Correlation of Serum Calcium level with Fasting Plasma Glucose and Lipid Profile in Type 2 Diabetes Mellitus

Tanmay Saha¹, Satyajit Koley²*, Moumita Mondal², Subir Kumar Das²

¹Department of Biochemistry, College of Medicine & JNM Hospital, WBUHS, Kalyani, India
²Department of Biochemistry & Biophysics, University of Kalyani, India

Abstract: Persistent hyperglycemia in type 2 diabetes mellitus affects all types of tissues through structural and biochemical alterations. Recent interest has been focused on the role of serum calcium (Ca²⁺) in development of insulin resistance (IR) in type 2 diabetes mellitus as well as dyslipidemia associated with it. In our study we have evaluated role of serum Ca²⁺ in type 2 diabetes mellitus and altered lipid profile in the disease. Newly diagnosed diabetic patients showed significantly higher fasting plasma glucose (FPG) (p<0.001), serum Ca²⁺ (p<0.005) and lipid profile parameters including total cholesterol (p<0.005), triacyl glycerol (TAG) (p<0.05), VLDL cholesterol (VLDLc) (p<0.05) and LDL cholesterol (LDLc) (p<0.001) were found significantly higher in comparison to equal number of age and sex matched healthy controls. However, HDL cholesterol (HDLc) was significantly lower (p<0.005) among cases. Serum Ca²⁺ showed significant positive correlation with FPG among the patients (r = 0.448, p<0.001) while weak but significant positive correlations with lipid profile parameters like total cholesterol (r=0.28, p<0.005), TAG (r=0.20, p<0.05), LDLc (r=0.28, p<0.005), VLDLc (r=0.20; p<0.05) but HDLc did not show any significant correlation.

Keywords: Type 2 diabetes mellitus, Calcium, Lipid profile.

INTRODUCTION
Persistent hyperglycemia in type 2 diabetes mellitus is known to have its deleterious effects on virtually all types of tissue through alterations in structural and biochemical changes.

In type 2 diabetes peripheral tissue fails to respond properly to insulin which is known as insulin resistance (IR) [1]. Insulin plays the central role in regulating blood glucose. Cells of pancreas are stimulated by increased blood glucose level after meals that induce insulin secretion [2]. After the ingestion of a carbohydrate meal, insulin lowers blood glucose immediately by enhancing glucose transport into adipose tissue and muscle by recruitment of glucose transporters (GLUT 4) on the plasma membrane. Glucose is partly utilized by most of the cells for energy and rest is converted into stores of energy as glycogen or fat [3]. Insulin level falls with decreasing blood glucose level. During fasting, glycogen and/or fat synthesize glucose again for energy supplementation under influence of glucogenic hormones like glucagon, epinephrine [4].

Ca²⁺ plays important roles in wide range of biological functions [5] including insulin secretion [6]. Previous studies have reported that serum total calcium levels are higher among type 2 diabetics than in non diabetic individuals [7]. Data from cross-sectional studies support association of elevated serum calcium levels with FPG, insulin secretion and IR in men with type 2 diabetes [8] or in both sexes as well [9]. Being related to insulin sensitivity, serum calcium might also be associated with the individual components of metabolic syndrome, such as dyslipidemia [10].

In this study our objective was to find if there is any association among serum Ca²⁺, fasting plasma glucose (FPG) and lipid profile in patients suffering from type 2 diabetes mellitus.

MATERIALS AND METHODS
Subject selection
It was a randomized hospital based case-control study involving total 120 research participants (60 newly diagnosed type 2 diabetic cases; 60 healthy controls), aged between 18 to 75 years, irrespective of sex who visited the college of medicine and J.N.M hospital, biochemistry department Kalyani. The study was conducted after receiving permission from

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Institutional ethics committee (No. F-24/PR/COMJNMH/IEC/17/1077). Details of the study including its benefits and risks had been explained to the patient and written consent obtained before their participation. Presence of diabetes mellitus was determined by FPG ≥ 126mg/dl & glycated haemoglobin (HbA1c) ≥ 6.5%. Follow up cases of type 2 DM, patients with known hypertension or pre-existing renal disease (determined by urinary albumin: creatinine ratio), pregnant mothers, patients with any other pathology that can influence study results, patients receiving treatment for any other concurrent disease with type 2 DM were excluded from the study.

Methods
12 hrs FPG and lipid profile were measured from venous blood samples by conventional lab methods using biochemical kits. Serum Ca\(^{2+}\) was measured by ion selective electrodes method. Participants presented with hypoalbuminemia (albumin <4 g/dL), albumin-adjusted serum Ca\(^{2+}\) was calculated using the formula: albumin-adjusted serum Ca\(^{2+}\) (mg/dL) = serum Ca\(^{2+}\) (mg/dL) + [0.8 × (4 − albumin [g/dL])]) [11,12].

STATISTICAL ANALYSIS
All statistical calculations were performed by Statistical Package for Social Sciences (SPSS) version 17 using bivariate correlation tests of one way analysis of variance (ANOVA). Significance of mean difference between cases and controls were determined using Student’s ‘t’ test. Obtained results were expressed as mean ± SE (standard error of mean). A ‘p’ value < 0.05 was considered significant.

RESULTS
Analysis of the obtained results from the study suggested significantly higher mean serum Ca\(^{2+}\) (p< 0.005) among cases when compared to control group. Mean FPG (p< 0.001) and Lipid profile parameters were also found significantly higher among the cases including Total cholesterol (p< 0.005), Triacyl glycerol (TAG) (p< 0.05) and VLDL cholestrol (VLDLc) (p< 0.05) and LDL cholesterol (LDLc) (p<0.001) while HDL cholesterol (HDLc) was significantly lower (p< 0.005) (Table – 1). Serum Ca\(^{2+}\) also found to have significant positive correlation with FPG among the patients (r = 0.448, p< 0.001). Moreover Pearson’s correlation found that serum Ca\(^{2+}\) has weak but positive & significant correlations with lipid profile parameters like Total cholesterol (r= 0.28, p< 0.005), TAG (r= 0.2, p< 0.05), LDLc (r= 0.28, p< 0.005), VLDLc (r= 0.2, p< 0.05), respectively. However HDLc showed no significant correlation with serum Ca\(^{2+}\) level (Table – 2).

Table 1: Comparison of FPG, HbA1c, Serum Ca\(^{2+}\), and Lipid profile parameters among healthy controls & type 2 diabetes mellitus cases (means ± SE)[Values are expressed as mean ± SE (n=60)]

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normoglycemic controls (n = 60) Mean± SE of means</th>
<th>Type 2 DM cases (n=60) Mean± SE of means</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG (mg/dL)</td>
<td>89.53 ± 1.29</td>
<td>178.25 ± 6.91*</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>4.94 ± 0.07</td>
<td>9.24 ± 0.31c</td>
</tr>
<tr>
<td>Serum Ca(^{2+}) (mg/dL)</td>
<td>8.97 ± 0.11</td>
<td>9.44 ± 0.11b</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>175.10 ± 4.03</td>
<td>202.90 ± 7.04b</td>
</tr>
<tr>
<td>TAG (mg/dL)</td>
<td>164.07 ± 9.26</td>
<td>192.73 ± 7.8c</td>
</tr>
<tr>
<td>HDLc (mg/dL)</td>
<td>50.63 ± 1.25</td>
<td>44.88 ± 1.51b</td>
</tr>
<tr>
<td>LDLc (mg/dL)</td>
<td>91.93 ± 3.25</td>
<td>119.47 ± 6.49a</td>
</tr>
<tr>
<td>VLDLc (mg/dL)</td>
<td>32.85 ± 1.85</td>
<td>38.55 ± 1.55c</td>
</tr>
</tbody>
</table>

p values: a < 0.001, b < 0.005, c < 0.05 compared to healthy controls

Table 2: Correlation coefficients of FPG and lipid profile parameters with serum Ca\(^{2+}\) among type 2 diabetes mellitus cases [(n=60)]

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Type 2 DM cases (n=60) Correlation coefficients with serum Ca(^{2+}) (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG (mg/dL)</td>
<td>0.448 *</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>0.300 *</td>
</tr>
<tr>
<td>TAG (mg/dL)</td>
<td>0.280 *</td>
</tr>
<tr>
<td>LDLc (mg/dL)</td>
<td>0.297 *</td>
</tr>
<tr>
<td>VLDLc (mg/dL)</td>
<td>0.282 *</td>
</tr>
</tbody>
</table>

p values: a < 0.001, c < 0.05

DISCUSSION
It has already been demonstrated that insulin secretion is a calcium-dependent process [13] and release of secretory granules containing insulin from pancreatic β-cells depends on the level of Ca\(^{2+}\) influx through voltage-gated calcium channels on cell membrane [14]. Thus Ca\(^{2+}\) is associated with blood glucose homeostasis and any alteration in serum Ca\(^{2+}\)
concentration may be responsible for defect in insulin secretion [15]. In fact, Homeostasis model assessment of β-cell function has been found negatively associated with total serum Ca\(^{2+}\) levels [9,15]. Prolonged high Ca\(^{2+}\) concentrations could induce a decrease in insulin secretion from pancreatic β-cells [15]. GLUT4 expression is regulated by calcium in a time and dose dependent manner and persistent exposure to elevated cytosolic calcium concentration decreases AMPK-induced GLUT4 expression in skeletal muscle [16]. Further, increased intracellular calcium level has been shown to decrease the effect of insulin in adipocytes not only by reducing the numbers of GLUT4 but also by decreasing insulin receptor activity [15]. Thus, increased calcium levels can reduce GLUT4 transporter expression and decrease glucose uptake which is responsible for hyperglycemia. The situation is further worsened by decreased insulin receptor activity.

Dyslipidemia in type 2 diabetes is triggered by insulin deficiency and IR [17]. The most common type of dyslipidemia in diabetes are hypertriglyceridemia, low HDL cholesterol concentration and increased concentration of small dense LDL-cholesterol particles [18]. Increased flow of substrates in the form of glucose and fatty acids and reduced clearance of VLDL among type 2 diabetics are responsible for increased VLDL concentration. Apolipoproteins play an important role for dyslipidemia in these patients. The extent of overproduction of VLDL triglyceride is greater than the scavenging ability of apoB in type 2 diabetics and consequently production of larger triglyceride-rich VLDL particles. Thus, altered VLDL and apoB ratio is an important factor [19] and this alteration results from impaired action of insulin [20]. Diabetics also have suppressed activity of the enzyme lipoprotein lipase (LpL) that is required for clearance of about 90% of the triacylglycerol from chylomicrons. Finally, these patients also have decreased number of LDL receptors [21]. All these factors are associated with increased VLDL and LDL concentration that results in hypertriglyceridemia and / hypercholesterolemia, among diabetic patients. Hypothesis has been made about link between serum calcium and metabolic syndrome, IR and dyslipidemia [22]. Elevated intracellular calcium inhibits mitochondrial oxidation, ATP production and may also induce IR, responsible for lipid metabolism abnormality and hyperlipidemia [23-25]. In vitro calcium supplementation increases serum cholesterol [26] by decreasing the activity of the 7α hydroxylase (CYP7A) enzyme responsible for cholesterol catabolism and also by stimulation of Sterol Regulatory Element Binding Protein (SREBP)1c expression that is an important transcription factor involved in de novo lipid synthesis [27].

Present study clearly shows positive and significant correlation between serum calcium and lipid profile parameters except HDLc which has been supported by earlier research works [28,29,30]. Persistent exposure of cells (including beta cells of pancreas) to hypercalcemic environment worsens their GLUT expression as well as resistance to insulin in the long run which further negatively effects the disease status. The condition continues to be deteriorated as persistent hypercalcemia also worsens the lipid profile among them.

**CONCLUSION**

Our study suggests that serum calcium level is significantly associated with both plasma glucose level as well as with dyslipidemia among type 2 diabetic patients. Further study with larger population in future can be helpful to establish more concrete conclusion or interpretation regarding the research work.

**REFERENCES**