Original Article

The Relation of Serum Calcium and FBS with Vitamin D Deficiency among Type 2 Diabetic Patients

** Begum N,[1] Naahin SJ,[2] Biswas P,[3] Pinki SB[4]*

ABSTRACT

Background: Diabetes mellitus, especially Type 2, is a primary endocrine disorder that has become highly prevalent because of unhealthy food habits and sedentary lifestyle-related factors, and nowadays people of all ages all over Bangladesh report suffering from vitamin D deficiency despite having adequate sunshine at this latitude. Worldwide, the number of people who have diabetes is expected to more than double, from 171 million to 366 million people, by 2030, among them 90% with T2DM. **Objective:** To determine the relationship between Serum Calcium and Fasting Blood Sugar in Deficient Type 2 Diabetic patients. **Material and Methods:** A randomized, placebo-controlled interventional study was conducted with 44 diagnosed Diabetic patients (22 in the treatment group and 22 in the placebo group) who were on oral hypoglycemic agents, aged 30 to 70 years, enrolled between 1st October 2022 and 1st March 2023. Data collection has been done from Zainul Haque Sikder Women's College & Hospital. The study population was selected into treatment and placebo groups through a proper randomization procedure(SRS). The treatment group received 20,000 IU cholecalciferol weekly, and the placebo group received a placebo (Microcrystalline Cellulose BP), which was supplemented simultaneously with the treatment group for 3 months. Biochemical parameters (vitamin D, calcium, and FBS) were measured at baseline and after intervention. The Ethical Committee of the Faculty of Biological Science, University of Dhaka, has approved the research protocol. **Results:** The study found significant improvement in vitamin D levels among the treatment group($p=0.000$) but no statistically significant difference in FBS or calcium levels between treatment and placebo groups after supplementation($p>0.05$). Baseline comparability between groups was reasonable (no significant differences in socio-demographics). **Conclusion:** A favorable effect was observed between Vitamin D-deficient Type 2 diabetic patients and glycemic control (in terms of reduction in fasting blood glucose) over a 3-month treatment period. However, these effects were not significantly different.

Keywords: Vitamin D deficiency, β-cell, Type 2 Diabetes

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Introduction

Calcium Intake and T2D

Among the electrolytes, calcium is essential for many critical biological functions. This may play a vital role in glucose homeostasis, as it regulates insulin-mediated intracellular signaling in insulin-responsive

Author's Affiliation

1. *Nadia Begum, Professor and Head Department of Community Medicine and Public Health, Zainul Haque Sikder Women's Medical College and Hospital.
2. Sabila Jahan Naahin, Lecturer, Department of Community Medicine and Public Health, Zainul Haque Sikder Women's Medical College and Hospital.
3. Prantik Biswas, Lecturer, Department of Community Medicine and Public Health, Zainul Haque Sikder Women's Medical College and Hospital.
4. Srabonti Bose Pinki , MBBS Final Year, Zainul Haque Sikder Women's Medical College and Hospital.

Address of Correspondence: *Prof. Dr. Nadia Begum, Professor and Head Department of Community Medicine and Public Health, Zainul Haque Sikder Women's Medical College and Hospital.

tissues, facilitates pancreatic beta-cell secretory function, and phosphorylates insulin receptors. Calcium also downregulates specific regulatory genes encoding pro-inflammatory cytokines involved in insulin resistance. Insulin secretion is a calcium-dependent process. It is vital for insulin-mediated intracellular processes in tissues that respond to insulin, such as skeletal muscle and adipose tissue. There is a minimum range of intracellular calcium concentrations needed for optimal insulin-mediated functions. An accurate range of intracellular calcium concentration is also necessary for some insulin-mediated activities in tissues such as the liver, adipose, and skeletal muscle. It is crucial to maintain a relatively low intracellular calcium level in these target tissues to have a positive effect on the insulin signal transduction cascade and insulin sensitivity peripherally. Additionally, low intracellular calcium attenuates cytokine-induced inflammation, inhibits platelet aggregation, and augments vascular relaxation. In the context of dairy intake and dairy products, it is necessary to keep in mind that calcium intake should be considered, which provides other important nutrients besides calcium. [1]

Optimal calcium intake is essential for bone mineralization and helps prevent osteoporosis and fractures among the elderly. However, the mean daily intake of calcium in the postmenopausal population is estimated to be less than 600 mg/d, and the recommended dietary allowance for this age group is 1200 mg/d together with vitamin D at 800 IU/d. The efficiency of calcium absorption determines the amount of calcium absorbed from the diet, and in a normal situation, a low calcium intake leads to higher absorption from the gut, whereas a high calcium intake leads to lower calcium absorption; this adaptive process first described by Nicolaysen *et al*, is now known to be regulated by 1,25(OH)2D. According to The Endocrine Society Guidelines, it was suggested that calcium absorption reached a threshold at a serum 25OHD level of 30 ng/ml. [2]

Calcium is essential for insulin-mediated intracellular processes. Intracellular calcium levels are tightly controlled within a narrow range to maintain insulin signaling. Secretion of parathyroid hormone due to calcium deficiency, which enhances calcium influx from extracellular fluid into intracellular compartments, resulting in impaired insulin sensitivity and cellular calcium overload. In epidemiological studies, calcium intake was positively associated with insulin sensitivity. Insulin regulation is also regulated by Vitamin D.[3]

Mechanism of vitamin D on β cells

Vitamin D is reported to be insulin-mimetic. It also reduced the long-term prevalence of type 2 diabetes (Yousefi et al., 2014).[4] It directly facilitates insulin secretion from pancreatic β cells by interacting with the 1.25(OH)2D3-RXR-vitamin D receptor complex, which increases insulin synthesis and decreases insulin resistance (when a large amount of insulin is needed to deposit a given amount of glucose). Secretion of insulin depends on a calcium-related process; indirectly, by altering calcium flux within β islet cells, it increases calcium concentration. Additionally, insulin sensitivity is regulated by vitamin D and calcium, which activate the peroxisome proliferator-activated receptor (PPAR) and induce insulin receptor expression.[5]

The major pathogenic mechanisms of T2DM are chronic inflammation and disorders of insulin action and secretion. Deficiency of vitamin D has been linked to an increased risk of diabetes, impaired glucose tolerance (IGT), and decreased risk of cardiovascular disease. Vitamin D receptor polymorphism was linked to the alteration of insulin secretion and sensitivity, indicating that 25-hydroxyvitamin D plays a role in both forms of diabetes etiology. Many intracellular insulin-mediated functions in target tissues, including muscle and adipose tissue, require Calcium to function correctly. For effective insulin action, an optimal intracellular calcium concentration is required. Peripheral insulin resistance can be caused by impaired insulin signaling, which is linked to lower glucose transporter function owing to changes in target tissues' intracellular calcium levels. Insulin sensitivity is influenced by the "1, 25(OH)2D, which regulates extracellular calcium concentration and flow across cell membranes"(Hashim Z. R).[6]

Material and Methods:

A randomized placebo-controlled interventional study was conducted with 44(22 cases, 22 controls) diabetic patients (Type 2) aged between 30 years and 70 years who were being treated with oral hypoglycemic agents between 1st October 2022 and 1st March 2023. At first, make a list of serial no of all the participants, then a simple random sampling technique has been applied through a lottery method, and the treatment and placebo groups have been finalized. Information was obtained through informed consent, using a pretested, semi-structured, interviewer-administered questionnaire during face-to-face interviews. The treatment

group supplemented with 20,000 IU cholecalciferol weekly, and the Placebo group received a placebo simultaneously for 3 months. According to the advice of the physician, patients were advised to continue their drugs, diet, and exercise, but they were asked to refrain from taking any other vitamins or minerals. Data were collected from Zainul Haque Sikder Women's College & Hospital. The study was overseen after ethical clearance was approved by the ethical review board of the Faculty of Biological Sciences.

Statistical Analysis:

Statistical methods were used respectively to measure the changes of biochemical indices across different time-points and to estimate the biochemical predictors of Vitamin D levels following (3-months) vitamin D supplementation.

Sample size estimation:

Sample size for clinical trial (comparing two means; Rashidi F et al., 2016) [7]

Formula: n = $\frac{(Z_{\propto/2} + Z_{\beta})^2 * 2(SD)^2}{D^2}$

Were,

n = sample size required in each arm/group

D=μt- μc= minimally significant difference between the treatment and placebo group

(*Yousefi Rad et al.*, 2014) [4]

μt= Mean change of A1C in treatment group

μc = Mean change of A1C in placebo/control group

SD= Standard deviation

Zα/2 =Level of significance is 1%

Zβ =Power of the Test is 90%

Specimens Collection and Preparation

In the morning, fasting venous blood specimens were collected from the subjects and were frozen at −70 °C until analysis. After venipuncture, approximately 5ml of venous blood was collected from each fasting participant for analysis using automated biochemistry devices for each biomarker, involving Vitamin D, FBS, and Calcium.

Biochemical Analysis

The enzymatic method with hexokinase was used to measure fasting blood sugar on the Cobas Integra 400 plus biochemistry Analyzer. To measure the serum concentration of Calcium, the calcium EDTA complex method was used on the Cobas Integra 400 plus biochemistry Analyzer.

Results:

Table 1: Socio-demographic profile of the Respondents(n=44)

Variables	Treatment (n=22)	Mean±SD	Placebo(n=22)	Significance Chi-Square, p-value
Age				
<40	7(31.8)		7(31.8)	43.31±10.31
40-50	8(36.4)	44.72±10.79	9(40.9)	
>50	7(31.8)		4(18.2)	
Education				
No education	9(40.9)		8(36.4)	1.909±.8111
Upto primary	7(31.8)	1.901±.921	8(36.4)	
Upto secondary	5(22.7)		6(27.3)	
Others	1(4.5)		00	
Occupation				
Service	7(31.8)		6(27.3)	2.86±1.67
Bussiness	00	3.136±1.807	6(27.3)	
Housewives	7(31.8)		2(9.1)	
Others	8(36.4)		8(36.4)	
Monthly Income(BDT)				
<20,000	6(27.3)		7(31.8)	1.86±.774
20,000-30,000	14(63.6)	1.81±.588	12(54.5)	
>30,000	2(9.1)		3(9.1)	

BMI(kg/m2)				
<25	10(45.5)	29.54±12.23	14(63.6)	24.64±2.16
>25	12(54.5)		8(36.4)	

Table 2: Difference of different parameters among treatment and placebo group

Vitamin D(ng/ml)	**Treatment(n=22)%**	**Mean±SD**	**Placebo(n=22)%**	**Mean±SD**	**p-value (between-group)**
Baseline:					
Severedeficient	00		00		
(<10ng/ml)	5(22.72)	12.80±3.40	3(13.63)	15.27±4.86	.058
Deficient (10-20ng/ml)	16(72.72)		15(68.18)		
Insufficient(21-29.9ng/ml)	1(4.54)		4(18.18)		
Sufficient ≥ 30ng/ml					
Endline:					
Severe deficient	00		00		.
(<10ng/ml)	00	38.70±7.30	20(90.90)	14.66±3.93	000
Deficient(10-20ng/ml)	1(4.54)		2(9.09)		
Insufficient(21-29.9ng/ml)	21(95.45)		00		
Sufficient ≥ 30ng/ml					
P –value(within group)	.000		.124		
FBS(mmol/l)					
Baseline					
<6.9	4(18.18)	10.31±4.00	3(13.63)	10.74±3.61	.712
6.9-13	14(63.63)		14(63.63)		
>13	4(18.18)		5(22.72)		
Endline					
<6.9	6(27.27)	10.13±3.17	1(4.54)	9.83±2.04	.751
6.9-13	11(50)		20(90.90)		
>13	5(22.72)		1(4.54)		
P –value(within group)	.753			.177	
Calcium(mg/dl)					
Baseline					
<8.6	4(18.18)		9(40.90)		
8.6-10.3	15(68.18)	9.42±1.15	12(54.54)	8.14±1.60	.004
>10.3	3(13.63)		1(4.54)		
Endline					
<8.6	3(13.63)		8(36.36)		
8.6-10.3	15(68.18)	9.49±0.870	14(63.63)	8.31±1.08	.000
>10.3	4(18.18)		00		
P –value(within group)	.791			.440	

Discussion

A low calcium intake can cause or aggravate vitamin D deficiency. In contrast, a high calcium intake can spare vitamin D. Clinical trials of vitamin D with or without calcium sometimes yield contradictory results. The effect size and significance regarding a decrease in fracture incidence depend on baseline calcium intake, baseline vitamin D status, calcium and vitamin D supplement doses, age, housing situation, and compliance. Meta-analyses on vitamin D for fracture prevention indicate that vitamin D and calcium combinedly are more effective than vitamin D alone. One should consider the interaction between calcium and vitamin D when prescribing vitamin D or calcium supplements.[8]

According to the American Endocrine Society

(Holick et al., 2011; Waterbury, 2018).[9,10] study showed strongly significant(P=.000) level of 25(OH)D3 from deficient (baseline: 14.033±3.970 ng/mL) to sufficient levels (end line 31.953±9.65 ng/mL). End line 25(OH)D levels were significantly higher in the treatment group as compared to placebo (treatment: 31.953 ±9.365ng/mL, p=0.000 and placebo: 19.543±10.617, p=0.026). A couple of studies also observed the same findings. [11,12,13]

The present study demonstrated a significant improvement in vitamin D status among T2DM patients, accompanied by a correction in FBG levels. However, end FBG levels were not significantly lower in the treatment group than in the placebo group (treatment: 11.020±4.465 mmol/l, p=.406; placebo: 11.428±6.432 mmol/l, p=0.808). Similar findings were also observed by Krul-Poel YHM (2017, December).[14] Opposite relation in several findings by Al-Zahrani M K et al., 2014; Haidari F, 2016, and Hu Z et al., 2019.[15-17.] The Study revealed that calcium levels increased in the treatment group (baseline: 9.554±1.609mg/dl vs. endpoint: 10.403±0.170mg/dl) compared with the placebo group (baseline: 8.574±2.061 mg/dl vs. endpoint: 9.817±1.435 mg/dl). Slight increment of serum calcium in the treatment group due to vitamin D supplementation was also observed by Thani et al. (2019).[10]

In the present study, vitamin D deficiency has been connected to an increased risk of elevated FBS and reduced calcium levels. According to Table 2, in individuals with Type 2 diabetes, Vitamin D levels were significantly lower compared to pre-diabetes and controls. Low vitamin D levels negatively affect the increase in FBS and calcium, as shown in Table 2. Another study by Hashim Z. R. (2022) found the same results. [5]

Conclusion:

Vitamin D deficiency has become a global concern. Vitamin D-deficient Type 2 diabetic patients showed a favorable effect on glycemic control (reduction in fasting blood glucose) over 3 months in the treatment group, but the difference was not significant. Although our country receives abundant sunlight, we have a significant number of cases of vitamin D deficiency. Exposure to sunlight is an effective way of enhancing vitamin D status. Additionally, encouraging people to consume dietary sources of vitamin D, such as eggs, can be beneficial.

Strength:

In selecting the treatment and placebo groups, unbiased randomization methods were used.

Limitation: 1. The sample size was too small.

2. Vitamin D estimation has been done twice at baseline and end line; however, vitamin D estimation between baseline and end line (1st follow-up) can make the results more precise.

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