Is Osteocalcin Implicated in the Regulation Of Energy Metabolism in Active Rheumatoid Arthritis?

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Abstract

The purpose of this study was to determine the relationship of osteocalcin with insulin resistance, insulin-like growth factor-1 (IGF-1) and inflammatory markers in women with RA.

The study population comprised of 35 postmenopausal women with RA. The significant negative correlations were noted between the osteocalcin and resistin levels (P < 0.05), glucose and resistin levels (P ≤ 0.01), glucose and interleukin-8 levels (P ≤ 0.01), interleukin-6 and insulin-like growth factor binding protein-3 (IGFBP-3) levels (P < 0.05). The positive correlations were found between insulin level and disease duration (P < 0.05), index of insulin resistance (HOMA-IR) level and disease duration (P < 0.05), IGF-1 and IGFBP-3 levels (P ≤ 0.01), the IGF-1/IGFBP-3 ratio and erythrocyte sedimentation rate (P ≤ 0.01), and the IGF-1/IGFBP-3 ratio and C-reactive protein levels (P < 0.05).

The present study suggests that inflammatory factors may modify in distinct ways the relationship between osteocalcin and carbohydrate metabolism in patients with RA. However, limitations of this study are: lack of control group, small sample size and that we did not measure uncarboxylated OC.

Keywords: Osteocalcin; Insulin resistance; IGF-1; Cytokines

Introduction

Rheumatoid arthritis (RA), an inflammatory disease that causes joint damage, can result in development of comorbidities including type 2 diabetes [1] or osteoporosis [1]. Pro-inflammatory factors play an important role in the development of such complications [2,3] which induce insulin resistance [3] and may affect levels of hepatic insulin-like growth factor-1 (IGF-1) mRNA and plasma IGF-1 [4].

Animal studies have confirmed the mutual association between carbohydrate and bone metabolism, demonstrating the contribution of uncarboxylated osteocalcin (OC), released from bone, in the stimulation of insulin secretion and the regulation of energy metabolism [5]. Both insulin and IGF-1 initiate cellular responses in bone by binding to and activating their endogenous tyrosine kinase receptors [6]. It has been suggested that insulin signalling in osteoblasts enhances OC carboxylation and impacts glucose homeostasis by promoting the ability of osteoclasts to enhance bone resorption [7]. On the other hand energy metabolism and bone remodelling may be co-regulated by several cytokines, between others by resistin or interleukin 6 (IL-6), which play a role in the pathogenesis of RA [8]. It has been suggested that both cytokines are implicated in insulin resistance in obesity and inflammatory disorders, in that in RA [3,9]. Previous research performed in animals has shown the effects of resistin on the insulin/IGF-1 signaling pathway in insulin-sensitive tissues (e.g., muscle, fat, and liver) [10]. However, it is much of the controversy regarding IL-6 and insulin sensitivity [11].

Studies conducted on postmenopausal women without RA have shown that total serum OC is negatively associated with insulin resistance indices [12]. However, the associations between carbohydrate metabolic indices and OC in postmenopausal women with RA are less recognised. We hypothesize that inflammatory factors may contribute to this process. RA is characterized by impaired bone formation [13], and in vitro studies [14] showed that pro-inflammatory cytokines reduced OC expression. Therefore, the purpose of this study was to determine the relationship of osteocalcin with insulin resistance, IGF-1 and inflammatory markers in women with RA.

Materials and Methods

Patient selection and basic measurements

The study population comprised of 35 postmenopausal women with RA, aged between 50 and 65 years, diagnosed according to the American College of Rheumatology criteria [15] which was in force at the time of this research. We included patients admitted to the Rheumatology Department within two consecutive months, who agreed to participate in this research. We excluded patients who presented disease known to affect bone metabolism like diabetes mellitus, hyperthyroidism and hyperparathyroidism, received biologic or bisphosphonate therapies, and underwent hormone replacement therapy.

The study protocol was approved by the Ethics Committee for Human Studies at K. Marcinkowski University of Medical Sciences in Poznan. All the participants provided informed consent. The disease activity score (DAS28) was determined by using the number of swollen and tender joints, score on the visual analogue scale (VAS), and erythrocyte sedimentation rate (ESR) [16].

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Analytical procedures

Blood was collected fasting, between 8 and 10 a.m. Samples were centrifuged at 1540 rcf and 4°C. In the serum samples, stored at -70°C, the following indices were measured: glucose concentrations with a commercially available assays (Cormay, Poland), insulin, IGF-1, and insulin-like growth factor binding protein-3 (IGFBP-3) levels with radioimmunoassays (BioSource Europe S.A., Belgium), rheumatoid factor (RF) levels using BioSystems kit (Spain), and high sensitivity C-reactive protein (hsCRP) concentrations with a high sensitive nephelometer method (Orion Diagnostica, Finland), ESR was measured using Medlab Products kit (Poland). Serum concentrations of resistin and high sensitivity IL-6 were analyzed by immunoenzymatic ELISA method using kits by R&D Systems (UK) and intact OC using a kit by Bender MedSystems (Austria) (Lombardi et al 2012). The insulin sensitivity index HOMA-IR (homeostasis model assessment of insulin resistance) was calculated [17].

Statistical analysis

The Kolmogorov–Smirnov test was used to check the data for normal distribution, whereas the Levene’s test for homogeneity of variance. The calculation of Pearson correlation coefficient and the Spearman rank test were used to determine associations for normally and non-normally, respectively, distributed variables. All analyses were performed using Statistica 8.0 package, and a P value of <0.05 was considered statistically significant.

Results

Table 1 presents clinical and biochemical characteristics of RA patients. In the group of women with RA, significant negative correlations were noted between the OC and resistin levels (p <0.05), glucose and resistin levels (p < 0.01), glucose and IL-6 levels (p < 0.01), IL-6 and IGFBP-3 levels (p < 0.05) (Table 2). The positive correlations were found between insulin level and disease duration (p < 0.05), HOMA-IR level and disease duration (p < 0.05), IGF-1 and IGFBP-3 levels (p < 0.01), the IGF-1/IGFBP-3 ratio and ESR (p < 0.01), and the IGF-1/IGFBP-3 ratio and hsCRP levels (p < 0.05).

Discussion

In the group of women with RA we found positive correlations between insulin resistance indices and disease duration, which may confirm the results of other studies that showed that RA leads to metabolic carbohydrate disturbances [18]. However, no associations were observed between OC and carbohydrate metabolic indices. We found the negative relationship of OC with resistin levels, which may be a part of a complex energy metabolism-bone network in patients with RA. This association is in line with results obtained by other authors in the group of old patients with hip fractures [19] or in obese children and adolescents [20]. However, the mechanism of resistin contribution in inhibiting bone formation seems unclear. Vergely et al. [21] showed that OC is also down regulated by steroid therapy. In previous our study we observed the inverse correlation between OC and resistin only in patients with steroids treatment when we divided them into subgroups using or no using glucocorticoid therapy. [22] Thus we cannot excluded that adverse effect of glucocorticoid treatment on bone tissue is associated with resistin in our patients.

In the general population, the development of insulin resistance is a major metabolic consequence of obesity, particularly proinflammatory cytokines secreted from macrophages and/or adipocytes, between others resistin and IL-6 [9]. However, in the present study, insulin resistance indices did not correlate with body mass parameters. Moreover, we found the negatively associations of resistin and IL-6 levels with glucose levels. Experiments in primary human cultured muscle have demonstrated that IL-6 increases glucose uptake, enhances glycogen synthesis and also increases skeletal muscle β-oxidation of fatty acids [23] and therefore their deleterious effects on glucose metabolism are discussed [11]. On the other hand the excess production of IL-6 may provide an explanation for some of the clinical manifestations associated with active RA, including weight loss and poor appetite [24].

Matsumoto and Tsurumoto [25] have showed a weak positive association of OC with IGFBP-3, a predominant carrier of IGF-1 in serum, in women with RA, suggesting its relationship with the activity...
of osteoblasts. We did not observe any correlations between levels of OC and IGF-1 or IGFBP-3 but we found the negative relationship between IGFBP-3 and IL-6 levels and positive correlations between IGF-1/IGFBP-3 ratio and ESR and hsCRP. It has been demonstrated that chronic overproduction of IL-6 causes decreased IGFBP-3 levels, resulting in a decreased association of IGF-1 in the 150-kDa complex [26]. In patients with systemic juvenile idiopathic arthritis levels of intact IGFBP-3 have inversely correlated with serum IL-6, CRP and ESR and positively correlated with IGF-1 levels as in our study in RA.

We can not exclude the contribution of pharmacotherapy on our results. Although it has been documented that glucocorticosteroids are responsible for glucose intolerance in RA [27], the low doses of steroids used by our patients and their beneficial effect on inflammation might counteract their effects on bone formation and insulin resistance [28]. Moreover, Russo and colleagues [29] have demonstrated that treatment with low doses of methotrexate may improve carbohydrate metabolism by increasing the expression of skeletal muscle glucose transporter type 4.

In conclusion, the present study suggests that inflammatory factors may modify in distinct ways the relationship between osteocalcin and carbohydrate metabolism in patients with RA. However, limitations of this study are lack of control group, small sample size and that we did not measure uncarboxylated OC. The relationship between OC and energy metabolism in patients in RA should be studied further.

Acknowledgments

The authors declare no conflict of interest.

References