Influence of Type 2 diabetes Mellitus with and without cardiovascular disease or myocardial infarction on levels of calcium, sodium, and some vital variables in Iraqi men

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Abstract:
The objective of this study was to find out whether any important variables are affected by T2DM, and does this have a particular impact when heart problems arise through diabetes? This study included eighty-four participants of Iraqi male; they were divided into four groups. Twenty-one Iraqi men with T2DM, twenty-one Iraqi men with T2DM with the acute phase of myocardial infarction (MI), and other twenty-one with other cardiovascular disease CVD (atherosclerosis and arrhythmia). For comparison purposes Twenty-one of healthy controls (HCs) this study included. All patients had chronic high blood pressure (BP) and were over 40 years old. The serum level of the hormone insulin was measured for the purpose of estimating insulin resistance (HOMA-IR) as well as estimated S. T. protein, Albumin, globulin, calcium, and sodium. The results were recorded as mean differences in weight, T. protein, Albumin, globulin, calcium, sodium, and HOMA-IR of 82.57 Kg, 9.41 g/dL, 5.67 g/dL, 3.74g/dl, 8.69 mg/dL, 131.38 mmol/L respectively among T2DM group and HCs were detected. While non-significant differences among MI groups and HCs were detected in levels of T. protein, Albumin, and globulin, as well as non-significant differences between other CVD and HCs in levels of Albumin. The correlation which was observed established negative important correlations between HOMA-IR with S. Ca⁺⁺ and S. Na but it presents a positive correlation with other parameter but it is not statistically significant. In conclusion, this study shows there was a moderate negative correlation between HOMA-IR with Ca⁺⁺ and Na in T2DM patients, there is a noticeable alteration in the concentration of S. Ca and S. Na, especially when cardiovascular events occur, as well as the serum levels of globulin. Serological concentrations of sodium, calcium, T. Protein, and globulin were affected by a condition of hyperglycemia, hypertension, insulin resistance, and cardiovascular events. Also, our findings did not show significant alteration in the Albumin concentrations in patients compared to HCs subjects.

Keywords: Calcium, Sodium, Globulin, type 2 diabetic, CVD

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Introduction:
The definition of diabetes mellitus (DM) depends on a personal perspective because of a group of disorders not involving a single disorder, from the medical side, it represents a range of metabolic disorders correlation with hyperglycemia which occurs due to a defect in the function of insulin partially or completely (1). Type 2 diabetes mellitus (T2DM) is a common metabolic disorder predisposing to diabetic cardiomyopathy and CVD, which could lead to heart failure (HF) through a variety of mechanisms, including myocardial infarction (MI) and chronic pressure overload (2).

The coexistence of hypertension in patients of DM promote the possibility to develop CVD, there is some likelihood suggested that the renin-angiotensin-aldosterone system (RAAS) and blood flow can be related to insulin resistance and hypertension (3). Proteins have an important role in the function and structure of the cell, Sera comprises a mixture of protein differing in function and source, the amount of protein in the vascular system depends on the balance between the average of anabolism and rate of catabolism (4).

Some studies demonstrated no association between serum Albumin and T2DM (5), but other studies have shown negative associations between Albumin and T2DM (6). Serum albumin concentrations may be associated
with future risk of type 2 diabetes, but the epidemiological evidence is limited and uncertain, giving rise to uncertainty regarding the nature of the association. Furthermore, Serum Ca⁺⁺ plays an important role in the regulation of glucose level in the blood, particularly postprandial glucose level, therefore Ca⁺⁺ should be measured in patients with T2DM who have uncontrolled hyperglycemia, and oral supplementation of both Vit. D and Ca⁺⁺ from sources other than diet is recommended. Through this study, we seek to find out whether any important variables are affected by T2DM, and does this have a particular impact when heart problems arise through diabetics?

Subjects and methods
Case-control was used for comparison in this study.

Healthy Controls group (HCs) (n = 21)
This group includes 21 of Iraqi men identical with patients in sex, age, and do not have diabetes or high blood pressure and ischemic heart disease (IHD), in addition, they had no history of smoking or alcohol drinking, also they do not have acute illness or infection at the time of sampling, HCs were not specific for any prescribed drugs or dietary restrictions and other diseases that were excluded. They were whose ages ranged from 45 to 60 years.

Patients’ group (n = 64)
Sixty-four of T2DM patients (Males of age group 45 → 60 years and previously diagnosed with T2DM) and have high blood pressure and were taking antihypertensive drugs, diagnosis of T2DM was according to the statement of the Expert Committee on the Diagnosis and Classification of DM in 1997, T2DM was identified by one of the following characteristics: Fasting blood sugar (FBS) > 130 (mg/dL), Fasting serum insulin (FSI) > 10 (μlU/mL) HbA1c > 6.5 (%) and random blood sugar concentration. They were further divided into three groups: Group I: patients with T2DM (n = 21) without any complications of the heart. Group II: patients of T2DM with myocardial infarction (MI) (n = 21). Group III: patients of T2DM with other CVD (n = 21).

Methods
Fasting whole blood (samples of blood taken without binding the arm) was collected (5.0 mL) from the patients and healthy individual, kept in a tube without any anticoagulant at room temperature for 1 hr. Then the tube was centrifuged, the clear serum was pipetted into a clean dry test tube and then stored at (-20) °C for subsequent analysis.

Total protein concentration in the sera sample was determined using a modified Biuret method. While the method of measured Albumin depends on the binding an anionic dye bromocresol green (BCG) and albumin at acid pH to form complex color, the intensity of this color is symmetrical to the Albumin concentration in the test sample. The concentration of globulin in the sera sample of healthy and patients was calculated, using the following equation:

\[
S. \text{ Globulin (g/dL)} = \text{T.S. P (g/dL)} - \text{S. Albumin (g/dL)}
\]

Serum calcium was determined by the O-Cresol phthalein complex one (CPC) method was derived by Morehead and Briggs. Serum sodium was determined by the colorimetric method. The serum level of insulin was determined by enzyme-linked immunosorbent assay (ELISA) for all subject of study, the homeostasis model assessment of insulin resistance (IR) index (HOMA-IR) was calculated using the equation:

\[
\text{HOMA _ IR} = \text{F.S.G (mg/dL)} \times \text{F.S.I (μlU/mL)} \div 405
\]

The cutoff point to define insulin resistance match to HOMA-IR ≥ 3.8 (9).

Statistical Analysis:
All study variables were expressed as mean ± standard deviation (SD) and Std. Error. The significance of differences among the groups was determined by one-way ANOVA test. Followed by post-test Pearson’s correlation test was performed to determine the correlation between HOMA-IR with S. Ca⁺⁺ and S. Na. A P-value of less than 0.05 was considered to be significant. All data were analyzed with descriptive statistical analysis using the Statistical Package for the Social Sciences (SPSS) (SPSS Inc., Chicago, IL, USA) software, version 25.0.

Results:
Sixty of T2DM patients and Twenty-four of HCs, (Range of age 45 → 60 years), mean of weight in HCs (73.10 Kg) and was differences compared to three groups of the patient (82.57, 83.71 and 84.48 Kg) respectively. Serum T. protein in HCs (8.20 g/dL) was a significant difference as compared with the T2DM group and other CVD (9.41 and 9.60 g/dL), as well as, the date refers to a significant difference (p < 0.05) in Albumin levels (Fig. 1) in HCs as compared with T2DM patients (4.89 and 5.67 g/dL) respectively, also our results shown
significant difference between T2DM group compared to other CVD group as shown in table (1.1). As been shown in table (1.1, Fig. 2), there is a slight increase in the level of globulins in patients, but this increase is not important statistically significant when compared between HCs with T2DM and MI groups (3.31, 3.74 and 3.72 g/dL) respectively, but when compared to other CVD group was significant difference. Our date refers that the Ca²⁺ ion level (Fig. 3) has a significant difference between HCs compared with three groups of patient T2DM, MI, and other CVD). S. Na in this study has a significant difference between HCs compared with three groups of the patient tables (1.1, Fig. 4). Correlation coefficients (r) at P-Value < 0.01 showed was a moderate negative correlation between Ca²⁺ and Na with HOMA-IR as shown in table 1.1 and Fig (5, 6), we did not notice any significant statistical correlation between HOMA-IR with T. protein and globulin although there was correlation tend to positively trend, also with Albumin the correlation was a negative trend and was non-significant statistical.

![Figure 1: Mean for Albumin in study groups](image1.png)

![Figure 2: Mean for globulins in study groups](image2.png)
Table 1: Clinical and biochemical properties of subjects studied

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Healthy Controls</th>
<th>Std.Error</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I</td>
<td>Group II</td>
<td>Group III</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.57 ± 9.79b</td>
<td>83.71 ± 13.48b</td>
<td>84.48 ± 14.91b</td>
</tr>
<tr>
<td>T. protein</td>
<td>9.41 ± 0.84b</td>
<td>8.21 ± 1.10a</td>
<td>9.60 ± 1.65b</td>
</tr>
<tr>
<td>Albumin</td>
<td>5.67 ± 0.82b</td>
<td>4.49 ± 1.19ab</td>
<td>5.36 ± 0.97ab</td>
</tr>
<tr>
<td>Globulins</td>
<td>3.74 ± 0.91bc</td>
<td>3.72 ± 1.34a</td>
<td>4.24 ± 1.49bc</td>
</tr>
<tr>
<td>Ca⁺⁺</td>
<td>8.69 ± 0.81b</td>
<td>7.18 ± 0.45c</td>
<td>8.05 ± 0.61d</td>
</tr>
<tr>
<td>Na</td>
<td>131.38 ±6.90b</td>
<td>129.29±7.10b</td>
<td>131.38 ± 7.60b</td>
</tr>
</tbody>
</table>

Pearson Correlation r

- HOMA-IR – Ca⁺⁺ (mg/dL) - 0.632** < 0.01
- HOMA-IR – Na (mmol/L) - 0.500** < 0.01

Similar letters: means there is non-significant difference. Different letters: Mean there is significant difference at p < 0.05. Std. Error: standard error, T. protein: total protein, Ca⁺⁺: Calcium. Na: Sodium.

Figure 3: Mean for Ca⁺⁺ in study groups
Figure 4: Mean for Na in study groups

Figure 5: Correlation of S. Ca^{++} with insulin resistance
Discussion
It is a well-established and evidence-based fact that the plasma of proteins can alteration during disease (10). Because of the high levels in the circulatory system, and long half-life than other proteins, sera Albumin is a protein of plasmatic that is very sensitive to glycation, in case of DM when levels of glycated Albumin elevated can lead to irreversible damage associated with metabolic disorders such as coronary artery disease, retinopathy, and nephropathy (11). Our results showed less difference between T2DM with HCs in the levels of Serum Albumin. When the return to our results we observe the levels of globulins were highly in T2DM with CVD. This result may occur when increasing in level concentration of glucose which occurred because of damage of the natural feedback inhibition of gluconeogenesis in the liver, therefore increment breakdown of proteins and fats (12), and due to the globulins is one of the proteins of positive acute-phase which consider marker for inflammation (13).

Hypocalcemia was associated with both the development of Mets and T2DM (14). Ca\(^{\text{++}}\) is important for insulin-mediated intracellular processes in insulin-responsive tissues such as adipose tissue and skeletal muscle with a very narrow range necessary for optimal insulin action, in addition, Ca\(^{\text{++}}\) is necessary for insulin receptor phosphorylation and proper signal transduction and thus optimal GLUT-4 transporter activity (15). Previous studies have shown that S. Ca\(^{\text{++}}\) levels are elevated in diabetes individual comparison to those without, while insulin hormone secretion as a response to increases in levels of plasma glucose which is a dependent process on Ca\(^{\text{++}}\), although there is some inconsistency, between these studies and our results, the results referred that Ca\(^{\text{++}}\) involved in the progress of T2DM (16). In HCs group the levels of Ca\(^{\text{++}}\) was in normal range but has a significant difference when compared with patients, increasing cytosolic -Ca\(^{\text{++}}\) has been correlated with increased expression of GLUT4 -transporters in the myocyte which in turn, improves insulin-stimulated, glucose- transport, activity in these cells (17), because disorder in insulin action and insulin secretion are an association to T2DM, therefore it is expected to be, abnormal in Ca\(^{\text{++}}\) homeostasis, it plays a significant role in the progress of T2DM (16).

Sultan et al. (18) reported that serum Ca\(^{\text{++}}\) levels in T2DM patients were significantly lower than HCs, and indicated that the reduction in serum Ca\(^{\text{++}}\) levels were most likely due to several factors: Reduction in insulin levels that impair bone formation due to stimulation of osteoblast proliferation and impairment of Ca\(^{\text{++}}\) homeostasis; and hyperglycemia, which increases the excretion of Ca\(^{\text{++}}\) and phosphorus in urine, is proportional to the degree of glucosuria. Accordingly, our results showed a negative correlation between S. Ca\(^{\text{++}}\) and insulin resistance in T2DM patients (Fig. 5). Accurate measurement of Na level is difficult. Part of the problem is a significant in-person daily variation in sodium intake, whereas an increase in sodium intake has been demonstrated to increase BP and cause harmful cardiovascular effects in humans (19).

In this study, patients had hypertension, first, very significant note that one effect of insulin is a vasodilator and this effect may be lost in T2DM (Insulin Resistance) but the renal effect on Na reabsorption has been maintained (20). In the Renin-Angiotensin-Aldosterone System (RAAS), angiotensinogen is turned to
angiotensin I (Ang I) by renin, then Ang I converted to Ang II by angiotensin-converting enzyme (ACE), which in turn (Ang II) has many roles such as effect on elevation in BP, increased cardiac contractility, retention of renal sodium, vasoconstriction, reabsorption of H2O and aldosterone release (21). One of the aldosterone’s roles is to increase sodium reabsorption in the distal nephron (22).

On another matter, an up-regulation of RAAS in the cardiovascular system has been found in T2DM patients, which participant to the development of several T2DM complications including macrovascular and microvascular diseases (23, 24). Our results indicate that there was a significant difference between patients compared to HCs in the sodium levels, the possible reason for the presence of significant difference, maybe due the patients taking antihypertensive drugs ACEI (Angiotensin-converting-enzyme inhibitors) and ARBs (Angiotensin II receptor blocker) with Taking into account the diet less of salts. In addition, excess sodium intake attenuates the useful effects of several antihypertensive drugs, including blockers of RAAS, thus decreasing sodium intake improves such effects (25). In conclusion, Ca⁺⁺ unbalance hemostasis Ca²⁺ level in hyperglycemia, insulin resistance and its complication of cardiovascular events moreover, moreover hypertension in male with T2DM influence on RAAS, therefore, levels of Na effected and A salt-free diet in addition to antihypertensive drugs is able to improve the concentration of Na in the blood. on the other hand, sera proteins can change during disease and inflammation.

Reference:


