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Original Article

Homeostatic model assessment of β-cell function may be an emerging predictor of bone resorption in metabolically unhealthy obesity

Solaleh Emamgholipour [1], Zhila Maghbooli [2*], Mohammad Talebpour [3], Sattar Gorgani-Firuzjaee[4], Arash Shirvani [5*]

[1] *Department of Clinical Biochemistry, School of Medicine, Tehran University of Medical Sciences*
[2] *Multiple Sclerosis Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran*
[3] *Department of Surgery, Sina Hospital, Tehran University of Medical Sciences*
[4] *Department of Medical Laboratory Sciences, Faculty of Paramedicine, AJA University of Medical Sciences, Tehran, Iran*
[5] *Department of Medicine, Section of Endocrinology, Nutrition, Diabetes and Weight Management, Boston University Medical Center, Boston, Massachusetts, United States of America*

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* **Corresponding Author:**

Zhila Maghbooli,
Multiple Sclerosis Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran
Email: z-maghbooli@sina.tums.ac.ir

Arash Shirvani,
Department of Medicine, Section of Endocrinology, Nutrition, Diabetes and Weight Management, Boston University Medical Center, Boston, Massachusetts, United States of America
Email: hn@bu.edu

ABSTRACT

Objectives: The aim of this study is to compare three distinct bone markers in metabolically healthy and unhealthy obese and non-obese subjects, according to various metabolic health criteria.

Methods: The study enrolled a total of 35 subjects, including 11 healthy normal-weight and 23 obese subjects. Based on HOMA-Beta, all participants were divided into three groups: normal weight (HOM-Beta<100%, n=11), obese (HOMA-Beta <100%, n=12), and obese (HOMA-Beta >100%, n=12). The serum levels of osteocalcin, procollagen I amino-terminal propeptide (P1NP), and beta-cross Laps as bone turnover markers, as well as serum levels of 25 (OH) vitamin D3, and PTH were analyzed.

Results: Significant differences were observed in BMI, age, 25(OH)D3, FBS, Insulin, HOMA-IR, and HOMA-Beta among the groups. Analysis of bone markers revealed that the serum levels of Beta-cross Laps, P1NP, and osteocalcin were significantly different among all studied groups categorized by the HOMA-Beta model. In this context, circulating levels of osteocalcin and Beta-cross Laps in the normal weight group (HOMA-Beta<100%) were significantly higher than the obese group (HOMA-Beta <100%). In obese patients with HOMA-Beta <100%, Beta-cross Laps and P1NP levels were lower compared to the obese group with HOMA-Beta >100%.

Conclusion: The data suggests that HOMA-Beta, as an index of β-cell function, can be used in part of metabolically healthy obese (MHO) criteria and bone remodeling is altered in the context of metabolically healthy obesity.

Keywords: HOMA-beta, bone marker, metabolically healthy obesity

Abbreviations: P1NP: Procollagen type 1 amino-terminal propeptide; OC: Osteocalcin; Beta-CTx: Beta-cross Laps; MHO: Metabolically healthy obese; HOMA; Homeostatic model assessment of insulin resistance; BMI: Body mass index; LGP: laparoscopic gastric placation; WC: Waist circumference; WHR: Waist-to-hip ratio; FBG: Fasting blood glucose; HDL-C: High-density lipoprotein cholesterol; TG: Triglycerides; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HbA1c: Glycated hemoglobin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PTH: Parathyroid Hormone

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Introduction

Obesity, a complex and heterogeneous condition resulting from a chronic imbalance between energy intake and energy expenditure, has a significant impact on several public health problems (1, 2). Although substantial evidence supports the view that fat mass is associated with increased bone mass and a reduced risk of osteoporosis, accumulating data suggest that obesity is detrimental to bone health (3-5). Therefore, in recent years, much attention has been focused on a potential link between bone homeostasis and obesity. Despite numerous studies, the mechanisms responsible for linking obesity to bone metabolism remain undetermined. Emerging evidence indicates that there is cross-talk among bone, adipose tissue, and energy metabolism. A possible mechanism may be that adipose tissue and the skeleton (specifically osteoblasts and osteoclasts) form a homeostatic feedback system by secreting adipokine and several molecules such as osteocalcin, procollagen type 1 amino-terminal propeptide (P1NP), and Beta-cross Laps (beta-CTx) (6-8).

Osteocalcin (OC), an osteoblast-derived molecule, is a vitamin K-dependent non-collagenous protein with 49 amino acids. Apart from its well-known role as a bone formation marker, this protein contributes to regulating energy, fat storage, and glucose homeostasis likely by promoting insulin secretion and sensitivity. Procollagen type 1 N-terminal propeptide (P1NP) is another bone formation marker that is released by osteoblasts during collagen type I synthesis and has been involved in bone matrix remodeling. Accordingly, it has been utilized in osteoporosis management (9, 10).

Beta-CrossLaps (beta-CTx) are the C-terminal telopeptides of type I collagen, a component mainly located in the bone matrix. Beta-CTx is secreted into the circulation during the degradation of mature type I collagen from bone, thus generally employed as a defined biomarker for bone resorption (11, 12).

Although ample evidence asserts the view that a large fat mass is associated with an increased risk of metabolic complications, a subset of obese individuals is metabolically normal and has been identified as metabolically healthy obese (MHO). Specifically, individuals with MHO phenotype exhibit fewer detrimental levels of cardiometabolic risk factors, diabetes, and mortality in comparison with metabolically abnormal obese (13-15).

Considering the importance of obesity and related health problems, the notion of MHO needs more attention to prevent inevitable public health messages. It is more complicated when extending MHO for bone health. Although ample data supports the alteration in bone turnover markers in obesity and its association with indices of energy metabolism (11, 16, 17), no study has specifically looked at bone turnover markers in individuals with MHO. Therefore, in this study, the serum levels of OC, P1NP, and beta-CTx in healthy normal-weight and morbid obese subjects were investigated. These subjects were categorized based on homeostatic model assessment (HOMA) of β-cell function (HOMA-Beta) for evaluating metabolic status in the studied population.

Methods

Population study

The study enrolled a total of 35 participants, including 11 healthy non-obese and 23 obese subjects. All obese subjects were selected from individuals undergoing laparoscopic gastric placation (LGP) for severe obesity [body mass index (BMI): 47.51±11.6 Kg/m2] at Sina Hospital affiliated with Tehran University of Medical Sciences, Tehran, Iran. Non-obese patients (BMI: 24.06±0.35) were selected as control subjects from individuals who required elective abdominal surgery. All participants were classified based on the HOMA-Beta model for evaluating metabolic status into three groups: normal weight (HOMA-Beta<100%, n=11), obese (HOMA-Beta <100%, n=12), and obese (HOMA-Beta >100%, n=12). The study was approved by the Ethics Committee of the Endocrinology and Metabolism Research Institute. A comprehensive questionnaire was administered, and written informed consent was obtained from all participants. The primary exclusion criteria were a history of cancer or chronic disorders such as rheumatoid arthritis, liver disease, and cancer, current smoker, pregnancy at the time of the study, and type 1 diabetes.

The diagnosis of type 2 diabetes was carried out and/or confirmed following the American Diabetes Association criteria, which includes fasting blood glucose ≥126 mg/dL on two separate occasions, random (non-fasting) blood glucose ≥200 mg/dL on two separate occasions or blood glucose >200 mg/dL at 2 h during a standard oral glucose tolerance test (18).

The Body Mass Index (BMI) was calculated by dividing the weight (in kilograms) by the square of height (in meters). Waist circumference (WC) was measured to the nearest 0.1 cm at the level of the iliac crest with a flexible inch tape while the subject was at minimal respiration. Hip measurements were taken at the maximum circumference of the buttocks. The Waist-to-Hip Ratio (WHR) was calculated as waist circumference (in centimeters) divided by hip circumference (in centimeters) (19).

The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was calculated as follows: fasting blood glucose (mg/dL) × fasting blood insulin (μU/mL) / 405. HOMA-Beta was also calculated as

Table 1: Anthropometric and laboratory characteristics of all study population

Characteristics		Normal weight (HOMA-Beta<%100) (n=11)	Obese (HOMA-Beta <%100) (n=12)	Obese (HOMA-Beta >%100) (n=12)	Total Difference *p*-value
Age	years	48.3±11.95	41.3±14.4	29.8±8.03	p<0.05
BMI	Kg/m^2	28.12±11.95	46.1±13.73	47. 58±9.2	p<0.001
FBG	mg/dL	115.1±25.9	121±48.8	86.4±12.52	p<0.001
Insulin	µU/mL	4.8±2.25	5.63±2.34	18.14±13.32	p<0.001
HOMA-IR	-	1.43±0.86	1.86±1.67	4.06±3.2	p<0.001
HOMA-Beta	%	40.9±22.3	47.47±31	290.5±204.6	p<0.001
HbA1c		5.1±0.3	5.8±0.9	5.5±0.38	ns
PTH	Pg/ml	41.9±17	52.9±30.7	48±22.6	ns

follows: [360 × fasting blood insulin (µU/mL)] / [fasting blood glucose (mg/dL)- 63]%.

Biochemical and laboratory measurements

Venous blood was collected following overnight fasting and divided into two aliquots, in a clot activator tube and vacutainer containing EDTA, for biochemical analyses and bone markers measurement, respectively. Samples were centrifuged and serum and plasma were separated and either used immediately or stored at-80 ºC until assayed.

Fasting blood glucose (FBG) was measured using the glucose oxidase method. Insulin was assessed using an enzyme-linked immunosorbent assay (ELISA) kit (Monobind Inc., USA). Serum triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and total cholesterol (TC), creatinine, and urea were assessed using a commercially available kit (Pars Azmoon, Tehran, Iran).

The levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured using enzymatic colorimetric assays (Pars Azmoon kit, Tehran, Iran). Glycated hemoglobin (HbA1c) levels were evaluated using ion exchange chromatography with a DS5 set (DREW, United Kingdom).

Bone turnover biomarkers

Serum 25(OH)D was measured by radioimmunoassay (RIA) using a Biosource kit (Biosource Europe SA, Belgium); intra- and intra-assay coefficients of variation (CV) were 5.2% and 7.5%, respectively. Procollagen type 1 N-terminal propeptide (P1NP) was measured by a quantitative sandwich enzyme immunoassay technique (intra- and inter-assay CV was <8% and <10%) (Cusabio). Osteocalcin and Beta-CrossLaps (Beta-CTx) were measured using an electrochemiluminescence assay (Roche). Parathyroid Hormone (PTH) was measured using a quantitative sandwich enzyme immunoassay technique.

Statistical analysis

Data analysis was performed using SPSS 18 (SPSS, Chicago, IL, USA). Descriptive analysis was applied and normality was evaluated using the Shapiro-Wilk test for all quantitative variables. The data of variables with normal distribution are expressed as means ± standard error of the means (SEM). Comparisons between subjects divided according to HOMA-Beta were done by Student's t-test and analysis of variance (ANOVA) for data with normal distribution, and Mann-Whitney U and Kruskal-Wallis tests were used for non-normally distributed variables. The results are considered statistically significant if p-value <0.05.

Results

A total of 35 subjects participated in the study, comprising 11 healthy normal-weight and 23 obese individuals. The optimal model associating metabolic status with bone markers in obese subjects was HOMA-Beta, serving as an index of β-cell function (%B). Participants were divided into three groups based on HOMA-Beta: normal weight (HOMA-Beta<100%, n=11), obese (HOMA-Beta <100%, n=12), and obese (HOMA-Beta >100%, n=12).

Table 1 presents the anthropometric variables and biochemical characteristics of the participants. No significant differences were observed in PTH, HbA1c, AST, TC, HDL-C, and LDL-C among the groups. However, age, FBS, insulin, TG, HOMA-B, HOMA-IR, ALT, AST, 25(OH)D3, and BMI showed significant differences among the three groups based on one-way ANOVA.

Before classifying all subjects according to HOMA-Beta values, no significant difference was found between

Table 2: Circulating levels of bone turnover markers and 25(OH) vitamin D in all study population

Variables	Normal weight (HOMA-Beta<%100) (n=11)	Obese (HOMA-Beta <%100) (n=12)	Obese (HOMA-Beta >%100) (n=12)	Total Difference *p*-value
25(OH)D3 (ng/ml)	35.4±19	15.34±9.1	20.18±12.4	P<0.05
Beta-cross Laps (ng/ml)	0.7±1.1	0.23±0.09	0.5±0.3	P<0.05
P1NP (pg/ml)	87.83±49.46	62.22±38.02	111.95±62.69	P<0.05
Osteocalcin (ng/ml)	20.73±7.43	14.69±15.9	21.7±12.1	P<0.05

healthy normal-weight and obese subjects in terms of circulating levels of bone markers; Beta-cross Laps, P1NP and osteocalcin and 25(OH)D3. Interestingly, upon analyzing bone markers, it was found that the serum levels of Beta-cross Laps, P1NP, and osteocalcin significantly differed among all groups categorized by the HOMA-Beta model (Table 2). Specifically, circulating levels of osteocalcin and Beta-cross Laps in the normal weight group (HOMA-Beta<100%) were significantly higher than those in the obese group (HOMA-Beta <100%). In obese patients with HOMA-Beta <100%, Beta-cross Laps and P1NP levels were lower compared to the obese group with HOMA-Beta >100%.

Discussion

While several human clinical studies have reported alterations in circulating bone markers in obesity, none have evaluated them in the context of Metabolically Healthy Obesity (MHO). This study presents, for the first time, a comparison of three well-known biomarkers of bone remodeling in MHO, unhealthy obese, and non-obese subjects, using the HOMA-Beta model to evaluate metabolic health criteria.

Although no difference was observed between obese and non-obese subjects in terms of circulating levels of 25(OH)D3, OC, P1NP, and Beta-CTx, interestingly, morbidly obese patients with HOMA-Beta <100% (MHO subjects) had the highest level of OC compared with unhealthy obese and non-obese subjects. Significant differences were also found in P1NP and Beta-CTx levels between morbidly obese patients with HOMA-Beta <100% (MHO subjects) and unhealthy obese patients. Furthermore, 25(OH)D3 levels showed an increasing trend in non-obese subjects compared with morbidly obese patients with HOMA-Beta <100% (MHO subjects).

In line with these findings, no significant difference was observed between MHO and metabolically unhealthy obese individuals in terms of 25(OH)D levels. Moreover, a correlation was found between 25(OH)D levels and metabolic health status or insulin resistance and adiposity degree in morbidly obese patients. It should be noted that this study used the HOMA-IR criteria for dividing obese patients into two groups: MHO and metabolically unhealthy obese (20). Similar results were also found in the Korean National Health and Nutrition Examination Survey by Hang et al (21).

In contrast, a recent study revealed lower serum 25(OH) vitamin D levels in metabolically unhealthy obese adults compared to MHO, suggesting that vitamin D deficiency could be a key part of metabolically unhealthy obesity (22). The results regarding measuring bone turnover markers are greatly conflicting. For example, Iglesias et al. reported that the mean serum level of OC in obese patients with type 2 diabetes was markedly lower compared with patients with a reduced degree of glucose tolerance. However, they observed no significant differences in P1NP and Beta-CTX levels among obese patients with normal glucose tolerance tests, prediabetes and T2D (11). In contrast, obese individuals showed a reduced level of bone turnover markers; P1NP and collagen type 1 C-telopeptide (CTX) in comparison with normal-weight adults. Moreover, alterations in bone density and related microstructure were different (17). Furthermore, bone-derived factors and bone turnover markers; osteoprotegerin (OPG); Dickkopf-1 (DKK1); and the P1NP and carboxy-terminal telopeptide of type I collagen (CTx), in obese children were different, suggesting altered fat-bone signaling resulting (16).

In this study, the HOMA-Beta value increased in the following order: non-obese group, morbidly obese patients with HOMA-Beta <100% (MHO subjects), and unhealthy obese patients. The Homeostatic Model Assessment (HOMA) of β-cell function is used to evaluate β-cell function from basal glucose and insulin (23, 24). This model reflects the balance between hepatic glucose output and insulin secretion based on the relationship between glucose and insulin in the basal state, providing a metabolic status (25-27). Dysregulated insulin secretion and impaired insulin signaling pathways, estimated by the HOMA-Beta model in this study, exert detrimental effects on energy-related pathways, endothelial function, inflammatory responses, and lipid and glucose metabolism (28-30). These physiological derangements cause an imbalance between bone resorption and bone

formation in morbidly obese subjects, altering metabolic conditions. This finding could partly support the concept that disturbances in metabolic status in obese subjects, in the context of changes in β-cell function, may affect the bone-adipose tissue axis, resulting in changes in bone remodeling biomarkers.

In summary, this study provides novel insight into the alteration of bone remodeling in the context of MHO and the cross-talk between metabolic status and skeleton in obesity. The study was limited by the absence of Bone Mineral Density (BMD) measurements. Future studies with larger sample sizes are required to confirm these results.

Conflict of interest

The authors have nothing to declare.

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