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Arrieta F[1,2]*, Iglesias P[2], Piñera M[3], Arrieta A[4],Quiñones J[2], Balsa J[5] and Vazquez C[6]

[1]Centro de Investigación Biomédica en Red-Fisiopatología de Obesidad y Nutrición (CIBERobn), Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Spain

[2]Department of Endocrinology and Nutrition, Hospital Universitario Ramón y Cajal, Universidad de Alcalá, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Spain

[3]Department of Primary Care, Direction Asistencial Este, Centro Salud Benita de Avila, Spain

[4]Department of Medicine, Universidad Autónoma de Madrid, Spain

[5]Department of Endocrinology and Nutrition, Hospital Infanta Sofía, Madrid, Spain

[6]Department of Endocrinology and Nutrition, Hospital Fundación Jimenéz Diaz, Universidad Autónoma de Madrid, Spain

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***Corresponding author:** Francisco Arrieta Blanco, Centro de Investigación Biomédica en Red-Fisiopatología de Obesidad y Nutrición (CIBERobn), Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Spain, E-mail: arri68@hotmail.com; francisco.arrieta@salud.madrid.org

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Research Article

Serum Concentrations of Osteocalcin (OC) and Beta-Cross Laps (Beta-CTx) and Insulin Resistance in Morbid Obese Women with and without DM2

Abstract

Aim: The present study was intended to establish the role of bone in grade III obese women with and without type 2 diabetes mellitus (T2DM).

Material & Methods: Serum osteocalcin (OC), Beta Cross-Laps (Beta-CTx), parathormone (PTH) separar and y 25-hydroxyvitamin D (25OHD) concentrations were measured in 48 morbid obesity women (11 with T2DM and 37 control group). Insulin resistance and insulin secretion was assessed by measuring the HOMA-IR and the HOMAβ index and its association with OC and Beta-CTx.

Results: Serum OC was significant lower in the diabetic group compared with non-diabetic patients 15.4 ± 3.6 ng/ml vs 22.1 ± 3.5 ng/ml, p<0.001 without significant differences in Beta-CTx (0.24 ± 0.1 vs 0.31 ± 0.2 ng/ml, ns). Both bone biomarkers, OC and Beta-CTx, showed a positive correlation (r=0.76; p<0.01) in the whole group subjects and in the control group (r=0.80, p<0.00), but no in the T2DM group (r=0.50, p ns). In the whole group of patients, OC correlated significantly with HOMA-IR (r=0.36; p<0.01) and HOMA-ß (r=0.36, p<0.01). Beta-CTx also correlated with HOMA-IR (r= 0.40, p<0.01) and HOMA-ß (r= 0.41, p<0.001. OC also significantly correlated with HOMA-IR (r=0.41, p<0.01) in non-diabetic patients and almost reached statistical significance with HOMA-ß (r=0.32, p=0.053), but was not significantly correlated with HOMA-ß (r= -0.53, ns) and with HOMA-IR index (r=0.52, ns) in the T2DM group. When we performed the multivariate logistic regression the serum level of OC was the only covariate found significantly with DM2 with a coeficient -6.65 , (95% CI, -12.75049 -.5674469); p=0.03). Both groups showed secondary hyperparathyroidism (T2DM, 78.4 ± 19.4 pg/ml vs non-diabetic group, 75.4 ± 35.6 pg/ml; ns). The majority of the patients showed 25OHD deficiency 62.5%, followed by 25OHD insufficiency 27.1% and normal 25OHD levels in only 10.4%. The 25OHD deficiency was present in both study groups (T2DM patients, 18.3 ± 7.4 pg/ml and nondiabetic group, 19.7 ± 9.6 pg/ml; ns).

Conclusion: OC and Beta-CTx could play a role in glucose metabolism and insulin resistance. Serum OC concentrations are significantly reduced in T2DM morbidily obese women compared with non-diabetic group, and add new evidence on the possible role of bone as an endocrine organ with metabolic implications specially the levels of OC.

Introduction

The emergence of bone as an endocrine regulator has prompted a reevaluation of the role of several bone mineralization factors in the development of metabolic disease. Recently, some of them have been postulated to be risk biomarkers for the development of type 2 diabetes mellitus (T2DM) [1].

Osteocalcin (OC) is an osteoblast-specific secreted non-collagenous, vitamin K-dependent protein synthesized and secreted into the general circulation from osteoblastic cells [1]. This protein contains three residues of the amino acid gamma-carboxyglutamic acid. The carboxylation of OC is a complex process, and the esp gene, encoding the osteotesticular protein tyrosine phosphatase, has been implicated in the carboxylation process. Hormonally active OC (carboxylated and uncarboxylated forms) acts increasing β-cell proliferation, insulin secretion, peripheral insulin sensitivity and energy expenditure [2-4]. In fact, it has been reported that low OC levels have been associated with insulin resistance and obesity, particularly in older adults and cardiovascular risk [1,5-7].

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Beta-CrossLaps (Beta-CTx) is the C-terminal telopeptide of type I collagen, the main component (~90%) of the protein matrix of bone. Beta-CTx is released into the bloodstream during bone resorption and almost entirely excreted by the kidney. Its quantification serves as a specific marker for the degradation of mature type I collagen from bone [8,9]. In the same way there is an accumulating evidence of a cross-sectional association between high serum Beta-CTx concentrations and a lower prevalence of metabolic syndrome (MetS) or T2DM [1].

The connection between bone formation OC and bone resorption Beta-CTx markers and parameters of glucose metabolism in severely obese subjects has not been evaluated in detail and more investigations in humans are required to demonstrate the role of bone hormones in the regulation of human metabolism [10-13]. Therefore, our aim was to assess the relationship of bone metabolism markers (OC and Beta-CTx) and insulin resistance in morbidly obese women and valorated the diference between morbidly obese with and without T2DM.

Material and Methods

Patients and design

In this cross-sectional study we investigated a group of 48 grade III obese adult women. T2DM diagnosis was established following the American Diabetes Association criteria (ADA, 2010) (14). Exclusion criteria were T1DM, gestational diabetes, obstructive liver disease, advanced renal failure (clearance creatinine < 60 ml/min), drugs such as, sex steroids, glitazones, insulin, incretin mimetics, corticosteroids, vitamin D, calcitonin, and bisphosphonates. Physical examination included height, body weight, body mass index (BMI), waist-hip ratio (WHR), and blood pressure. Blood pressure was measured twice and average reading was taken in every patient. Analytical study was performed on each patient on a single occasion. The study was approved by our Local Ethical Committee. Participants were provided written informed consent before entering the study.

Analytical data

Fasting samples of venous blood were obtained from an antecubital vein between 8:30 and 9:00 h after an overnight fast and 12 h of abstinence from smoking for estimation of hormonal and general analytical data. Blood samples were centrifuged immediately and the serum samples were drawn and immediately processed for biochemical analysis. Biochemical assays on the serum concentrations of glucose, total cholesterol (TC), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), and triglycerides were performed with a multi-channel Architect ci8200 analyzer (Abbot Diagnostics, Berkshire, UK). Hemoglobin A1c (HbA1c) was measured by high-performance liquid chromatography (HPLC) (Diamat,Bio-Rad, Viena, Austria) using a Merck-Hitachi model L9100 autoanalyzer. Normal range was 4.0-6.0%. Insulin was determined by a commercial radioinmunoanalysis (RIA) kit (Incstarcorp, Stillwater, Minnesota). Normal range for insulin was 41.7-187.5 pmol/l. Insulin sensitivity and insulin secretion was estimated by Homeostasis Model Assessment (HOMA) based on plasma levels of fasting plasma glucose (FPG) and inmunorreactive insulin (IRI) levels. Insulin resistance was estimated by using HOMA-IR, which was defined as [FPG (mg/dl)×fasting IRI (μU/ml)]/405. Homeostatic model assessment (HOMA) of β-cell function (HOMA-β) was calculated by using [360×fasting IRI (μU/ml)]/[FPG (mg/dl)-63] formula (15). For the determination of 25-dihydroxyvitamin D (25OHD), plasma EDTA was used. Plasma 25OHD concentration was measured by enzyme-linked immunosorbent assay (IDSLtd, Bolton, UK). Normal range was 30.0-57.6 ng/ml. Intact parathormone (iPTH), OC, and Beta-CTx were measured by electrochemiluminescence Elecsys 2010 (Roche Diagnostics, Basel, Switzerland). Normal ranges in our hospital central laboratory were iPTH, 12.0–65.0 pg/ml; OC, 15.0-46.0 ng/ml; and beta-CTx <0.550 ng/ml. The intra-and interassay detection limits for these assays were below 10%.

Statistical analysis

For quantitative variables, results are expressed as mean ± SD. Normal distribution was tested by the Kolmogorov-Smirnov test. Comparisons between study groups was tested by the U de Mann-Whitney test. Relationship between quantitative variables (age, body mass index, BMI, blood pressure, lipid profile and carbohydrate metabolism parameters) was examined by using simple correlation analysis coefficient, and multivariate logistic regression. Analysis was performed using SPSS for Windows, version 19 (SPSS Inc., Chicago, IL, USA) and Stata (vs 4.2). $P<0.05$ was considered to be statistically significant.

Results

Clinical features, lipid profile, and carbohydrate metabolism parameters

The whole study group consisted of 48 adult women with grade III obesity (mean age 43.6 ± 12.2 years; BMI 47.4 ± 5.6 kg/m2), T2DM patients (n=11) and non-diabetic patients (n=37). Clinical features are summarized in table 1. Both study groups showed similar age, gender, BMI, systolic and diastolic blood pressures. Diabetic patients showed significant higher levels of HbA1c, serum fasting glucose and triglycerides concentrations with lower levels of HDL-C than non-diabetic patients (Table 1).

25-hydroxyvitamin D and parathyroid hormone

The majority of the patients (n=30; 62,5%) showed 25OHD deficiency (<20 ng/ml), followed by 25OHD insufficiency (20 to 30 ng/ml) and normal 25OHD levels (>30 ng/ml) that were detected in 13 (27.1%) and 5 (10.4%) patients, respectively. We did not find significant differences in 25OHD paramentes between diabetic and non-diabetic women (Table 1).

Serum iPTH concentrations were similar in both groups of patients. iPTH was slightly above the normal range both in diabetic and non-diabetic groups (table 1). The percentage of patients with iPTH>65 pg/ml was 63.6% and 62.1% in diabetic and non-diabetic groups, respectively. In the whole group, a significant negative correlation between 25OHD and

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iPTH values was found (r=-0.36, p<0.02). No correlation was found between iPTH with HOMA-IR (r=0.22, ns) and HOMA-ß (r=0.14, ns).

Osteocalcin and Beta-CrossLaps

Both study groups presented with OC into the normal range; however, diabetic group showed significant lower serum OC levels than non-diabetic patients 15.4 ± 3.6 ng/ml vs 22.1 ± 3.5 ng/ml, p<0.001) (Table 1).

Both bone biomarkers, OC and Beta-CTx, showed a positive correlation (r=0.76; p<0.01) in the whole and control group (r=0.80, p<0.00), but no in the T2DM group (r=0.50, ns). In the all patients, OC correlated significantly with HOMA-IR (r=0.36; p<0.01) and HOMA-ß (r=0.36, p<0.01). Beta-CTx also correlated with HOMA-IR (r= 0.40, p<0.01) and HOMA-ß (r= 0.41, p<0.001). OC significantly correlated with HOMA-IR (r=0.41, p<0.01) in non-diabetic patients and almost reached statistical significance with HOMA-ß (r=0.32, p=0.053). On the other hand, OC was not significantly correlated with HOMA-ß (r= -0.53, ns) and with HOMA-IR index (r=0.52, ns) in the T2DM group. Beta-CTx correlated significantly with HOMA-IR index (r=0.41; p=0.01) and HOMA-ß (0.42, p<0.01) in non-diabetic group. This correlation was not found in diabetic patients (table2). OC and Beta-CTx did not correlateds with 25OHD (Table 2).

In table 3 we can see the multivariate logistic regression analysis, of the Osteocalcin and Beta-CrossLaps serum level, osteocalcin was the only covariate found significantly with DM2 (coeficiente -6.658968 , (95% CI, -12.75049 -.5674469); P = 0.03).

Table 1: Clinical features, metabolic parameters and bone markers in women with grade III obesity with and without T2DM.

	T2DM group (n=11)	Non-diabetic group (n=37)
Clinical and antropometric parameters		
Age (yr)	48.0 ± 9.1	46.9 ± 7.8
BMI	44.5 ± 3.4	43.7±2.1
SBP (mmHg)	134.1 ± 9.7	131.7 ± 16.8
DBP (mmHg)	78.9 ± 10.9	80.2 ± 9.1
Metabolic parameters		
Glucose (mg/dl)	164.7±68.9**	90.6±9.7
Cholesterol mg/dl)	197.5 ± 26.1	203.4 ±38.9
LDL-C(mg/dl)	115.8 ±27.5	127.0 ± 32.2
HDL-C (mg/dl)	39.5 ±6.8***	45.3 ±7.1
Tg (mg/dl)	183.7 ± 85. **	139.6± 100.2
HbA1c (%)	6.8 ±1.2**	5.0 ±0.4
Bone markers		
Osteocalcin (ng/ml)	15.4 ±3.6***	22.1 ± 8.5
Beta-CTx (ng/ml)	0.24± 0.1	0.31 ± 0.2
25OHD (ng/ml)	18.3 ± 7.4	19.7 ± 9.6
iPTH (pg/ml)	78.4 ± 19.4	75.4 ± 35.6

Data indicate mean ± SD or the number of patients in each studied group.
**p<0.01; ***p<0.001.
Abbreviations: BMI, body mass index; Beta-CTx, Beta-CrossLaps; 25OHD, 25-hydroxyvitamin D; and iPTH, intact parathyroid hormone.

Discussion

Our study showed a significant reduction in serum OC concentrations in diabetic severely obese adult women compared with non-diabetic severely obese patients. This finding confirm the obtained results from previous studies recently reported [2,16-19]. In this setting, this finding supports a possible role of skeleton as an endocrine organ.

Several studies performed in animals with OC genetic deficiency have shown that bone regulates both glucose metabolism and fat mass via OC. These animals show a deficiency on proliferation of pancreatic beta cell [19-21]. In a previous report we found a relationship between glucose/insulin and lipid metabolism in obese patients with varying degrees of carbohydrate metabolism in Spanish population. In this study, serum OC concentrations were lower in T2DM compared with patients with normal glucose tolerance (22). Animal's models have shown that the lack of osteoblasts has been associated not only to alterations on bone density but also to impaired glucose metabolism, such as high blood glucose, low insulin secretion, and insulin resistance The administration of OC can restore glucose and insulin level in circulation but only partially the insulin sensitivity [23-25]. In our study, we also observed an association between OC levels and Beta-CTx with insulin resistance, as it has been reported in obese subjects [17,22]. Overweight and obesity are important risk factors for T2DM and; they have been associated with insulin resistance (measured by HOMA-IR), which is known to increase the risk of developing diabetes, and is closely associated with obesity, though the significant positive association of OC and Beta-CTx with insulin resistance and insulin secretion could be secondary to the obesity and /or to influence in the DM2 risk. Our study don't found a correlation in the group of T2DM with OC and Beta-CTx with e HOMA-β and the HOMA-IR.

It is known that T2DM has an elevated risk of fracture compared with non-diabetic subjects, despite higher bone mineral density. Quantitative changes in skeletal turnover can be assessed easily and non-invasively by the measurement of serum OC for bone formation, and the cross linked C (CTX) for bone resorption. In our study the decrease of circulating OC, a

Table 2: Simple correlation analysis between bone markers and different parameters of glucose metabolism in morbidly obese women.

	25OHD (T) (48)	25OHD (C) (37)	(T2DM) (11)	OC (T) (48)	OC (C) (37)	OC (T2DM) (11)	Beta-CTx (T) (48)	Beta-CTx (C) (37)	Beta-CTx (T2DM) (11)
HOMA-IR	*r = -0.22* n.s	*r =-0.22 n.s*	*r = -041 n.s*	***r=0.36 p=0.01***	***r=0.41 p=0.01***	***r= 0.52 n.s***	***r = 0.40 p =0.00***	***r = 0.41 p =0 .01***	*r = 0.48 n.s*
HOMA-ß	*r = -0.16 n.s*	*r =-0.15 n.s*	*r =-0.32 n.s*	***r = 0.36 p =0 .01***	*r =0.32 p = 0.05*	***r = -0.53 n.s***	***r =0.41 p =0.00***	***r = 0.42 p =0.01***	*r = -0.32 n.s*

Abbreviations: T total patients, C Control group (non T2DM), T2DM Diabetes type 2 group, Beta-CTx, beta-CrossLaps;25OHD, 25-hydroxy vitamin D; PTH, parathyroid hormone.

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Table 3: The Multivariate regression analysis for serum levels of OC and... Beta-CTx serum level.

Osteocalcin	Coef	Std. Err	t	P>t	[95% Conf. Interval]	
T2DM (*)	-10.48	4.77	-2.19	0.03*	-20.14	-0.82
GLUCOSE	0.15	0.20	0.74	0.46	-.26.85	0.57
HOMA-IR	-2.36	4.19	-0.56	0.57	-10.86	6.12
HOMA-β	-.024	0.02	-0.99	0.32	-.073	0.02
INSULIN	1.01	1.21	0.83	0.41	-1.4	3.47
Cons	1.92	21.28	0.09	0.92	-41.14	44.98
Osteocalcin	**Coef**	**Std. Err**	**t**	**P>t**	**[95% Conf. Interval]**	
T2DM	-6.65	3.02	-2.20	0.03*	-12.75	-0.56
betacross	**Coef**	**Std. Err**	**t**	**P**	**[95% Conf. Interval]**	
T2DM	-0.05	0.11	-0.50	0.62	-.297	0.17
GLUCOSE	0.00	0.00	0.08	0.94	-.010	0.01
HOMA-IR	115258	0.10	0.11	0.91	-.198	0.22
HOMA-β	0.00	0.00	0.44	0.66	-.0009	0.001
INSULIN	-.0006	0.03	-0.02	0.98	-.061	0.06
Cons	0.15	0.52	0.29	0.77	0.91	1.21

*p<0.05

osteoblastic biochemical marker of bone formation, with normal Beta-CTx, a bone resorption biomarker in T2DM patients with the lost of correlation between OC and Beta-CTx might be predictive and could explain the increased fracture risks, independently of bone mineral density in T2DM (26). Vitamin D is also well known for its critical role in bone and mineral metabolism. 25OHD, the main metabolite in the synthesis pathway of the active hormone, and the 1,25-dihydroxyvitamin D [1,25(OH)2D] as the most important biomarker of the activity of the vitamin D endocrine system, have been also studied. Vitamin D facilitates intestinal absorption of calcium and phosphate, thereby making these materials available for bone mineralization. In 2011, the Endocrine Society defined a 25OHD concentration of 30 µg/L as the lower limit of normal, 21–29 µg/L as insufficiency, and <20 µg/L as deficiency. Although there is no universal consensus on the criteria for vitamin D deficiency. In our study both nondiabetic and diabetic groups had vitamin D deficiency with an increase in PTH levels (secondary hyperparathyroidism (SHPT). SHPT is a common complication in patients with obesity which is characterized by elevated parathyroid hormone (PTH) levels and a series of bone-mineral metabolism alterations [27]. It has been suggested that an increase in serum 25OHD concentrations may have beneficial effects on glucose and insulin homeostasis [28]. However, cross-sectional and interventional studies of vitamin D supplementation provide conflicting results and demonstrate no clear beneficial effect of vitamin D on insulin resistance. The relationship between 25OHD and obesity and T2DM is not completely understood [29]. We found a higher number of subjects with vitamin D deficiency and iPTH levels between control group and DM2, as have been refer in the obese patients with SM, and T2DM (30). We did not find any correlation between PTH and 25OHD with HOMA-IR and HOMA-ß. OC, but no Beta-CTx levels is a biomarker of T2DM, Serum OC levels are 6-fold lower in T2DM patients.

The study has limitations, among them are the scanty number of study patients and the cross-sectional design which did not allow us to infer causal relationships between studied bone biomarkers and insulin resistance in this population. In conclusion, these results suggest that bone metabolism biomarkers OC and Beta-CTx seem to play a role in glucose metabolism and insulin resistance. Serum OC concentrations are significantly reduced in T2DM morbidily obese women compared with non-diabetic control group, our results add new evidence of the role of bone as an endocrine organ with metabolic implications. Further experimental studies are needed to determine mechanisms by which bone metabolic hormones such as OC and Beta-CTx, would affect glucose metabolism in T2DM patients.

Declaration of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author Contribution Statement

F Arrieta , P iglesias , M Piñera , J Balsa and C Vazquez designed the study, researched data, analyzed the results and wrote the final version of the manuscript. F Arrieta, and J Quiñones researched data, drafted the manuscript and contributed to the discussion. All authors read and approved the final manuscript.

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