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Assessing the Vitamin-D (Calciferol) Supplementation Impact on Glycemic Levels among Patients with Type-2 Diabetes (DM-2); A Quasi-Experimental Trial

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ABSTRACT

Objective: To determine the effect of Vitamin D (calciferol) on the control of blood glucose in patients with insufficient controlled DM-2.

Methodology: A Quasi-Experimental trial at the Department of Medicine, Fauji Foundation Hospital, Rawalpindi for 06 months was conducted after, meeting inclusion and exclusion criteria. 115 patients were enrolled and the effect of calciferol on levels of blood glucose was assessed by measuring HbA1c levels, and pre-& post calciferol supplementation.

Results: Results showed a mean of ages was 57.80 ± 7.64 years, 39(33.91%) patients were male and 76(66.09%) patients were females. On pre-intervention, the mean HbA1C of the patients who participated was 7.99 ± 0.48 while on post-intervention the mean HbA1C of the patients was 7.97 ± 0.48 (p-value=0.7523).

Conclusion: The effect of calciferol on glycemic control (measured in terms of mean reduction of ≥1 in HbA1c) in calciferol-deficient and insufficient diabetics was insignificant. Therefore, vitamin D supplementation appears to have no effect on blood glucose control in diabetes individuals who have low levels of calciferol—both inadequate and deficient—both of which are low.

Keywords: Calciferol (Vitamin-D), Levels of blood sugar, Poorly Controlled Type-2 Diabetes

Authors' Contribution:
[1,2]Conception; Literature research; manuscript design and drafting; [3,4]Critical analysis and manuscript review; [5,6]Data analysis; Manuscript Editing.

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Introduction

A chronic metabolic disorder called diabetes mellitus (DM) is characterized by persistently high blood glucose levels, the causative contributing factor could either be a rise in insulin resistance a decline in insulin production, or even both.[1] In the year 2015, 415 million cases of DM worldwide, according to the "International Diabetes Federation (IDF)".[2] In the entire world, diabetes mellitus (DM) is a public health concern and is one of the most commonly existing complicated diseases, Since 1980, the number of people affected by diabetes has nearly doubled (rising from 108 million people in 1980 to around 422 million people in 2014), especially the underdeveloped nations have experienced a more rapid increase Hence, implying an imminent need to reduce the disease burden by taking early preventive measures.[3]–Diabetes is a global pandemic, due to evolving lifestyles and an increase in obesity, diabetes incidence has increased internationally. In 2017, there were 425 million cases of diabetes worldwide. According to the

International Diabetes Federation in 2015, about 10% of Americans had diabetes, and seven million of them were undiagnosed, however, the likelihood of diabetes cases among aged people showed 25% compared to people less than the age of 65 years.[4]

In a long-term analysis, researchers found that advanced type 2 diabetes patients who had a median of 5.6 years of intensive glucose control, experienced a delayed cardiovascular benefit after almost 10 years of improved glucose control, but, no overall cardiovascular benefit was observed during the full 15+ years of follow-up. No significant improvement in hospitalization rates or quality of life was noticed in the long run other than a neutral, long-term effect on all-cause mortality, and a slight, long-term weight gain for the intensive-control group.[5]

A lot of research, over the last few decades, has been done to calculate the impact of attributable risk factors modification, including calciferol, as a preventive & therapeutic strategy to improve global health status.[6,7]

The conclusive evidence of a study carried out in Duhok has revealed an association of calciferol with Diabetes, as a high percentage (71%) of hypovitaminosis D was documented amongst the diabetics.[8] Short-term calciferol supplementation was found to have significantly reduced the HbA1c levels (SMD with 95% CI was −0.17 (−0.29, −0.05, $p<0.05$) as evaluated by a systematic review of 19 randomized control trials. Studies showed the effect of short-term calciferol administration (>2000IU/day) on blood sugar parameters among Asians, non-obese diabetics (SMD Fasting insulin = -1.80; 95%CI: -2.66~-0.95) and those with good baseline levels of blood sugar (WMDFBG = -4.09; 95%CI: -15.44~7.27).[9] While a study conducted over 6 month period including 140 subjects with mean HbA1c of 7.92 ± 1.54 before intervention and post-intervention HbA1c of 7.18 ± 1.53, has identified no significant effect of calciferol (400IU/day) on levels of blood sugar.[10] Hence, studies on the relationship between calciferol levels and blood sugar levels have not reached a consistent conclusion. Moreover, the optimal dosage & duration of calciferol supplementation has not been well established either.[11]

In 1983, the Diabetic Control and Complications Trial was launched to examine the therapeutic advantages of stringent blood sugar levels in reducing diabetes comorbidities.[12] Hence, the present study planned to gather data about the role of calciferol in glycemic control (measured in terms of mean reduction of ≥1 in HbA1c) using high-dose calciferol supplements (2000IU/day) among our local population. The results, if significant, will help improve our future management of DM effectively, simply by administration of calciferol supplements Current study aims to determine the effect of calciferol on levels of blood sugar (measured in terms of mean reduction of ≥1 in HbA1c) in calciferol deficient and insufficient diabetics, who have poorly controlled DM-2.

Methodology

A Quasi-Experimental Study was conducted at the Department of Medicine, Fauji Foundation Hospital, Rawalpindi Six (06) months after approval of synopsis i.e., 5-5-2022 to 5-11-2022 Sample size is determined by the WHO formula.[13] The level of confidence was 95% Absolute-Precision required: 0.3 Population Mean: 7.188 Population standard deviation: 1.538 Sample Size (n): 115 cases minimum8 Consecutive non-probability sampling was used to collect the samples, patients with diagnosed cases of DM with calciferol levels ≤30ng/ml & HbA1c > 7% & ≤ 9% of ages from 30 to 70 years of both genders were included for samples, however patients with chronic diseases interfering with calciferol metabolism (CKD, DCLD, hypo/hyperparathyroidism) and patients on drugs interfering with calciferol & calcium metabolism

were excluded from the study. The study was conducted after the approval of the synopsis from Fauji Foundation Hospital [Ref No. 507/RC/FFH/RWP]. All patients presenting to the Outpatient department, satisfying the inclusion and exclusion criterion, were educated and offered intervention for 3 months once an informed consent was taken. The identification of diabetics was as per operational definitions. The effect of calciferol on blood sugar levels was assessed by measuring HbA1c levels, and pre-& post calciferol supplementation. A sample of 5cc blood for calciferol and HbA1c levels was taken from all the patients on the same day in the hospital laboratory, once before offering the calciferol supplements and after 3 months of intervention. All the information was recorded in predesigned structured proforma. Later the Data was analyzed by SPSS version 23. Frequency and percentages were calculated for qualitative variables like gender, BMI category, and calciferol sufficiency status. For quantitative variables like age, BMI, pre-intervention calciferol levels, duration of diabetes, & HbA1c levels (pre-& post-intervention), values were described as mean and standard deviation. Data on the role of calciferol in blood sugar levels was further stratified for effect modifiers like age, gender, BMI, duration of diabetes, and calciferol status. For comparison of post-pre HbA1c levels, a paired sample t-test was applied *P*-value of ≤0.05 was considered significant

Results

In this study, a total of 115 patients showed a mean age of the patients was 57.80 ± 7.64 years the maximum number of patients was 42 years of age & minimum of 70 years respectively. According to this study, 39(33.91%) patients were male and 76(66.09%) patients were females however the male-to-female ratio was 0.5:1. The mean BMI was 26.16 ± 3.48 kg/m^2 with minimum and maximum BMI of 19 & 33 kg/m^2 respectively. There were 35 (30.43%) patients with normal BMI, 65 (56.5%) were overweight and 15 (13.0%) were obese. According to this study, the mean duration of DM was 9.26 ± 4.67 years with a minimum and maximum duration of 2 & 19 years respectively. In our study on pre-intervention, the mean calciferol level was 21.49 ± 6.21 mg/ml with Minimum and maximum values of 7 & 29 ng/ml respectively. Of 115 patients, 67 (58.3%) had calciferol insufficiency while 48 (41.7) had calciferol deficiency. On pre-intervention, the mean HbA1C was 7.99 ± 0.48, and post-intervention the mean HbA1C was 7.97 ± 0.48. A non-significant difference was observed in pre- and post-intervention whereas the value observed p-value=0.7523. In patients aged>60 years; on pre-intervention, the mean HbA1c value was 8.01 ± 0.52 and on post-intervention, the mean HbA1c value was 7.98 ± 0.52 (p-value=0.7714). In male patients; on pre-intervention, the mean HbA1c value was 7.94 ± 0.47 and on post-intervention, the mean HbA1c value was 7.92 ± 0.47 (p-value=0.8530). In female patients; on pre-intervention, the mean HbA1c value was 8.01 ± 0.48 and on post-intervention, the mean HbA1c value was 7.99 ± 0.48 (p-value=0.7679).

Table 01: Descriptive statistics and comparison of HbA1C levels pre-and post-intervention

Descriptive Statistics of Patients	Age in Years	BMI Kg/m^2	Comparison of Intervention HbA1C		p-value
			Pre-intervention	Post-intervention	
n	115	115	115	115	0.7523
Mean ± SD	57.80 ± 7.64	26.16 ± 3.48	7.99 ± 0.48	7.97 ± 0.48	
Minimum	42.00	19.00	7.10	7.10	
Maximum	70.00	33.00	8.90	8.90	

Table II: Comparison of HbA1C stratified by age groups, Gender & Duration of Disease						
Age Groups		**Intervention**	**N**	**HbA1C**		**p-value**
				Mean	**Standard Deviation**	
Gender	Male	Pre	39	7.94	0.47	0.8530
		Post	39	7.92	0.48	
	Female	Pre	76	8.01	0.48	0.7976
		Post	76	7.99	0.48	
Age group	≤ 60	Pre	64	7.97	0.44	0.7975
		Post	64	7.95	0.44	
	>60	Pre	51	8.01	0.52	0.7714
		Post	51	7.98	0.52	
Duration of DM (years)	≤ 10	Pre	75	8.09	0.52	0.7244
		Post	75	8.06	0.52	
	>10	Pre	40	7.82	0.33	0.6854
		Post	40	7.79	0.33	

Table no. III: Comparison of pre and post-intervention of HbA1C stratified by BMI (Kg/m^2)					
BMI (Kg/m^2)	**Intervention**	**HbA1C**			**p-value**
		N	**Mean**	**Standard Deviation**	
Normal	Pre	35	8.02	0.59	0.8322
	Post	35	7.99	0.59	
Overweight	Pre	65	8.02	0.46	0.7107
	Post	65	7.99	0.46	
Obese	Pre	15	7.81	0.15	0.7177
	Post	15	7.79	0.15	

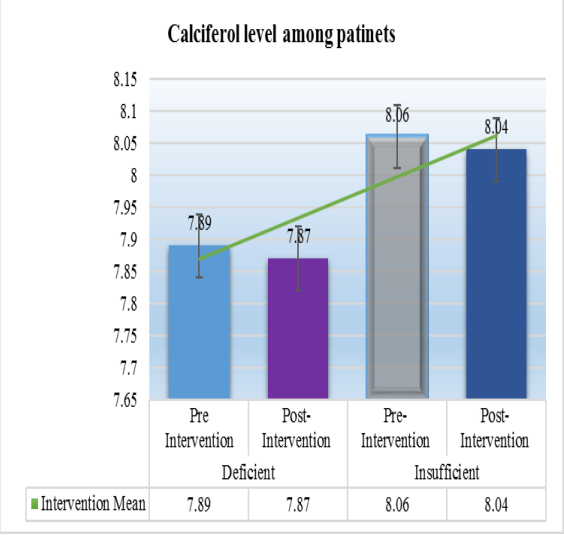

Figure 1: Changes in calciferol level among the study population

In patients having normal BMI (≤25 kg/m^2); on pre-intervention, the mean HbA1c value was 8.02 ± 0.59 and on post-intervention, the mean HbA1c value was 7.99 ± 0.59 (p-value=0.8322). In overweight patients; on pre-intervention, the mean HbA1c value was 8.02 ± 0.46 and on post-intervention, the mean HbA1c value was 7.99 ± 0.46 (p-value=0.7107).

In obese patients; on pre-intervention, the mean HbA1c value was 7.81 ± 0.15 and on post-intervention, the mean HbA1c value was 7.79 ± 0.15 (p-value=0.7177). In patients having calciferol deficiency; on pre-intervention, the mean HbA1c value was 7.89 ± 0.52 and on post-intervention, the mean HbA1c value was 7.87 ± 0.51 (p-value=0.8495). In patients having calciferol level >15; on pre-

intervention, the mean HbA1c value was 8.06 ± 0.44 and on post-intervention, the mean HbA1c value was 8.04 ± 0.44 (p-value=0.7929). In patients having a duration of DM ≤10 years; on pre-intervention, the mean HbA1c value was 8.09 ± 0.52 and on post-intervention, the mean HbA1c value was 8.06 ± 0.52 (p-value=0.7244).

In patients with a duration of disease >10 years, the mean HbA1c value was 7.82 ± 0.32 pre-intervention, and 7.7 ± 0.33 post-intervention (p-value=0.6854).

Discussion

Calciferol deficiency is widespread throughout most of the world. Its insufficiency or deficit is linked to metabolic illnesses such as type 2 DM, autoimmune and endocrine disorders, certain malignancies, infectious diseases, heart disease, and bone diseases.[14] As calciferol2 and calciferol3, which are also fat-soluble vitamins, they carry out their biological tasks. Patients with Type 2 diabetes and prediabetes had reduced serum 25(OH)D3 levels, according to epidemiological research.[15]

In this study on pre-intervention, the mean HbA1C of the patients was 7.99 ± 0.48; on post-intervention, the mean HbA1C was 7.97 ± 0.48. This difference was statistically non-significant. i.e., p-value=0.7523. However, Li et al. in their meta-analysis have also concluded the favorable effect of short-term calciferol administration (>2000IU/day) on blood sugar parameters among Asians, non-obese diabetics (SMD Fasting insulin = -1.80; 95%CI: -2.66~-0.95) and those with good baseline levels of blood sugar (WMDFBG = -4.09; 95%CI: -15.44~7.27)[16] The finding contrasts with the results of our study.

Previous investigations support the association between HbA1c and lipid and bone indicators. According to earlier research, 25(OH) D, the active form of calciferol, promotes glucose transport into muscle cells, controls the expression of the insulin receptor gene, and inhibits the expression of the renin gene. The involvement of 25(OH)D in the etiology of diabetes has also been substantiated by the discovery of calciferol receptors in cells.[17]

The 25(OH)D levels are linked to more than just direct blood sugar management since studies have shown that people with well-controlled diabetes who are calciferol deficient are more likely to develop serious complications including retinopathy. Calciferol treatment improved fasting blood glucose, HbA1c, and FINS in pre-diabetes patients. Still, it did not affect improving BMI, 2h-plasma glucose, or insulin resistance, according to a meta-analysis.[18]

According to a cross-sectional examination of data from the U.S. National Health and Nutrition Examination Survey (2007–2012), those with low blood 25(OH)D levels (50 nmol/L) or inadequate levels (50.1–74.9 nmol/L) are more likely to have pre-diabetes than people with high levels (>75 nmol/L).[19]

Studies have shown conflicting results on the relationship between HbA1c and calciferol, possibly as a result of variations in calciferol levels. Only the group with vitamin 25(OH)-D levels of 25 nmol/L had a significant increase in the number of patients with HbA1c values of 7.0%; the group with calciferol levels ranging from 75.0 to 25.0 nmol/L did not.[20,21]

Recent research showed that calciferol supplementation had no impact on diabetes risk outcome indicators when participants received 28,000 IU of calciferol via fortified cheese every week, the results aligned with the previous research conducted by Nik et al.[25] Similar to this, Davidson et al. found that taking a high dose of calciferol supplement weekly (88,865 IU) for a year had no effect on insulin sensitivity or glucose metabolism but, the calciferol group's HbA1c levels were lower.[22,23] However, on the contrary, a study conducted over 6 month period in Jamshoro, Pakistan, including 140 subjects with mean HbA1c of 7.92 ± 1.54 before intervention and post-

intervention HbA1c of 7.18 ± 1.53, has identified no significant effect of calciferol (400IU/day) on levels of blood sugar.[24]

Conclusion

The effects of vitamin D on glycemic control (as determined by a mean reduction of ≥1 in HbA1c) in calciferol deficient and insufficient diabetics, were insignificant. Hence no impact of calciferol on the control of blood glucose has been established. Thus, in the future, further studies must be done in different settings with larger sample sizes to get more reliable results and also in calciferol-sufficient patients.

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