Scholars Journal of Applied Medical Sciences (SJAMS)
Abbreviated Key Title: Sch. J. App. Med. Sci.
©Scholars Academic and Scientific Publisher
A Unit of Scholars Academic and Scientific Society, India
www.saspublishers.com

ISSN 2320-6691 (Online)
ISSN 2347-954X (Print)

Biochemistry

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

Tanmay Saha[1], Satyajit Koley[1*], Moumita Mondal[2], Subir Kumar Das[2]
[1]Department of Biochemistry, College of Medicine & JNM Hospital, WBUHS, Kalyani, India
[2]Department of Biochemistry & Biophysics, University of Kalyani, India

Original Research Article

***Corresponding author**
Satyajit Koley

Article History
Received: 03.01.2018
Accepted: 13.01.2018
Published: 30.01.2018

DOI:
10.36347/sjams.2018.v06i01.020

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 (Ca^{2+}) 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 Ca^{2+} 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 Ca^{2+} ($p< 0.005$) 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 Ca^{2+} 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 glucagone, epinephrine [4].

Ca^{2+} 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 Ca^{2+}, 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

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 Ca2+ (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 cholesterol (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)]

Parameters	Normoglycemic controls (*n* = 60) Mean± SE of means	Type 2 DM cases (*n*=60) Mean± SE of means
FPG (mg/dL	89.53 ± 1.29	178.25 ± 6.91[a]
HbA1c (%)	4.94 ± 0.07	9.24 ± 0.31[c]
Serum Ca^{2+} (mg/dL)	8.97 ± 0.11	9.44 ± 0.11[b]
Total Cholesterol (mg/dL)	175.10 ± 4.03	202.90 ± 7.04[b]
TAG (mg/dL)	164.07 ± 9.26	192.73 ± 7.78[c]
HDLc (mg/dL)	50.63 ± 1.25	44.88 ± 1.51[b]
LDLc (mg/dL)	91.93 ± 3.25	119.47 ± 6.49[a]
VLDLc (mg/dL)	32.85 ± 1.85	38.55 ± 1.55[c]

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)]

Parameters	Type 2 DM cases (*n*=60) Correlation coefficients with serum Ca^{2+}(*r*)
FPG (mg/dL	0.448 [a]
Total Cholesterol (mg/dL)	0.300 [c]
TAG (mg/dL)	0.280 [c]
LDLc (mg/dL)	0.297 [c]
VLDLc (mg/dL)	0.282 [c]

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

1. Petersen KF, Shulman Gl. Etiology of insulin resistance. Am J Med. 2006; 119(5 Suppl 1): S10-S16.
2. Pia V Roder, Bingbing Wu, Yixian Liu, Weiping Han. Pancreatic regulation of glucose homeostasis. Exp Mol Med. 2016; 48(3): e219
3. Philipp Mergenthaler, Ute Lindauer, Gerald A. Dienel, and Andreas Meisel. Sugar for the brain: the role of glucose in physiological and pathological brain function. Trends Neurosci. 2013; 36(10): 587–97.
4. Freychet L, Rizkalla SW, Desplanque N, Basdevant A, Zirinis P, Tchobroutsky G, Slama G. Effect of intranasal glucagon on blood glucose levels in healthy subjects and hypoglycaemic patients with insulin-dependent diabetes. Lancet 1988; 1: 1364–66.
5. Peacock M. Calcium metabolism in health and disease. Clin J Am Soc Nephrol. 2010; 5 (Suppl.1): S23–S30.
6. Rajan AS, Aguilar-Bryan L, Nelson DA, Yaney GC, Hsu WH, Kunze DL, Boyd AE. Ion channels and insulin secretion. Diabetes Care. 1990; 13(3): 340-63.
7. Levy J, Stern Z, Gutman A, Naparstek Y, Gavin JR 3rd, Avioli LV. Plasma calcium and phosphate levels in an adult noninsulin-dependent diabetic population. Calcif Tissue Int. 1986; 39: 316–18.
8. Yamaguchi T, Kanazawa I, Takaoka S, Sugimoto T. Serum calcium is positively correlated with FPG and IR, independent of parathyroid hormone, in male patients with type 2 diabetes mellitus. Metabolism. 2011; 60: 1334–39.
9. Sun G, Vasdev S, Martin GR, Gadag V, Zhang H. Altered calcium homeostasis is correlated with abnormalities of fasting serum glucose, IR, and beta-cell function in the Newfoundland population. Diabetes. 2005; 54: 3336–39.
10. Haglin L, Tornkvist B & Backman L. Prediction of all-cause mortality in a patient population with hypertension and type 2 DM by using traditional risk factors and serum phosphate, -calcium and -magnesium. Acta Diabetologica. 2007; 44: 138–43.

11. Walker MD, Dempster DW, McMahon DJ, Udesky J, Shane E, Bilezikian JP, Silverberg SJ. Effect of renal function on skeletal health in primary hyperparathyroidism. J Clin Endocrinol Metab. 2012; 97: 1501–07.
12. Bushinsky DA, Monk RD. Electrolyte quintet: calcium. Lancet 1998; 352: 306–11.
13. Mears D. Regulation of insulin secretion in islets of Langerhans by Ca(2+) channels. J Membr Biol. 2004; 200: 57–66.
14. Jing X, Li D-Q, Olofsson CS. CaV2.3 calcium channels control second-phase insulin release. J Clin Invest. 2005; 115: 146–54.
15. Becerra-Tomás N, Estruch R, Bulló M, Casas R, Díaz-López A, Basora J, Fitó M, Serra-Majem L, Salas-Salvadó J. Increased Serum Calcium Levels and Risk of Type 2 Diabetes in Individuals at High Cardiovascular Risk. Diabetes Care. 2014; 37: 3084–91
16. Park S, Scheffler TL, Gunawan AM, Shi H, Zeng C, Hannon KM, Grant AL, Gerrard DE. Chronic elevated calcium blocks AMPK-induced GLUT-4 expression in skeletal muscle. Am J Physiol. 2009; 296: C106–C115.
17. Kruass RM. Lipids and lipoproteins in patients with type 2 diabetes. Diabetes Care. 2004; 27: 1496-1504.
18. Mooradian AD. Dyslipidemia in type 2 diabetes mellitus. Nat Clin Pract Endocrinol Metab. 2009; 5(3): 150-59.
19. Howard BV, Howard WJ. Pathophysiology and Treatment of Lipid Disorders in Diabetes. In: C. Ronald Khan, Gordon C. Weir, George L. King, Alan M. Jackobson, Alan C. Moses, Robert J. Smith eds. Joslin's Diabetes Mellitus. Noida: Gopson Papers Ltd. 2005:568.
20. Howard BV, Abbott WG, Beltz WF, Harper IT, Fields RM, Grundy SM, Taskinen MR. Integrated study of low density lipoprotein metabolism and very low density lipoprotein metabolism in non-insulin-dependent diabetes. Metabolism. 1987; 36: 870-77.
21. Duvillard L, Florentin E, Lizard G, Petit JM, Galland F, Monier S, Gambert P, Vergès B. Cell surface expression of LDL receptor is decreased in type 2 diabetic patients and is normalized by insulin therapy. Diabetes Care. 2003; 26(5): 1540-44.
22. Luigia Gallo, Maria C. Faniello, Giovanni Canino, Cesare Tripolino, Agostino Gnasso, Giovanni Cuda, Francesco S. Costanzo, and Concetta Irace. Serum Calcium Increase Correlates With Worsening of Lipid Profile. Medicine (Baltimore). 2016; 95(8): e2774.
23. Gadallah MF, el-Shahawy M, Andrews G, Ibrahim M, Ramdeen G, Hanna D, Gorospe W, Morkos A, Abbassian M, Moles K. Factors modulating cytosolic calcium. Role in lipid metabolism and cardiovascular morbidity and mortality in peritoneal dialysis patients. Adv perit Dial. 2001; 17: 29-36.
24. Querfeld U, Hoffmann MM, Klaus G, Eifinger F, Ackerschott M, Michalk D, Kern PA. Antagonistic effects of vitamin D and parathyroid hormone on lipoprotein lipase in cultured adipocytes. J Am SOC Nephrol. 1999; 10: 2158-64.
25. Deighan CJ, Caslake MJ, McConnell M, Boulton-Jones JM, Packard CJ. Atherogenic lipoprotein phenotype in end stage renal failure: origin and extent of small dense low – density lipoprotein formation. Am J Kidney Dis. 2000; 35: 852-62.
26. Li S, Li Y, Ning H, Na L, Niu Y, Wang M, Feng R, Liu L, Guo F, Hou S, Chu X, Wang Y, Zhang Y, Zhang H, Huang L, Bi M, Huang Y, Hao L, Zhao Y, Wang C, Wang Y, He Y, Sun C. Calcium supplementation increases circulating cholesterol by reducing its catabolism via GPER and TRPC1dependent pathway in estrogen deficient women. Intern J Cardiol. 2013; 168: 2548–60.
27. Revankar CM, Cimino DF, Sklar LA, Arterburn JB, Prossnitz ER. A transmembrane intracellular estrogen receptor mediates rapid cell signaling. Science 2005; 307: 1625–30.
28. Emokpae MA, Uadia PO. Serum calcium level is associated with lipids in young Nigerian women using low-dose oral contraceptive pills. J Basic Clin Reprod Sci. 2014; 3(2):105-10.
29. Prabha AGT. Evaluation of serum calcium and lipid profile in premenopausal women. Ejpmr. 2017; 4(3): 260-62.
30. Farhangi MA, Ostadrahimi A, Mahboob S. Serum calcium, magnesium, phosphorous and lipid profile in healthy Iranian premenopausal women. Biochem Med (Zagreb). 2011; 21(3): 312-20.