The Association between Osteocalcin and Type II Diabetes in Egyptian Male Patients

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Abstract: Type 2 Diabetes Mellitus (T2DM) is a growing concern worldwide. It is multifactorial and if it is not managed properly, complications will appear both in short-term and long-term incidence. Recent studies have demonstrated a link between bone and glucose metabolism. Serum osteocalcin (OC) level and percentage of glycated haemoglobin (HbA\textsubscript{1c}) were assessed in 60 Egyptian male adults. Serum OC levels were significantly decreased in newly diagnosed T2DM patients compared with nondiabetic subjects (\(p<0.001\)). Percentage of HbA\textsubscript{1c} was higher in the newly T2DM patients as compared to the control subjects (\(p<0.001\)). In partial correlation analysis adjusted for age, serum OC level was inversely correlated with HbA\textsubscript{1c} (\(r = -0.68, p < 0.05\)). Our data suggest that low serum OC level might have a role in the pathogenesis of impaired glucose metabolism in Egyptian T2DM male patients.

Key words: Osteocalcin, Diabetes Mellitus, Glycated haemoglobin and glucose metabolism.

Introduction

Osteocalcin (OC) was described by Booth et al. (2013) as a vitamin K-dependent protein manufactured in the osteoblast. OC is found in the extracellular matrix of bone and in the serum of circulating blood. Both carboxylated (cOC) and uncxoxylated (ucOC) forms are found in serum, with the latter as the main component of total OC (TOC) (Chen et al 2017). The osteocalcin is encoded by the BGLAP gene. This gene encodes a great quantity bone protein secreted by osteoblasts that regulate bone remodelling and energy metabolism (Lumachi et al., 2009).

The role of OC in modulating glucose and lipid metabolism has attracted increasing attention recently. OC increases adiponectin expression which in turn stimulates the proliferation, differentiation and mineralization of osteoblastic cells [3, 4]. Adiponectin, one of the adipocytokines, also enhances insulin sensitivity, suggesting an interaction among bone, adipose-derived factors and glucose/lipid metabolism.

Several clinical studies have investigated the association between OC and glucose/lipid metabolism [5–8]. However, the results were inconsistent, probably owing to the different ethnic origin which is specific to the study population enrolled in the different studies. A recent study had reported differences in the associations between TOC and glucose metabolism in Han and Uygur Type II diabetes mellitus (T2DM) patients, indicating genetic factors may play a role in modulating OC and glucose metabolism in different ethnic population (Chen et al., 2017). Therefore the present study aims to investigate the relationship between OC and T2DM among Egyptian male patients.

Methodology

Participants

A total of 60 male Egyptian participants were recruited in this research. The participants were divided into 2 groups; 30 diabetic patients and 30 nondiabetic subjects (control group). Subjects were excluded from this study if they were female gender to rule out the possible role of oestrogen influencing OC level, have any history of previous or existing metabolic bone, thyroid diseases or recent history of a fracture (less than 6 months), and recent intake of medications affecting bone or glucose metabolisms. All diabetic patients were newly-diagnosed with T2DM for less than 3 months based on the American Diabetes
Association criteria. All participants signed written informed consent.

**Assay of OC and HBA₁c**
Both serum OC and HbA₁c levels were determined by enzyme-linked immunosorbent assay (ELISA) method. The ELISA kit was provided by CIS BioInternational, Baglos/Ceze, France.

**Statistical Method**
The statistical software package (SPSS version 20.0) was used for data management and analysis. The data were subjected to the Kolmogorov-Smirnov test to determine the distribution and method of analysis. As the data were normally distributed, student’s t-test and Pearson correlation coefficient were used. All the results are expressed as mean ± standard error of the mean (SEM), and with the level of significance set at $P<0.05$.

**Results:**
A total of 60 Egyptian male subjects were finally included, consisting of 30 diabetic patients and 30 nondiabetic subjects. The average age of the diabetic subjects was older than that of the nondiabetic subjects ($49.61 \pm 2.48$ years versus $40.23 \pm 6.60$ years), but there was no significant difference between the average ages of both groups.

Table 1 showed the characteristic of participants and their laboratory findings. There were significant differences with respect to the OC and HBA₁c levels between diabetic and nondiabetic subjects (all $P < 0.001$). Diabetic patients had a significantly higher HBA₁c level and lower OC level compared with nondiabetic subjects ($8.5 \pm 0.86\%$ versus $5.30 \pm 0.67\%$). Meanwhile, diabetic patients had significantly lower OC level compared with nondiabetic subjects ($14.75 \pm 1.41$ ng/ml versus $23.47 \pm 3.28$ ng/ml). The OC level was inversely correlated with the HBA₁c level of diabetic patients ($r = -0.068$, $P<0.05$).

**Table (1):** Clinical Characteristics and laboratory findings of the studied subjects

<table>
<thead>
<tr>
<th></th>
<th>Nondiabetic (n= 30)</th>
<th>Diabetic (n= 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.61 ± 2.48</td>
<td>40.23 ± 6.60</td>
</tr>
<tr>
<td>Osteocalcin, ng/ml</td>
<td>23.47 ± 3.28</td>
<td>14.75 ± 1.41*</td>
</tr>
<tr>
<td>HbA₁c, %</td>
<td>5.30 ± 0.67</td>
<td>8.5 ± 0.86*</td>
</tr>
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</table>

Values are expressed as mean ± SEM and with the level of significance set at $P < 0.05$.

**Figure (1):** Glycated haemoglobin (HbA₁c) levels of nondiabetic (control) and diabetic groups.
Discussion
The association between serum OC and energy metabolism has been extensively studied in T2DM patients. However, so far contrasting results have been reported. In the present study, we measured serum OC and HbA1c levels of 30 male patients with T2DM and another 30 males without diabetes. We found significantly higher HbA1c level and lower OC level in T2DM patients compared with nondiabetic subjects. There was also a negative correlation between these 2 parameters. Similar negative correlations were observed in other studies involving different ethnic origins, gender and age groups. Kanazawa et al. (2011) surveyed 101 postmenopausal women and 152 men diagnosed with T2DM and concluded serum OC was negatively correlated with FPG and HbA1C. Iki et al. (2012) investigated the association of the serum OC and glycemic status and IR in an elderly Japanese male population and found serum OC was negatively correlated with FPG and HbA1C. A more recent study involving 2 different ethnic origins was conducted by Chen et al (2017). They found Uygur participants had higher BMI and lower serum TOC than their Han participants. However, similar negative correlations were noted between HbA1c and TOC in all Uygur and Han T2DM patients (Total: Uygur: t = −3.468, P = 0.001; Han: t = −4.169, P < 0.001).

However, some studies have showed contrasting results on the relationship between serum OC and glucose/lipid metabolism. Aoki et al. (2011) found that the circulating level of OC was increased and positively correlated with glycemia in the early stage of T2DM as compared to normal glucose tolerance. Abseyi et al (2012) later reported no significant association between insulin resistance, metabolic syndrome parameters and OC levels in obese children and adolescents. In another study by Mori et al. (2012) also found no association between OC level and insulin resistance in T2DM patients. However, they ignored some medications effect on bone metabolism. Additionally, Liatis et al (2014) found no correlation between total serum OC and the incidence of diabetes after a 3-year follow-up period in a high-risk cohort with T2DM. Previous studies have indicated several endocrine functions of OC. For example, OC increases insulin production and sensitivity, β-cell proliferation, glucose uptake, fatty acid uptake and decreases fat accumulation (Mizokami et al., 2017). Aoki et al., 2011 carried out a study examining whether or not circulating levels of OC changed in glucose-intolerant patients without administration of glucose lowering agent to these subjects. Their findings led to the conclusion that when OC and leptin levels are decreased in association with glucose intolerant states, in line with the finding of negative correlation between OC and HbA1c levels. Sarkar and Choudhury (2013) tried to explain the association of low serum OC levels with high glucose levels and proposed hyperglycaemia suppression of osteoblast function and thereby decrease production and secretion of OC in T2DM. They also suggested that increased glucose metabolism may intoxicate osteoblasts. Onyenekwu et al. (2016), in a more recent study, determining the levels of plasma OC in Nigerian adults with T2DM and compare these to levels in nondiabetic control. They measured the body mass index (BMI), blood pressure, and waist circumference, plasma OC, fasting plasma glucose (FPG), glycated haemoglobin HbA1c, high density lipoprotein cholesterol (HDL-C) as well as...
triglyceride levels of 200 subjects. Their findings revealed that plasma OC levels are inversely associated with good glycaemic control whereas the components of metabolic syndrome were lower in individuals with diabetes mellitus. These findings further corroborate the essential role of the bone in the regulation of energy metabolism and glucose levels.

Conclusions
We found significantly lower level of serum OC in newly diagnosed T2DM Egyptian adult patients compared to nondiabetic controls. The lower serum OC was associated with increased HbA1c levels. Our findings suggest that the OC may have a significant role in the pathogenesis of T2DM and on the other hand offer a possible relationship between glucose metabolism and the bone diseases.

References