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Low serum osteocalcin level is a potential marker for metabolic syndrome: results from a Chinese male population survey

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ABSTRACT

Osteocalcin has been recognized as a bone-derived hormone to regulate energy metabolism recently. Little is known about the role of osteocalcin as regards metabolic syndrome (MetS) in a Chinese population. Components of MetS, osteocalcin, body mass index (BMI), and prevalence of MetS were assessed in 2344 men aged 20 to 69 years who participated in the population-based Fangchenggang Area Male Health and Examination Survey, which was carried out in Guangxi province of China from September 2009 to December 2009. Osteocalcin had a statistically significant positive correlation with high-density lipoprotein cholesterol and a negative relationship with blood pressure, glucose, triglycerides, waist circumference, and BMI after adjustment for age (all $P < .001$). The strongest correlation was observed between osteocalcin and BMI ($r = -0.26$). In a multivariate analysis, decreased odds ratios (ORs) for the MetS and its components as well were observed from the first to the fourth osteocalcin quartiles. After adjustment for BMI, the OR decreased substantially. Statistically significant difference still existed in MetS (OR, 1.77; 95% confidence interval [CI], 1.10-2.85), hypertriglyceridemia (OR, 1.66; 95% CI, 1.22-2.27), hyperglycemia (OR, 1.42; 95% CI, 1.05-1.92), and low high-density lipoprotein cholesterol (OR, 1.83; 95% CI, 1.03-3.24) when these risks were compared in the lowest quartile of osteocalcin levels with those in the highest quartile. In a Chinese male population, we firstly identified an inverse association of serum osteocalcin

Author contribution statement: AT, YG, XY, HZ, NX, and ZM designed the study. LM, AT, and YG collected samples and conducted the osteocalcin measurement. XQ and TP supervised the laboratory work. XY and HZ conducted the statistical analyses. AT wrote the first draft of the paper. NX, YG, and ZM revised the manuscript for important intellectual content.

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levels with MetS, independent from the well-known MetS risk factors. This may represent a further mechanism for the elevated cardiovascular disease or type 2 diabetes mellitus risk.

1. Introduction

Metabolic syndrome (MetS) is a cluster of abnormal metabolic conditions that increases the risk of cardiovascular disease [1] and type 2 diabetes mellitus [2]. Typically, it includes abdominal obesity, dyslipidemia, hyperglycemia, and elevated blood pressure [3]. Individuals with MetS are associated with approximately 5- and 2-fold increased risk for type 2 diabetes mellitus [4] and cardiovascular disease [5], respectively. In addition, MetS is a considerable public health issue in both developed and developing countries now [6-8].

On the other hand, osteocalcin has recently been recognized as a bone-derived hormone to regulate energy metabolism. In 2007, Lee et al [9] found that, compared with wild-type mice, osteocalcin$^{-/-}$ knockout mice had an abnormal amount of fat mass and an increase in serum triglycerides, and exhibited impaired insulin secretion, insulin resistance, and glucose intolerance. Expression of insulin target genes in liver and muscle (Fox a2, Mcad, Nrft, etc) and adiponectin gene in adipose all decreased. In vitro, insulin expression was induced when pancreatic β-cells were cocultured with bacterially produced recombinant osteocalcin (3 ng/mL) [9]. Furthermore, osteocalcin$^{-/-}$ mice had higher insulin and lower glucose levels when injected with recombinant osteocalcin [9]. Similar results also appear in a population-based study. In humans, significant inverse associations of osteocalcin with insulin resistance, blood glucose, adiposity, and triglycerides have been described [10-13]. One recent study in blacks and non-Hispanic whites reported a negative relationship between serum osteocalcin and the presence of MetS [14]. However, this study was conducted in an older, predominantly hypertensive cohort, rather than younger and mainly normotensive adults. Besides, osteocalcin levels varied depending on ethnic background [15]. All these prompted us to perform the present study to examine the association of serum osteocalcin level with MetS in a Chinese male population.

2. Subjects and methods

2.1. Study population

The Fangchenggang Area Male Health and Examination Survey was a population-based study conducted among noninstitutionalized Chinese men aging from 17 to 88 years old in Guangxi, which was designed to investigate the effects of environmental and genetic factors and their interaction with the development of age-related chronic diseases. A comprehensive demographic and health survey was conducted among 4303 continuous men who participated in a large-scale physical examination in the Medical Centre of Fangchenggang First People's Hospital from September 2009 to December 2009. All participants provided written informed consents, and the study received local ethics committee approval. The current cross-sectional study was confined to men aging from 20 to 69 years old. In addition, participants were excluded from this study based on the following criteria: (1) currently diagnosed with diabetes mellitus, coronary heart disease, stroke, hyperthyroidism, rheumatoid arthritis, and cancer; (2) taking any kind of medication; (3) with impaired hepatic function (alanine transaminase >2.0 times upper limit of normal); or (4) with impaired renal function (serum creatinine >178 μmol/L). However, participants who had signs of high fasting blood glucose levels at the time of initial assessment were included in the study. In the end, 2344 unrelated participants were included.

2.2. Data collection

A face-to-face interview was conducted by trained physicians. Data on demographic characteristics (age, education, occupation, etc), lifestyle characteristics (smoking, alcohol consumption, and physical activity), health status, and medical history were collected using a standardized questionnaire. Smoking habit was defined as never, current (daily smoking, >6 months), and former (cessation of smoking, >6 months). The physical activity level was classified as low, moderate, or high according to the questionnaire scoring protocol [16]. Educational attainment of the participants was categorized into 3 groups according to the number of years of education (0-6, 7-9, and ≥10 years). Family history of chronic diseases was considered positive if the participants' parents or siblings had a history of one of the following diseases: hypertension, coronary heart disease, stroke, or type 2 diabetes mellitus. Anthropometric measurements were performed by trained personnel using a standardized protocol. Body weight and height were measured without shoes to the nearest 0.1 kg and 0.1 cm, respectively. Body mass index (BMI) was then calculated as weight (in kilograms)/height (in square meters). Participants were categorized as normal weight (<24.0 kg/m^2), overweight (24.0-27.9 kg/m^2), or obese (≥28.0 kg/m^2) [17]. Waist circumference was measured midway between the lowest rib and the iliac to the nearest 0.1 cm. Blood pressure was measured by trained nurses with a mercury sphygmomanometer on the right arm of the participants in a comfortable sitting position after at least 5-minute rest. Participants were asked to avoid vigorous exercise, drinking, and smoking for at least 30 minutes before the measurement.

2.3. Laboratory assay

Overnight fasting venous blood specimens were drawn. Blood samples were transported frozen to the testing center of Department of Clinical Laboratory at the First Affiliated Hospital of Guangxi Medical University in Nanning in 2 hours, which were centrifuged within 15 to 25 minutes and stored at –80°C until analysis. Triglycerides, high-density lipoprotein cholesterol (HDL-C), and serum glucose were measured enzymatically on a Dimension-RxL Chemistry Analyzer (Dade Behring,

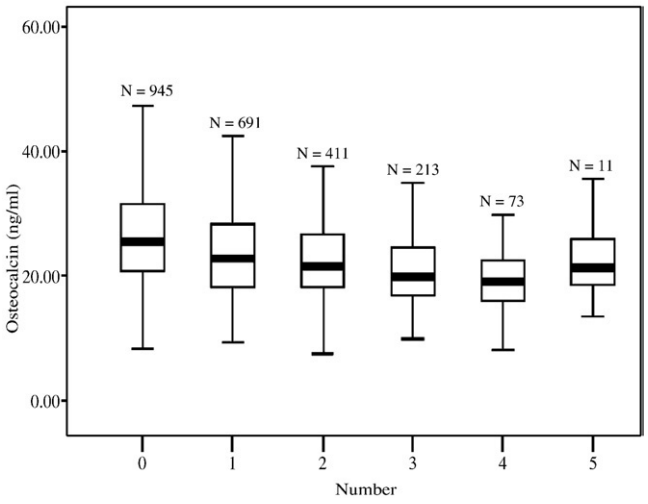

Fig. 1 – Distribution of osteocalcin levels according to the numbers of components of the MetS. The bars represent median, 25th, and 75th percentile of osteocalcin. P < 001 for trend.

Newark, DE) in the Department of Clinical Laboratory at the Fangchenggang First People's Hosptal. Serum osteocalcin was measured with electrochemiluminescence immunoassay on COBAS 6000 system E601(Elecsys module) immunoassay analyzer (Roche Diagnostics, GmbH, Mannheim, Germany) with the same batch of reagents. The interassay coefficient of variation was 4.5%.

2.4. *Definition of MetS*

The MetS was defined based upon the updated National Cholesterol Education Program Adult Treatment Panel III for Asian Americans [18] as having 3 or more of the following components: (1) waist circumference at least 90 cm, (2) triglycerides at least 1.7 mmol/L, (3) HDL-C less than 1.03 mmol/L, (4) blood pressure at least 130/85 mm Hg or current use of antihypertensive medications, and (5) fasting glucose at least 5.6 mmol/l or previously diagnosed with type 2 diabetes mellitus or on oral antidiabetic agents or insulin.

2.5. *Statistical analyses*

The current analysis was restricted to 2344 subjects with complete data on all features of the MetS and osteocalcin. Osteocalcin values showed a markedly skewed distribution, and natural logarithmic (ln) transformations were performed to approximate normality. Clinical characteristics were compared between cases (Mets) and controls (non-Mets) with Student *t* test and χ^2 where appropriate. Spearman partial correlation coefficients of osteocalcin, BMI, and elements of MetS were calculated after adjusting for age. The age was divided into 3 groups: 20 to 44 (youth), 45 to 59 (middle-aged), and 60 to 69 (elderly) years old. Furthermore, the associations of ln(osteocalcin) levels across age strata or MetS score were evaluated with a 1-way analysis of variance test followed by post hoc comparisons. Afterward, a multinomial logistic regression was performed with the number of MetS components as the outcome variable and osteocalcin as the predictor. The binary logistic regression model was used to estimate the odds ratios (ORs) for the components of MetS or MetS itself. Potential confounding variables including age (continuous), smoking, alcohol drinking, physical activity, education, family history of chronic diseases, and BMI were controlled in the regression models. The χ^2 statistic was used to obtain the probability value for the trend in both the logistic regression models and Fig. 1. Data management and statistical

Table 1 – Baseline characteristics of study population stratified for the absence and presence of MetS

	MetS	Non-MetS	P
No. of subjects	297	2047	
Age (y)	42.3 ± 10.3	36.9 ± 10.8	<.001
Osteocalcin (ng/mL)	20.29 ± 1.35	24.05 ± 1.38	<.001
SBP (mm Hg)	122 ± 1	110 ± 1	<.001
DBP (mm Hg)	81 ± 1	74 ± 1	<.001
BMI (kg/m^2)	27.1 ± 1.1	22.2 ± 1.1	<.001
WC (cm)	90.0 ± 1.1	81.5 ± 1.1	<.001
Glucose (mmol/L)	6.0 ± 1.2	5.2 ± 1.1	<.001
Triglyceride (mmol/L)	2.77 ± 1.86	1.07 ± 1.72	<.001
HDL (mmol/L)	1.22 ± 1.32	1.39 ± 1.22	<.001
Smoking status, n (%)			
Never	122 (41.1%)	965 (47.1%)	.060
Former	23 (7.7%)	67 (3.3%)	<.001
Current	152 (51.2%)	1015 (49.6%)	.603
Alcohol drinking, yes, n (%)	253 (85.2%)	1754 (85.7%)	.818
Physical activity, n (%)			
Low	193 (65.0%)	1347 (65.8%)	.783
Moderate	83 (27.9%)	523 (25.5%)	.372
High	21 (7.1%)	177 (8.6%)	.365
Education (y), n (%)			
0-6	8 (2.7%)	68 (3.3%)	.569
7-9	63 (21.2%)	369 (18.0%)	.180
≥10	226 (76.1%)	1610 (78.7%)	.338
Family history of chronic disease, yes, n (%)	76 (25.6%)	376 (18.4%)	.004

Data are mean ± standard deviation. The percentage may not sum to 100 because of rounding. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference.

Table 2 – Age-adjusted Spearman correlations between osteocalcin and select variables

Variable	R	P
SBP	−0.068	.001
DBP	−0.077	<.001
BMI	−0.258	<.001
WC	−0.234	<.001
Glucose	−0.086	<.001
Triglycerides	−0.159	<.001
HDL-C	0.097	<.001

DBP indicates diastolic blood pressure.

analyses were performed with SPSS 13.0 (SPSS, Chicago, IL). Statistical tests were 2-sided, and a P value < .05 was considered statistically significant.

3. Results

The characteristics of the participants were shown in Table 1. Data were presented for participants divided into MetS (n = 297) and non-MetS (n = 2047). Among all individuals, the prevalence of MetS was 12.7%. Compared with participants with non-MetS, men with MetS had lower serum osteocalcin levels (−3.76, P < .001) (Table 1).

The mean concentration of serum osteocalcin was 23.57 ng/mL in the study population, with a standard deviation of 1.38 ng/mL. A trend of decreased osteocalcin associated with age was observed, as evidenced by the serum osteocalcin level that was 24.29 ng/mL in participants 20 to 44 years old, 21.33 ng/mL in those 45 to 59 years old, and 20.69 ng/mL in those 60 to 69 years old (P < .001 for trend).

Table 2 provided the Spearman partial correlation coefficients between osteocalcin and variables of MetS. There was a statistically significant positive correlation between osteocalcin and HDL-C (P < .001) and a significant negative correlation of osteocalcin with BMI, waist circumference, blood pressure, glucose, and triglycerides after adjustment for age (all P < .001). The strongest correlation (r = −0.26) was observed between osteocalcin and BMI.

Besides, osteocalcin levels decreased basically with increasing numbers of MetS components (Fig. 1). The mean concentration of osteocalcin in groups with 0, 1, 2, 3, 4, and 5 features of MetS was 25.79, 22.87, 21.98, 20.49, 19.29, and 21.54 ng/mL, respectively (P < .001 for trend). Except for the group with all features of MetS, subjects with one or more components of MetS had lower serum osteocalcin levels than those with none (P < .001). The dose-response relationship between MetS score and serum osteocalcin levels was shown in Table 3. Participants with lower serum osteocalcin levels might be more prone to suffer from metabolic disorders. The prevalence of MetS decreased across osteocalcin quartile, with values of 22.0%, 15.0%, 9.2%, and 5.1%, respectively (P < .001 for trend).

The multivariate analysis results were shown in Table 4. Decreased ORs for the MetS or its components were observed from the first to the fourth osteocalcin quartiles. Compared with the subjects in the highest osteocalcin quartile, those in the lowest quartile had an OR of 3.75 (95% confidence interval [CI], 2.44-5.76) for the MetS, 3.60 (95% CI, 2.50-5.21) for central obesity, 1.33 (95% CI, 1.01-1.74) for elevated blood pressure, 2.83 (95% CI, 2.12-3.78) for hypertriglyceridemia, 2.78 (95% CI, 1.59-4.85) for low HDL-C, and 1.82 (95% CI, 1.37-2.43) for hyperglycemia, respectively, after adjustment for age, smoking, alcohol drinking, physical activity, education, and family history of chronic disease (model 2). After further adjustment for BMI (model 3), the ORs decreased substantially. Statistically significant difference still existed in MetS, hypertriglyceridemia, hyperglycemia, and low HDL-C, but not in central obesity and elevated blood pressure any longer. This was in accordance with the strong correlation of BMI and osteocalcin seen in Spearman partial correlation.

4. Discussion

This is the first large cross-sectional study to highlight the important relationship between osteocalcin levels and MetS in a Chinese male population. Consistent with the previous study[19], osteocalcin levels decreased with age. The prevalence of MetS (12.7%) in Fangchenggang area of Guangxi was similar to the prevalence of MetS in China in 2000-2001 (13.6%) based on the modified Adult Treatment Panel III criteria [7].

Our study revealed that serum osteocalcin levels were significantly associated with the individual components of MetS and with BMI after adjustment for age. The strongest relationship was found between BMI and osteocalcin. However, because the MetS represents a cluster of simultaneously

Table 3 – Multinomial logistic regression model examining associations of MetS score and osteocalcin

MetS score	Quartile of osteocalcin			
	Q4 (>28.97 ng/mL)	Q3 (23.27-28.97 ng/mL)	Q2 (18.96-23.26 ng/mL)	Q1 (<18.96 ng/mL)
	OR 95% CI	OR 95% CI	OR 95% CI	OR 95% CI
1 vs 0	1	1.3 (1.03-1.76)	1.65 (1.25-2.17)	2.68 (2.01-3.56)
2 vs 0	1	1.85 (1.30-2.63)	2.92 (2.07-4.12)	4.03 (2.82-5.75)
3 vs 0	1	2.33 (1.36-4.02)	4.52 (2.70-7.56)	8.82 (5.32-14.64)
≥4 vs 0	1	2.03 (0.83-4.98)	4.73 (2.09-10.73)	10.88 (4.96-23.85)

Sample size of each group is as follows: MetS score = 0, n = 945; MetS score = 1, n = 691; MetS score = 2, n = 411; MetS score = 3, n = 213; and MetS score ≥4, n = 84.

Table 4 – Odds ratios and 95% CI for MetS and its individual components according to quartile of osteocalcin: a multivariate analysis

	Quartile of osteocalcin				*P* value for trend
	Q4 (n = 585)	Q3 (n = 587)	Q2 (n = 586)	Q1 (n = 586)	
	>28.97 ng/ml	23.27-28.97 ng/ml	18.96-23.26 ng/ml	<18.96 ng/ml	
MetS					
Model 1	1.00	1.69 (1.06-2.68)	2.69 (1.74-4.17)	3.85 (2.50-5.91)	<.001
Model 2	1.00	1.66 (1.04-2.64)	2.63 (1.69-4.08)	3.75 (2.44-5.76)	<.001
Model 3	1.00	1.13 (0.68-1.90)	1.46 (0.90-2.39)	1.77 (1.10-2.85)	<.001
Central obesity					
Model 1	1.00	1.85 (1.26-2.72)	2.23 (1.53-3.25)	3.73 (2.59-5.38)	<.001
Model 2	1.00	1.79 (1.21-2.63)	2.13 (1.46-3.11)	3.60 (2.50-5.21)	<.001
Model 3	1.00	1.03 (0.59-1.80)	0.74 (0.42-1.30)	1.37 (0.80-2.34)	<.001
Elevated BP					
Model 1	1.00	1.08 (0.82-1.42)	1.23 (0.94-1.61)	1.35 (1.03-1.77)	<.001
Model 2	1.00	1.06 (0.80-1.40)	1.20 (0.92-1.58)	1.33 (1.01-1.74)	<.001
Model 3	1.00	0.90 (0.68-1.20)	0.92 (0.70-1.23)	0.92 (0.69-1.23)	NS
Hypertriglyceridemia					
Model 1	1.00	1.53 (1.15-2.05)	2.29 (1.72-3.04)	2.88 (2.16-3.85)	<.001
Model 2	1.00	1.53 (1.14-2.05)	2.25 (1.69-3.00)	2.83 (2.12-3.78)	<.001
Model 3	1.00	1.19 (0.87-1.63)	1.54 (1.13-2.09)	1.66 (1.22-2.27)	<.001
Low HDL-C					
Model 1	1.00	1.84 (1.05-3.24)	3.62 (2.14-6.13)	2.69 (1.54-4.70)	<.001
Model 2	1.00	1.87 (1.06-3.30)	3.73 (2.20-6.33)	2.78 (1.59-4.85)	<.001
Model 3	1.00	1.57 (0.89-2.79)	2.78 (1.62-4.75)	1.83 (1.03-3.24)	<.001
Hyperglycemia					
Model 1	1.00	1.22 (0.91-1.64)	1.49 (1.12-1.99)	1.86 (1.40-2.48)	<.001
Model 2	1.00	1.20 (0.89-1.61)	1.48 (1.11-1.97)	1.82 (1.37-2.43)	<.001
Model 3	1.00	1.07 (0.79-1.45)	1.24 (0.92-1.66)	1.42 (1.05-1.92)	<.001

Model 1 was adjusted for age; model 2 was further adjusted for smoking, alcohol drinking, physical activity, education status, and family history of hypertension, coronary heart disease, type 2 diabetes mellitus, and stroke; model 3 was further adjusted for BMI. NS indicates no significance.

occurring features, it may not be appropriate to look only at isolated variables. Indeed, our results showed that the serum osteocalcin levels declined as the number of manifestations of MetS increased, except for the group with all features of MetS. Specifically, the group with all features of MetS involved 11 men only; and the mean concentration of serum osteocalcin in participants with 4 and more components of MetS was still lower than that of participants with less than 3 features of MetS (data not shown). This phenomenon was later confirmed by the results of the osteocalcin profile on the overall risk of MetS. Although BMI was a pivotal mediator for the association of osteocalcin with the individual features of MetS and MetS itself, data from the present study showed that the decreased osteocalcin levels per se were associated with the MetS, hyperglycemia, hypertriglyceridemia, and low HDL-C, further conveying a possible serious link with an increased risk of coronary artery heart disease and type 2 diabetes mellitus. Furthermore, several studies have previously demonstrated that serum osteocalcin levels were reduced in patients with diabetes [20,21].

Our result was in line with the prior report of an inverse relationship between osteocalcin levels and the presence of MetS in blacks and non-Hispanic whites [14], extending the result to Asians. In addition, in a recently published cross-sectional study of 380 healthy ambulatory adults 65 years and older [11], serum osteocalcin concentration was inversely associated with homeostasis model assessment for insulin resistance ($P = .002$). Similar result was also reported in another population-based study [10]. Because insulin resistance plays a central role in the pathogenesis of the MetS, the inverse association of osteocalcin with insulin resistance might also have important implications in relation to MetS, which indirectly supported the results of present study. Besides, the effect of osteocalcin on insulin sensitivity, insulin secretion, and glucose in animals [9] and humans [22] was in line with the result of osteocalcin profile on the risk of hyperglycemia even after adjustment for the potential confounding factors. Furthermore, a recent prospective analyses [11] also showed that exposure to higher osteocalcin levels during follow-up was associated with a significantly lower rise in fasting plasma glucose at 3 years.

Consistent with the animal model study of obesity in which mice that received osteocalcin had normal levels of triglycerides compared with mice that were not given [9], our study also detected a significantly negative relationship between osteocalcin and hyperglyceridemia even after adjustment for BMI. The prevalence of central obesity was strongly associated with the osteocalcin levels after adjustment for age and lifestyle factors, which was in line with results from animal experiments and population researches. However, the association disappeared after further adjustment for BMI, supporting the high correlation of BMI with waist circumference. Risk of elevated blood pressure in categories of osteocalcin did not differ significantly; this effect was explained by BMI and lifestyle factors.

The cross-sectional design of our study could not offer information on the time sequence of events and thus does not permit identification of causal relationship. However, it was composed of a large population-based sample, which limits the selection bias often encountered in clinical settings. In addition, most confounding factors for the risk of MetS in this study were carefully taken into consideration in the regression analyses. Furthermore, the field study was completed within a relatively short period; thus, the seasonal variations on the biomarkers and other lifestyle factors are minimized. Participants who drank the day before examination were excluded; thus, the impact of alcohol on blood lipids is mostly restricted.

The circulating measure of total osteocalcin includes both carboxylated and uncarboxylated forms [23]. Animal and in vitro data implied that only the uncarboxylated form of osteocalcin functioned hormonally in the regulation of glucose homeostasis and energy metabolism [9,24]. The latest researches based on population showed that elevated levels of both carboxylated and uncarboxylated forms of osteocalcin were associated with improved glucose tolerance; but the uncarboxylated form was related to insulin secretion, and the carboxylated form was associated with insulin resistance [25,26]. Our study measured total osteocalcin and did not have measurements of uncarboxylated osteocalcin; therefore, we could not further verify this hypothesis. It may be of interest to elucidate this potential mechanism in the context of the uncarboxylated and carboxylated forms and determine the direction of causality in a further longitudinal study.

In conclusion, we found an inverse association between osteocalcin levels and MetS, independent of well-known MetS risk factors, in a Chinese male population, which was in line with the recent findings that bone exerted the regulation of energy metabolism by osteocalcin. This may represent a further mechanism for the elevated coronary heart disease or type 2 diabetes mellitus risk observed in these subjects.

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REFERENCES

[1] Dekker JM, Girman C, Rhodes T, et al. Metabolic syndrome and 10-year cardiovascular disease risk in the Hoorn Study. Circulation 2005;112:666-73.
[2] Meigs JB, Rutter MK, Sullivan LM, et al. Impact of insulin resistance on risk of type 2 diabetes and cardiovascular disease in people with metabolic syndrome. Diabetes Care 2007;30:1219-25.
[3] Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005;365:1415-28.
[4] Hanson RL, Imperatore G, Bennett PH, et al. Components of the "metabolic syndrome" and incidence of type 2 diabetes. Diabetes 2002;51:3120-7.
[5] Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288:2709-16.
[6] Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002;287: 356-9.
[7] Gu D, Reynolds K, Wu X, et al. Prevalence of the metabolic syndrome and overweight among adults in China. Lancet 2005;365:1398-405.
[8] Zuo H, Shi Z, Hu X, et al. Prevalence of metabolic syndrome and factors associated with its components in Chinese adults. Metab, Clin Exp 2009;58:1102-8.
[9] Lee NK, Sowa H, Hinoi E, et al. Endocrine regulation of energy metabolism by the skeleton. Cell 2007;130:456-69.
[10] Fernandez-Real JM, Izquierdo M, Ortega F, et al. The relationship of serum osteocalcin concentration to insulin secretion, sensitivity, and disposal with hypocaloric diet and resistance training. J Clin Endocrinol Metab 2009;94:237-45.
[11] Pittas AG, Harris SS, Eliades M, et al. Association between serum osteocalcin and markers of metabolic phenotype. J Clin Endocrinol Metab 2009;94:827-32.
[12] Kindblom JM, Ohlsson C, Ljunggren, et al. Plasma osteocalcin is inversely related to fat mass and plasma glucose in elderly Swedish men. Bone Miner Res 2009;24:785-91.
[13] Kanazawa I, Yamaguchi T, Yamamoto M, et al. Serum osteocalcin level is associated with glucose metabolism and atherosclerosis parameters in type 2 diabetes mellitus. J Clin Endocrinol Metab 2009;94:45-9.
[14] Saleem U, Mosley TH, Kullo IJ. Serum osteocalcin is associated with measures of insulin resistance, adipokine levels, and the presence of metabolic syndrome. Arterioscler Thromb Vasc Biol 2010;30:1474-8.
[15] Leder BZ, Araujo AB, Travison TG, et al. Racial and ethnic differences in bone turnover markers in men. J Clin Endocrinol Metab 2007;92:3453-7.
[16] Guidelines for data processing and analysis of the International Physical Activity Questionnaire. Available at: http://www.ipaq.ki.se/dloads/IPAQ%20LS%20Scoring%20Protocols_Nov05.pdf.
[17] Bei-Fan Z. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults: study on optimal cut-off points of body mass index and waist circumference in Chinese adults. Asia Pac J Clin Nutr 2002;11:S685-93.
[18] Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation 2005;112:2735-52.
[19] Bouillon R, Bex M, Van Herck E, et al. Influence of age, sex, and insulin on osteoblast function: osteoblast dysfunction in diabetes mellitus. J Clin Endocrinol Metab 1995;80: 1194-202.
[20] Pedrazzoni M, Ciotti G, Pioli G, et al. Osteocalcin levels in diabetic subjects. Calcif Tissue Int 1989;45:331-6.
[21] Rico H, Hernandez ER, Cabranes JA, et al. Suggestion of a deficient osteoblastic function in diabetes mellitus: the possible cause of osteopenia in diabetics. Calcif Tissue Int 1989;45:71-3.
[22] Zhou M, Ma X, Li H, et al. Serum osteocalcin concentrations in relation to glucose and lipid metabolism in Chinese individuals. Eur J Endocrinol 2009;161:723-9.

[23] Booth SL, Lichtenstein AH, O'Brien-Morse M, et al. Effects of a hydrogenated form of vitamin K on bone formation and resorption. Am J Clin Nutr 2001;74:783-90.
[24] Ferron MHE, Karsenty G, Ducy P. Osteocalcin differentially regulates beta cell and adipocyte gene expression and affects the development of metabolic diseases in wild-type mice. Proc Natl Acad Sci USA 2008;105:5266-70.
[25] Hwang YC, Jeong IK, Ahn KJ, et al. The uncarboxylated form of osteocalcin is associated with improved glucose tolerance and enhanced β-cell function in middle-aged male subjects. Diabetes Metab Res Rev 2009;25:768-72.
[26] Shea MK, Gundberg CM, Meigs JB, et al. Gamma-carboxylation of osteocalcin and insulin resistance in older men and women. Am J Clin Nutr 2009;90:1230-5.