual cycle, a diagnosis of polycystic ovary syndrome, physical exercise more than 2 h per week, currently breastfeeding, pregnant, use of any drug that could affect glucose metabolism or body composition, underlying disorders of glucose or lipid metabolism, and a current smoking habit. Both oral and written consents were obtained from all participants. Our study was approved by the Local Medical Ethics Committee of Pamukkale University (application number: 60116787-020/41760).

Anthropometric evaluation. Subjects were considered to be obese if their body mass index (BMI) was >30 kg/m^2. BMI was calculated as weight (kg) divided by height (m)^2. WC was measured midway between the lowest rib and the iliac crest while the participants were standing upright. Bioelectrical impedance analysis (BIA) was used to estimate total fat mass, and percentage body fat and fat mass of the trunk body (kg) were determined using TANITA BC-418 (Tanita Corp., Tokyo).

Ultrasound examination. All sonographic measurements were performed by a single radiologist with 15 years of experience in conventional ultrasonography (US). Subcutaneous fat (SCF) and preperitoneal fat (PPF) thickness measurements were done using a 5-12 MHz linear transducer, and visceral fat (VF) thickness measurements were done using a 3-5 MHz convex array transducer with a Logic E9 ultrasound machine (GE Healthcare, Milwaukee, WI, USA).

Abdominal fat measurements. All the abdominal fat measurements were obtained with the subject in the supine position by placing the probe perpendicular to the skin surface of the upper abdomen. Scanning was performed longitudinally from the xiphoid process to the umbilicus along the midline, and measurements were obtained from the image captured when the probe touched the skin surface lightly without applying pressure. SCF was defined as the minimum distance from the cutaneous boundary to the linea alba, while PPF was defined as the maximum distance between the linea alba and the surface of the left lobe of the liver. VF thickness was measured as the distance between the linea alba and the anterior aspect of the vertebral body. The measurement of VF thickness was obtained 1 cm above the umbilicus on the imaginary line drawn between the xiphoid process and the umbilicus. All measurements were repeated 4 times, and the averages of these 4 measurements were used as the final values of the SCF, PPF, and VF thicknesses.

CIMT measurements. CIMT measurements were performed with a 5-12 MHz linear transducer using the same US machine with the patient lying in a supine position with a small cushion placed under the shoulders to aid extension of the neck during neck rotateion to the side opposite to the common carotid artery (CCA) being measured. The CCAs on both sides were depicted in the longitudinal plane, and measurements were obtained from the far wall of the CCA 2 cm proximal to the carotid bulb. Three measurements were performed on both CCAs using the automatic intima-media thickness measurement program of the ultrasound system. The average of these three measurements was recorded as the final value.

Biochemical analyses. For biochemical analyses,

blood samples were taken after a period of overnight fasting. The levels of serum total cholesterol, high density lipoprotein (HDL) cholesterol, triglyceride, and fasting glucose were measured. Fasting insulin levels were measured by chemiluminescent immunoassays. The insulin resistance (IR) homeostasis model assessment (HOMA-IR) index was calculated using the formula: (fasting plasma glucose (mmol/L) x fasting plasma insulin (mIU/L))/22.5 [16]. A cut-off value of 2.7 was accepted to determine a state of IR. Serum 25-hydroxyvitamin vitamin D (25[OH]D) levels were measured by high performance liquid chromatography, serum parathyroid hormone (PTH) levels by electrochemiluminescence immunoassay, and serum OC levels by chemiluminescence immunoassay.

Statistical analyses. For the statistical analysis, SPSS v.18.0 for Windows (SPSS, Chicago, IL, USA) was used. Continuous and categorical data are shown as means ± standard deviations and as percentages, respectively. When parametric test assumptions were provided, an independent sample *t* test was used for intergroup comparisons. If assumptions were not provided, the Mann Whitney *U* test was used. Correlation between continuous variables was analyzed using the Spearman correlation coefficient. Multiple linear regression analysis was used to identify the factors associated with OC. A level of $p < 0.05$ was accepted as statistically significant.

Results

The anthropometric measurements of the subjects are shown in Table 1. Obese subjects had an increased WC, body fat mass, BMI indicating adiposity, and higher VF, PPF, and SCF compared to normal control subjects ($p < 0.01$). The biochemical and hormonal variables of obese subjects and controls are shown in Table 2. US measurements and evaluations of subjects are shown in Fig. 1.

The OC concentration was 18.26 ng/mL for obese subjects and 22.53 ng/mL for the controls, and the difference was statistically significant. While the 25(OH)D levels and calcium levels were similar, PTH levels were higher in obese subjects (61.94 pg/mL for obese subjects and 52.51 pg/mL for controls ($p = 0.049$)). We divided the obese groups into two subgroups based on HOMA-IR, and patients with IR had PTH, OC, and 25(OH)D levels comparable to those of patients without IR.

OC was positively correlated with PTH ($p = 0.007$, $r = +0.315$). There were no significant correlations between OC and other biochemical and hormonal parameters, including 25(OH)D. OC showed no correlation with WC, BMI, body fat mass, VF, or PPF. However, OC showed a weak positive correlation with SCF ($p = 0.035$, $r = 0.258$) in obese patients but no correlation with SCF in the controls ($p = 0.424$, $r = -0.127$). It also showed no correlation with CIMT.

Inverse correlations were observed between CIMT

Table 1 Antropometric measures and fat distrubution of obese and controls

	OBESE (n = 73)		CONTROL (n = 53)		
	Mean ± S.D	Med (min–max)	Mean ± S.D	Med (min–max)	*P*
Age	35 ± 6	37 (17–52)	32. ± 8	38 (18–55)	> 0.05
Weight (kg)	97.26 ± 15.75	93.8 (69.1–134.0)	61.03 ± 10.27	59.1 (42.4–90.7)	< 0.001* α
BMI (kg /m^2)	38.32 ± 5.38	37.7 (30.3–50.4)	23.46 ± 3.46	22.7 (16.7–30.4)	< 0.001* β
WC (cm)	107.38 ± 11.27	107 (80–131)	80.02 ± 9.95	79.5 (64–107)	< 0.001* α
Trunckal fat percent	38.73 ± 5.06	39. (23.5–49.4)	20.41 ± 8.72	22.4 (3.–38.8)	< 0.001* α
Total fat mass (kg)	42.9 ± 10.51	42.5 (22.8–68.5)	16.74 ± 6.82	16.4 (5.1–35.2)	< 0.001* α
Percent body fat	43.54 ± 4.15	44.4 (32.2–51.6)	26.5 ± 7.07	27.8 (10.6–40.4)	< 0.001* β
VF (mm)	54.18 ± 22.32	52. (17–149)	30.05 ± 11.55	29 (9.3–57.8)	< 0.001* β
PPF (mm)	20.37 ± 30.47	11 (7.3–18.8)	6.73 ± 3.06	6 (2–14.4)	< 0.001* β
SCF (mm)	34.39 ± 10.52	33 (3.8–60)	18.59 ± 8.55	18.05 (3–39)	< 0.001* α
CIMT (mm)	1.38 ± 1.97	0.7 (0.46–3.35)	0.54 ± 0.09	0.54 (0.4–0.71)	< 0.001* β

*$p < 0.05$ statistically significant; S.D, Standart Deviation; Med, Median; BMI, Body mass index; WC, Waist circumference; VF, Visseral fat; PPF, Preperitoneal fat; SCF, Subcutanous fat; CIMT, Carotis intima media thickness; α, Independent Samples *t* test; β, Mann Whitney *U* test

Table 2 Biochemical and hormonal variables of obese and controls

	OBESE (n=73)		CONTROL (n=53)		
	Mean ± S.D	Med (min-max)	Mean ± S.D	Med (min-max)	*P*
FBG (mg/dL)	96.36 ± 10.83	95 (74-132)	89.69 ± 7.62	88 (79-116)	<0.001 * α
Insulin (uIU/mL)	19.06 ± 10.42	16 (3.7-53)	9.13 ± 4.25	7.95 (3.68-25)	<0.001 * β
HOMA	4.55 ± 2.79	3.7 (0.8-16.61)	1.98 ± 0.93	1.79 (0.83-5.44)	<0.001 * β
Creatinine (mg/dL)	0.65 ± 0.11	0.64 (0.47-1.02)	0.64 ± 0.1	0.63 (0.41-0.92)	0.718 β
ALT (IU/L)	20.15 ± 11.12	17 (8-73)	16.04 ± 10.09	13 (5-62)	0.001 * β
LDL (mg/dL)	106.29 ± 27.21	107 (53-178)	93.33 ± 29.38	88 (40-166)	0.013 * α
HDL (mg/dL)	50.45 ± 11.2	51 (31-94)	66.49 ± 14.28	64 (43-102)	<0.001 * α
TG (mg/dL)	116.32 ± 54.83	104 (35-309)	85.18 ± 45.01	74 (36-295)	<0.001 * β
TSH (uIU/mL)	3.05 ± 5.70	2.23 (0.12-50)	1.98 ± 1.16	1.55 (0.29-5.37)	0.020 * β
Calcium (mg/dL)	9.11 ± 0.44	9.17 (7.78-10.26)	9.09 ± 0.42	9.05 (8.21-10.5)	0.385 β
PTH (pg/mL)	61.94 ± 24.68	57 (16-130)	52.5 ± 17.7	50.5 (23-119)	0.049 * β
Vitamin D (ng/mL)	13.39 ± 9.95	11 (3-50)	13.99 ± 15.51	10 (3-94)	0.433 β
Phosphorus (mg/dL)	3.21 ± 0.55	3.26 (2.02-4.39)	3.34 ± 0.45	3.46 (2.51-4.28)	0.17 β
Magnesium (mg/dL)	1.91 ± 0.15	1.92 (1.5-2.38)	1.94 ± 0.18	2 (1.5-2.25)	0.022 * β
ALP (IU/L)	77.15 ± 25.22	76 (36-221)	55.35 ± 16.18	53 (10-98)	<0.001 * β
Osteocalcin (ng/mL)	18.2 ± 5.27	18 (7.52-35)	22.53 ± 6.84	22 (11.93-40)	<0.001 * α

*$p<0.05$ statistically significant; S.D, Standard Deviation; Med, Median; FBG, Fasting blood glucose; ALT, Alanine transaminase; LDL, Low density lipoprotein; HDL, High density lipoprotein; TG, Triglyceride; TSH, Thyroid stimulating hormone; PTH, Parathyroid hormone; ALP, Alkaline phosphatase; α, Independent Samplest test; β, Mann Whitney *U* test

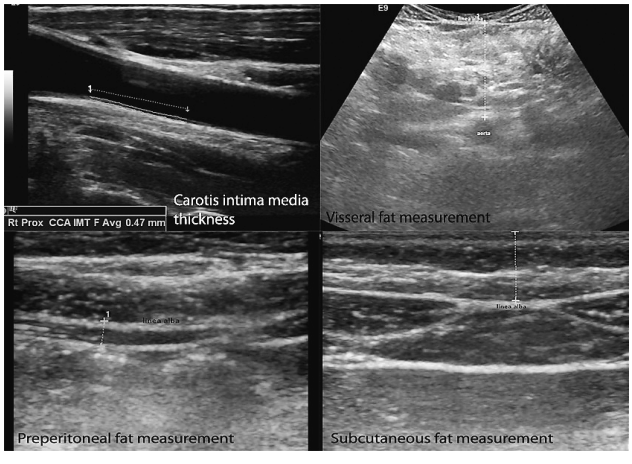

Fig. 1 Ultrasonographical measurement and evaluation of subjects.

and each of the following: vitamin D levels in obese patients ($p=0.028$, $r=-0.269$), VF ($p=0.002$, $r=-0.366$), and WC ($p=0.025$, $r=-0.263$). However, PTH showed positive correlations with CIMT ($p=0.018$, $r=+0.291$) and WC ($p=0.042$, $r=+0.241$).

There were no associations between OC and VF, PPF, or CIMT. A significant association was detected between PTH and VF ($p=0.021$, Beta = 0.284). The levels of 25(OH)D were inversely related to VF ($p=0.05$, Beta = −0.236). In multiple regression analysis (Table 3), OC was significantly positively associated with SCF ($p=0.04$, Beta = 0.284).

Discussion

We assessed OC levels in 73 obese premenopausal and 53 healthy women in this prospective observational study. The results revealed that OC levels were lower in premenopausal obese women than in healthy controls and that OC was positively associated with SCF. In premenopausal obese women, we observed that circulating serum OC was not associated with blood glucose levels, IR, WC, BMI, VF, or PPF. These findings are consistent with recent studies showing that bone and adipose tissue exert reciprocal regulation.

Little is known about body fat composition and serum OC levels in obese individuals. A previous report found an association between BMI and serum OC. BMI appears to be inversely correlated with serum OC in elderly people [7], postmenopausal women [17, 18], and premenopausal women [19]. When postmenopausal women without metabolic syndrome were examined, no relationship was observed between BMI and bone mineral density. However, OC showed a positive correlation with waist and hip circumference. This suggests that there might be a positive correlation between adipose tissue and bone formation in patients who do not have IR [20]. Some studies have reported

Table 3 Multivariate association between serum osteocalcin and adiposity indices in obese patients

	Standardized Coefficients Beta	Sig.	95% Confidence Interval for B Lower Bound	Upper Bound
Truncal Fat Percent	0.144	0.30	−0.139	0.439
WC	−0.313	0.06	−0.295	0.007
VF	0.134	0.37	−0.039	0.103
PPF	−0.113	0.37	−0.063	0.024
SCF	0.284	0.04*	0.004	0.282

*$p<0.05$ statistically significant; WC, Waist circumference; VF, Visceral fat; PPF, Preperitoneal fat; SCF, Subcutaneous fat

that there is no association between BMI and OC levels in postmenopausal women [21]; although the results of studies suggested that an association between BMI and OC might exist in obese individuals, but not in non-obese subjects [18]. A recent metaanalysis found that there was an inverse correlation between OC levels and BMI, but there was heterogeneity among the correlation coefficients across studies. A subgroup analysis revealed that this heterogeneity was mostly attributable to the inclusion of studies in which the subjects had metabolic syndrome [22].

These differing results may have been caused by a deficiency in the measurements of fat mass, or may have been related to inherent differences in the study populations. In addition, the relationship between bone and adipose tissue metabolism may vary in the pre- and postmenopausal periods. In our present study, we did not find any association between BMI and OC levels in premenopausal obese women. Measurement of the fat distribution rather than BMI may therefore be more informative regarding the relationship between energy and bone metabolism.

Kanazawa *et al.* stated that serum uncarboxylated OC and total OC were linked to body fat in type 2 diabetic men [11]. Pittas *et al.* also found that, after multivariate adjustments, the OC concentration remained inversely associated with markers of adiposity, BMI, body fat, and percentage of body fat in adults aged 65 years and older (mean age 71 years, BMI 26.9 kg/m^2, 5% with diabetes) [7]. Despite these studies showing a relationship between fat distribution and OC, similar studies in obese people without underlying comorbidities are limited.

In our study, we found that OC showed a positive association with SCF, although we could not find any correlation between OC and VF, PPF in obese premenopausal women without diabetes. In contrast to our study, Kim *et al.* found an inverse correlation between OC and visceral obesity in Korean overweight and obese men. They also found that there was no association between OC and the SF area (SFA) [23]. In their study, Kim *et al.* used computed tomography (CT) to measure the VF area (VFA), and SFA was calculated by subtracting the VFA from the total abdominal fat area. In our study, we used US to directly measure SCF instead of calculating it from the VFA. Similar to our study, the study population in the report of Kim *et al.* also included only obese and overweight people and did not include diabetics. Whereas they measured OC in male subjects, we measured OC in premenopausal obese women, and this may be one of the reasons for our conflicting results. Other potential contributing factors to the differences in our results could be variations in the selection criteria and in the demographic characteristics of the populations examined, including race/ethnicity. In another recent study, VFA was assessed by magnetic resonance imaging in middle-aged and elderly community-living subjects, and their results also demonstrated that serum OC levels showed an inverse correlation with visceral obesity [24].

Serum OC levels were also found to be significantly inversely correlated with, and to be significantly predictive of, fat and trunk fat in older Swedish men [8]. For both diabetic and nondiabetic subjects, plasma OC showed strong inverse correlations to BMI and fat mass, but it was not correlated to height or lean mass in this study. Total lean mass, total fat mass, percent body fat, and the fat mass of the trunk were assessed using dual-emission X-ray absorptiometry [8]. We also measured total fat mass, percentage body fat, and truncal fat mass by BIA. The serum OC level did not show any association with any of the above measurements. In a related study conducted in a Chinese population, serum OC was associated with HDL cholesterol and

percentage body fat in males, whereas serum OC levels in premenopausal women were associated with triglyceride levels [10]. In postmenopausal women, an inverse relationship was found between OC and abdominal obesity parameters; uncarboxylated OC levels also correlated inversely with the waist-hip ratio, VFA, and fat mass [25].

Studies have shown inconsistent findings regarding the relationship between serum OC levels and atherosclerosis [26, 27]. This might be due to differences in the study populations or to various confounding factors that are associated with serum OC levels. Serum OC levels showed a significant inverse correlation with CIMT ($r = -0.107$, $p < 0.01$) in Chinese postmenopausal women [27]. The Shanghai Changfeng Study looked at the correlation between OC levels and carotid atherosclerosis in Chinese middle-aged and elderly adult males and at the correlation of OC with carotid atherosclerosis in the euglycemic subgroup. Men with OC levels in the fourth quartile had a 0.57-fold reduced risk of carotid plaques compared to those in the lowest quartile after adjustment for traditional cardiovascular disease risk factors. These findings suggest that OC is independently associated with carotid atherosclerosis in euglycemic males and that OC may play a role not only in glucose metabolism but also in the development of atherosclerosis [28]. In our study, CIMT did not correlate with OC but correlated with PTH and vitamin D, probably due to the fact that subclinical atherosclerosis might not yet have developed in this age group. Additionally, even if VF measurements were increased, suggesting an increased risk of cardiovascular mortality, we found that VF showed an inverse correlation with 25(OH) vitD but not with OC levels. This suggests that, in the premenopausal period, low vitamin D levels may be a better indicator of increased cardiovascular risk than low OC levels. Gilardini *et al.* observed that PTH levels were higher in obese subjects with carotid calcifications than in those without calcifications [29]. Increased PTH levels in obese patients are believed to be due to the increased concentrations of vitamin D in adipose tissue [30].

Alkaline phosphatase (ALP) is a ubiquitous enzyme present in all tissues but mainly concentrated in the liver, kidney, and bone [31]. In this study, ALP levels were significantly higher in obese patients compared to healthy controls. This may be a result of underlying liver damage due to obesity. OC levels are closely related to bone metabolism, and numerous studies have supported this relationship. The findings of our study also suggest that OC has a positive association with SCF. Additionally, VF showed a positive correlation with PTH and an inverse correlation with vitamin D levels. We excluded patients with impaired lipid or glucose metabolism from our study, but we did observe a statistically significant association between obesity and CIMT. Our results suggest that OC may be an early indicator of diseases associated with obesity and bone metabolism. Further studies are needed to shed more light on this subject.

Study limitations. This study had several limitations. First, we measured total OC rather than uncarboxylated OC. However, Kanazawa *et al.* stated that levels of serum uncarboxylated OC as well as total OC were related to body fat in men with type 2 diabetes [12]. Secondly, we measured fat distribution using US and BIA, although CT might have been a better tool. A third possible limitation of our study was that sex hormone levels and some liver function parameters, e.g AST or γ-GTP of the subjects were not measured.

On the other hand, measuring SCF directly instead of calculating it from VF measurements is a definite strength of our study, as is the evaluation of body fat distribution using 2 different methods. Since we included only obese premenopausal women without any underlying comorbidities, our results may be more representative of the relationship between bone and adipose tissue.

Inconclusion. The study results indicated that OC levels were lower in premenopausal obese women compared to healthy controls, but no correlation was observed between OC levels and VF or PPF. However, there was a positive correlation between OC and SCF. Additionally, VF showed a positive correlation with PTH and an inverse correlation with vitamin D. The current study showed that serum OC levels are significantly associated with obesity. This observation suggests that bone might not merely be an endocrine target, but may also have an effect on obesity, and that OC levels may be an early indicator of lipid accumulation in the subcutaneous area and of the development of atherosclerosis.

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Referencess

1. Rosen CJ: Bone remodeling, energy metabolism, and the molecular clock. Cell Metab (2008) 7: 7–10.
2. Rosen CJ and Klibanski A: Bone, fat, and body composition: evolving concepts in the pathogenesis of osteoporosis. Am J Med (2009) 122: 409–414.
3. Lee NK and Karsenty G: Reciprocal regulation of bone and energy metabolism. Trends Endocrinol Metab (2008) 19: 161–166.
4. Na Kyung Lee, Hideaki Sowa, Eiichi Hinoi, Mathieu Ferron, Jong Deok Ahn, Cyrille Confavreux, Romain Dacquin, Patrick J Mee, Marc D McKee, Dae Young Jung, Zhiyou Zhang, Jason K Kim, Franck Mauvais-Jarvis, Patricia Ducy and Gerard Karsenty: Endocrine regulation of energy metabolism by the skeleton. Cell (2007) 130: 456–469.
5. Ferron M, Hinoi E, Karsenty G and Ducy P: Osteocalcin differentially regulates beta cell and adipocyte gene expression and affectsthe development of metabolic diseases in wild-type mice. Proc Natl Acad Sci USA (2008) 105: 5266–5270.
6. Kanazawa I, Yamaguchi T, Yamamoto M, Yamauchi M, KuriokaS, Yano S and Sugimoto T: Serum osteocalcin level is associated with glucose metabolism and atherosclerosis parameters in type 2 diabetes mellitus. J Clin Endocrinol Metab (2009) 94: 45–49.
7. Pittas AG, Harris SS, Eliades M, Stark P and Dawson-Hughes B: Association between serum osteocalcin and markers of metabolic phenotype. J Clin Endocrinol Metab (2009) 94: 827–832.
8. Kindblom JM, Ohlsson C, Ljunggren O, Karlsson MK, Tivesten A, Smith U and Mellström D: Plasma osteocalcin is inversely related to fat mass and plasma glucose in elderly Swedish men. J Bone Miner Res (2009) 24: 785–791.
9. Yeap BB, Chubb SA, Flicker L, McCaul KA, Ebeling PR, Beilby JP and Norman PE: Reduced serum total osteocalcin is associated with metabolic syndrome in older men via waist circumference, hyperglycemia, and triglyceride levels. Eur J Endocrinol (2010) 163: 265–272.
10. Zhou M, Ma X, Li H, Pan X, Tang J, Gao Y, Hou X, Lu H, Bao Y and Jia W: Serum osteocalcin concentrations in relation to glucose and lipid metabolism in Chinese individuals. Eur J Endocrinol (2009) 161: 723–729.
11. Kanazawa I, Yamaguchi T, Yamauchi M, Yamamoto M, Kurioka S, Yaho S, Hou X, Lu H. Bao Y and Jia W: Serum undercarboxylated osteocalcin was inversely associated with plasma glucose level and fat mass intype 2 diabetes mellitus. Osteoporos Int (2011) 22: 187–194.
12. Pennisi P, Signorelli SS, Riccobene S, Celotta G, Di Pino L, La Malfa T and Fiore CR: Low bone density and abnormal bone turnover in patients with atherosclerosis of peripheral vessels. Osteoporos Int (2004) 15: 389–395.
13. Bao Y, Zhou M, Lu Z, Li H, Wang Y, Sun L, Gao M, Wei M and Jia W: Serum levels of osteocalcin are inversely associated with the metabolic syndrome and the severity of coronary artery disease in Chinese men. Clin Endocrinol (Oxf) (2011) 75: 196–201.
14. Zhang Y, Qi L, Gu W, Yan Q, Dai M, Shi J, Zhai Y, Chen Y, Liu J, Wang W, Ning G and Hong J: Relation of serum osteocalcin level to risk of coronary heart disease in Chinese adults. Am J Cardiol (2010) 106: 1461–1465.
15. Sheng L, Cao W, Cha B, Chen Z, Wang F and Liu J: Serum osteocalcin level and its association with carotid atherosclerosis in patients with type 2 diabetes. Cardiovasc Diabetol (2013) Jan 23: 12: 22.
16. Matthews DR, Hosker JP, Rudenski AS Naylor BA, Treacher DF and 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.
17. Papakitsou EF, Marqioris AN, Dretakis KE, Trovas G, Zoras U, Lyritis G, Dretakis E K and Stergiopoulos K: Body mass index (BMI) and parameters of bone formation and resorption in postmenopausal women. Maturitas (2004) 47: 185–193.
18. Cifuentes M, Johnson MA, Lewis RD, Heymsfield SB, Chowdhury HA, Modlesky CM and Shapses SA: Bone turnover and body weight relationships differ in normal weight compared with heavier postmenopausal women. Osteoporos Int (2003) 14: 116–122.
19. Adami S, Bianchi G, Brandi ML, Giannini S, Ortolani S, DiMunno O, Frediani B, Rossini M and BONTURNO Study Group: Determinants of bone turnover markers in healthy premenopausal women. Calcif Tissue Int (2008) 82: 341–347.
20. Oros S, Ianas O, Vladoiu S, Giurcaneanu M, Ionescu L, Neacsu E, Voicu G, Stoiceanu M, RoscaR, Neamtu C, Badiu C and Dumitrache C: Does Obesity Protect Postmenopausal Women Against Osteoporosis? Acta Endoc-Bucharest (2012) 8: 67–76.
21. Trento LK, Pietropolli A, Ticconi C, Gravotta E, De Martino MU, Fabbri A and Piccione E: Role of type I collagen C telopeptide, bonespecific alkaline phosphatase and osteocalcin in the assessment of bone status inpostmenopausal women. J Obstet Gynaecol Res (2009) 35: 152–159.
22. Kord-Varkaneh H, Djafarian K, Khorshidi M and Shab-Bidar S: Association between serum osteocalcin and body mass index: a systematic review and meta-analysis Endocrine (2017) 58: 24–32.
23. Kim SH, Lee JW, Im JA and Hwang HJ: Serum osteocalcin is related to abdominal obesity in Korean and overweight men. Clin Chim Acta (2010) 411: 2054–2057.
24. Lee SW, Jo HH, Kim MR, Kim JH and You YO: Association between osteocalcin and metabolic syndrome in postmenopausal women. Arch Gynecol Obstet (2015) 292: 673–681.
25. Xu Y, Ma X, Pan X, He X, Xiao Y and Bao Y: Correlations between serum concentration of three bone-derived factors and obesity and visceral fat accumulation in a cohort of middle aged men and women. Cardiovasc Diabetol (2018) 17: 143.
26. Schafer AL, Sellmeyer DE, Schwartz AV, Rosen CJ, Vittinghoff E, Palermo L, Bilezikian, JP, Shoback, DM and Black DM: Change in undercarboxylated osteocalcin is associated with changes in body weight, fat mass, and adiponectin: parathyroid hormone (1–84) or alendronate therapy in postmenopausal women with osteoporosis (the PaTH Study). J Clin Endocrinol Metab (2011) 96: E1982–1989.
27. Yang R, Ma X, Dou J, Wang F, Luo Y, Li D, Zhu J, Bao Y and Jia W: Relationship between serum osteocalcin levels and carotid intima-media thickness in Chinese postmenopausal women. Menopause (2013) 20: 1194–1199.
28. Ma H, Lin H, Hu Y, Li X, He W, Jin X, Gao J, Zhao NQ and Gao X: Serum levels of osteocalcin in relation to glucose metabolism and carotid atherosclerosis in Chinese middle-aged and elderly male adults: the Shanghai Changfeng Study. Eur J Intern Med (2014) 25: 259–264.
29. Gilardini L, Pasqualinotto L, Di Matteo S, Caffetto K, Croci M, Girola A and Invitti, C: Factors associated with early atherosclerosis and arterial calcifications in young subjects with a benign phenotype of obesity. Obesity (SilverSpring) (2011) 19: 1684–1689.
30. Snijder MB, van Dam RM, Visser M, Deeg DJ, Dekker JM, Bouter LM, Seidell, JC and Lips, P: Adiposity in relation to vitamin D status and parathyroid hormone levels: a population-based study in older men and women. J Clin Endocrinol Metab (2005) 90: 4119–4123.
31. Kim SH, Shin KH, Moon SH, Jang J, Kim HS, Suh JK and Yang WK: Reassessment of alkaline phosphatase as serum tumor marker with high specificity in osteosarcoma. Cancer Med (2017) 6: 1311–1322.