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A cross-sectional study correlating serum calcium levels and the state of control of Type 2 Diabetes Mellitus

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Calcium plays a major role in secreting insulin in our body other than its various other function, the correlation of calcium and Type 2 Diabetes mellitus is a concept that needed much more justification and evident scientific proofs. This research aimed to study the association of serum calcium levels with Type 2 Diabetes Mellitus. **Methodology:** A total of 351 patients were included in this study which included both newly diagnosed cases of Type 2 Diabetes Mellitus and already known cases of Type 2 Diabetes Mellitus. The study parameters- Fasting blood glucose, post-prandial blood glucose, HbA1C score and Serum Calcium Levels were analysed. **Results:** The Fasting blood glucose levels and post-prandial blood glucose levels of known cases of Type 2 Diabetes Mellitus were 160.89 ± 22.60 mg/dL and 194.33 ± 22.70 mg/dL and that of newly diagnosed cases were 137.90 ± 4.21 mg/dL and 171.48 ± 4.59 mg/dL respectively. The HbA1C score in newly diagnosed cases was 7.20 ± 0.30 and that of known case was 8.90 ± 1.04. The Serum Calcium levels of the newly diagnosed cases was 8.87 ± 0.26 mg/dL and 7.36 ± 0.64 mg/dL for the already known cases. **Conclusion:** Changes in serum calcium levels are associated with the risk of T2DM in an Indian population. Thereby the patients with T2DM have to be supplemented with calcium which would help in progression of the disease furthermore.

Keywords: Type 2 Diabetes Mellitus, Serum Calcium Levels, Incidence of Diabetes, Level of control of Diabetes

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Introduction

Type 2 Diabetes Mellitus is a major metabolic disorder characterized by hyperglycaemia and it is associated with an increased risk of multiple chronic conditions. (1,2) Type 2 Diabetes Mellitus has been recognized as a leading cause of morbidity and mortality in the world. [1,3]

Calcium is an essential mineral, exerts a wide range of biological functions, including bone and tooth mineralization, blood coagulation, muscle contraction, nerve impulse transmission and cellular signalling transduction [3–7]. Additionally, it plays an important role in insulin secretion and glucose homeostasis [4,8,9]. Glucose-dependent insulin secretion is a calcium-regulated process as it depends on intracellular concentration of calcium in pancreatic β-cells [8,10]. Conversely, altered calcium homeostasis could potentially be involved with defects in insulin action and disorders in glucose homeostasis which contributes to the development of Type 2 Diabetes Mellitus [4,8,9,11,12]

Among the factors controlling the maintenance of normoglycemia under physiological conditions, the modulation of insulin release from the pancreatic islets play a central role. The regulation of the rate of insulin release is the result of an interplay between substrates and hormones reaching the islets via the circulation and direct neural influences via the autonomic nerve fibres ending in the pancreatic islets [13]. Alterations in the sensitivity of the p-cells to glucose, as well as in the dynamics of glucose-stimulated insulin release, lead to derangements of glucose homeostasis ranging from subclinical diabetes to overt forms of the disease. Calcium ions play a regulatory role in many cellular events [14, 15].

The role of calcium in secretion was first demonstrated for the release of epinephrine from the adrenal medulla [16]. By analogy with excitation-contraction coupling in muscle cells, an increase in the concentration of ionized calcium in a critical compartment of the cytosol is thought to lead to exocytosis. [17-19]. Accordingly, the secretory stimulus is recognized by the cell, signals are generated that couple the stimulus to the effector system, and the activation of the effector system leads to exocytosis and the release of proteins or peptides stored in secretory Granules. Although several steps in the chain of events resulting in exocytosis are still not understood, interactions between cyclic AMP, proposed as the second messenger of the action of certain hormones, and calcium have been emphasized [20-22].

This study is concerned with the involvement of calcium in the physiological stimulation of insulin release by glucose, cyclic AMP, and other agents and the inhibition of insulin release by epinephrine and somatostatin. [21-25]. Hence, this study will be useful in identifying the association of calcium and diabetic control in Type 2 Diabetes Mellitus patients.

This study aims to establish the association between serum calcium levels and blood glucose levels in type 2 diabetes mellitus patients.

Methodology

The study was conducted in the Departments of Medicine and Community Medicine, NCD clinic , Government Villupuram Medical College and Hospital in the year 2019. The Institutional Ethics Committee approval was obtained from Government Villupuram Medical College and Hospital.

This is a cross-sectional study that included 351 participants based on the inclusion and exclusion criteria. The inclusion criteria were adult patients aged between 18 and 60 of either sex diagnosed with type 2 Diabetes Mellitus. Patients with conditions that may alter the calcium metabolism such as patients with calcium supplementation, patients with bone disorders, patients with psoriasis and other systemic illness were excluded from the study. After getting the consent from the patient, their anthropometry parameters were recorded. A 5 ml venous blood sample was collected from them and the biochemical parameters were analysed and recorded. The recorded data was statistically analysed using SPSS 26 version.

Results

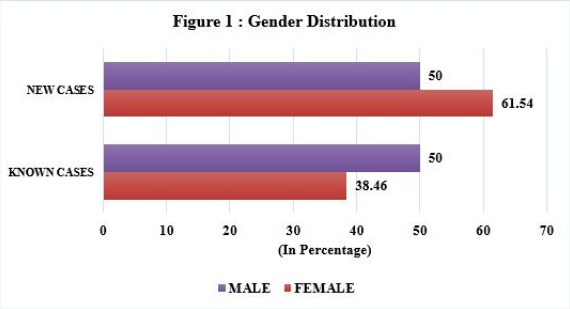
The study comprises of 192 newly diagnosed Type 2 Diabetes Mellitus cases and 159 already known case of Type 2 Diabetes Mellitus participants, a total of 351 participants were included in this study. The gender distribution of the population is tabulated in Table 1 and represented in Figure 1. The various study observed study parameters are enlisted in the Table 2.

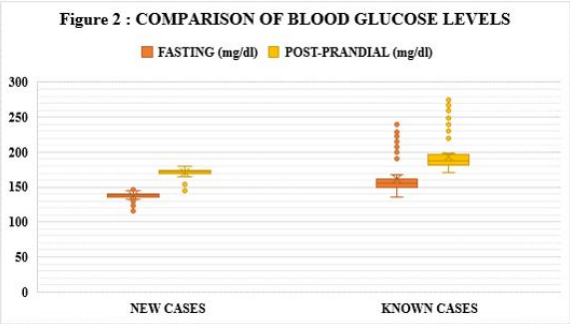
The Fasting blood glucose level in Known cases was 160.89 ± 22.60 mg/dl and that of the newly diagnosed was 137.90 ± 4.21 mg/dl. The Post prandial blood glucose levels were 194.33 ± 22.70 mg/dl and 171.48 ± 4.59 mg/dl for known cases and newly diagnosed cases respectively and their comparison is depicted in Figure 2.

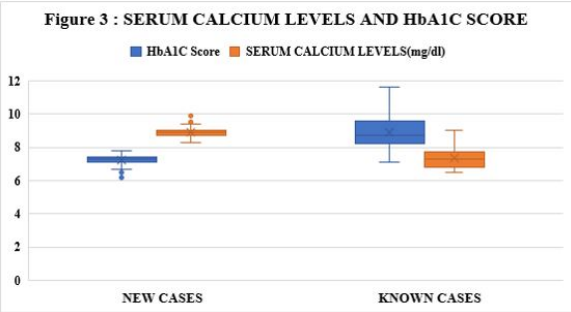
The HbA1C levels which is used as a marker for the level of control of diabetes in our study is observed to be 8.90 ± 1.04 in known cases and 7.20 ± 0.30 for the newly diagnosed cases. The serum calcium level of the known cases was found to be 7.36 ± 0.64 mg/dl and that of new cases was 8.87 ± 0.26 mg/dl. The serum calcium levels and HbA1c score are shown in Figure 3. The relation between the serum calcium levels and HbA1C score is tabulated in Table 3 and depicted in Figure 4. The Body Mass Index (BMI), Fasting blood glucose levels, post-prandial blood glucose levels, HbA1C score and Serum Calcium levels were statistically significant with p value less than 0.05.

Table 1: showing the Gender distribution

Gender	Known Cases	New Cases	Total
Female	55	88	143
	38.46%	61.54%	100%
Male	104	104	208
	50%	50%	100%
Total	159	192	351
	45.30%	54.70%	100%







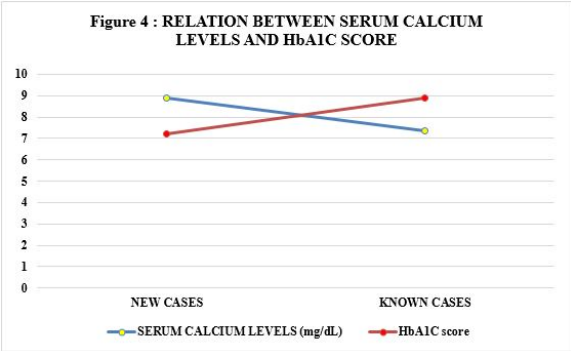


Table 2: showing the values of Study Parameters in Known cases and New Cases

S. No	Study Parameters	Values (Mean ± S.D)		P Value
		Known Cases	New Cases	
1	Age	45.98 ± 11.45	45.41 ± 10.90	0.63
2	Bmi	23.75 ± 2.10	25.03 ± 3.14	0*
3	Serum Urea	24.163 ± 9.02	24.26 ± 9.43	0.92
4	Serum Creatinine	0.866 ± 0.29	0.83 ± 0.29	0.39
5	Serum Total Bilirubin	0.55 ± 0.46	0.55 ± 0.52	0.89
6	Serum Direct Bilirubin	0.16 ± 0.15	0.164 ± 0.16	0.99
7	Serum Indirect Bilirubin	0.387 ± 0.35	0.394 ± 0.392	0.85
8	SGOT	36.06 ± 19.40	36.29 ± 18.93	0.90
9	SGPT	23.44 ± 12.59	23.84 ± 12.57	0.76
10	Serum Total Protein	7.28 ± 1.07	7.22 ± 1.00	0.55
11	Serum Albumin	3.57 ± 0.80	3.57 ± 0.77	0.97
12	Serum Globulin	3.71 ± 1.19	3.64 ± 1.12	0.50
13	A: G Ratio	1.21 ± 1.04	1.21 ± 1.01	0.90
14	Fasting Blood Glucose	160.89 ± 22.60	137.90 ± 4.21	0*
15	Post Prandial Blood Glucose	194.33 ± 22.70	171.48 ± 4.59	0*
16	Hba1c	8.90 ± 1.04	7.20 ± 0.30	0*
17	Serum Calcium	7.36 ± 0.64	8.87 ± 0.26	0*

*P value of less than 0.05 is considered to be statistically significant

Table 3: showing the relation between Serum Calcium levels and HbA1C score

Study Parameters	Known Cases	New Cases	P Value	R Value
Hba1c SCORE	8.90 ± 1.04	7.20 ± 0.30	0	-0.9326
Serum Calcium Levels (Mg/dl)	7.36 ± 0.64	8.87 ± 0.26	0	

Discussion

The present study is on the association between serum calcium concentrations and the development of diabetes. In our study, serum calcium level changes were positively correlated with changes in Plasma Glucose levels.

Western cohort studies have universally demonstrated that elevated serum calcium levels are associated with a greater risk of T2DM [13-17]. In a recent meta-analysis also showed that elevated serum calcium levels were associated with incident diabetes [24]. The continuum of diabetes risk is currently being emphasized, even for those within the accepted normal range of glycaemic levels, and it has been suggested that higher FPG and HbA1c levels within the presently-defined normal range may be independent risk factors for T2DM [25].

Given the positive correlation that has been reported between serum calcium and serum glucose levels [7,10,11], baseline glycaemic status could be a confounder when the longitudinal association between baseline serum calcium levels and diabetes development is assessed. However, the Tromsø Study [13] and the Atherosclerosis Risk in Communities (ARIC) study [17] did not include FPG as a covariate in their regression analysis. Also, the results of the Insulin Resistance Atherosclerosis Study (IRAS) were not adjusted for baseline HbA1c [14].

However, the association between serum calcium level changes and incidence of diabetes remained significant in this study, suggesting that serum calcium changes, rather than baseline levels within the normal range, may be associated with the incidence of diabetes independently.

T2DM is characterized by insulin resistance and impaired insulin secretion [26]. Insulin secretion is a calcium-dependent process [27], so alterations in calcium flux can adversely affect β-cell secretory function [28]. Calcium is essential for insulin-mediated intracellular processes in insulin-responsive tissues such as skeletal muscle and adipose tissue, and calcium is needed for optimal insulin-mediated functioning [5]. As insulin plays an important role in the regulation of blood glucose, the adverse effects of altered calcium flux on β-cell secretory function could increase the risk of diabetes development [29].

Moreover, Levy et al [30] suggested that cellular calcium levels may be associated with glucose metabolism, proposing that abnormal cellular calcium levels impair glucose tolerance and poor glucose tolerance alters cellular calcium levels. As such, abnormal calcium concentrations could promote the development of diabetes. In support of this hypothesis, one recent study demonstrated that serum calcium levels could independently predict β-cell function [31].

Previous studies have indicated that serum calcium levels correlate positively with insulin resistance [10,11]. Calcium can also modulate insulin sensitivity by other mechanisms. Changes in ionized calcium levels in primary insulin target tissues may contribute to peripheral insulin resistance by impairing insulin signal transduction, thereby impairing glucose transporter-4 (GLUT4) activity [5]. Skeletal muscle is considered to be the major organ responsible for glucose uptake under insulin-stimulated conditions [32], and is a major site of insulin resistance [33].

Calcium plays a critical role in muscle contractions and muscle-cell glucose uptake after insulin binding. Furthermore, calcium influences the insulin affinity and sensitivity of the insulin receptor [34]. The critical role of calcium in insulin secretion and resistance suggests that changes in serum calcium concentrations could be associated with an increased risk of T2DM. Unfortunately, in our study, plasma insulin measurements were not available for most of the population, so the association between serum calcium levels and insulin resistance or secretion could not be explored. While this study revealed that changes in calcium levels were significantly associated with the risk of developing diabetes, further research is needed to define the precise role, if any, that calcium plays in the pathogenesis of diabetes.

However, our study had several limitations that should be considered for results interpretation. First, all study subjects were enrolled in the non-communicable diseases outpatient department of our hospital, and the study was conducted at single centre, so the results may not represent the entire population of the country. Second, we did not have data on vitamin D and parathyroid hormone levels. The concentrations of these hormones have been associated with metabolic disorders such as diabetes in several studies [12,35].

Vitamin D and parathyroid hormone work in concert to maintain calcium homeostasis. Thus, the measurement of these hormones could elucidate the association between serum calcium levels and diabetes risk observed in our study.

However, randomized clinical trials have not got any consistent results on the association between vitamin D levels and T2DM risk [24]. Lastly, ionized calcium should be used as it is regarded as the best measure of calcium homeostasis [36], but it was not measured for this study. Instead, we used serum calcium levels for the analysis.

Conclusion

In conclusion, our results suggest that changes in serum calcium levels are associated with the risk of T2DM in an Indian population. Future studies are needed to define the clinical role of calcium and to assess calcium modulation as a potential intervention for the prevention and management of T2DM. Such studies will have significant public health implications, and these interventions could be implemented easily and inexpensively in clinical practice.

Author's contribution: Harissh Ganesan: Designed the work plan, write up and collected data, Dr.Saravanakumari Arumugham Dhanaraj - Statistical Analysis and proof read the article, Aishwarya T N – collected data

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