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Impact Of Vitamin D Supplementation On HBA1C Level In Type 2 Diabetes Mellitus Patients Having Asymptomatic Vitamin D Deficiency In Northern Region Of Khyber Pakhtunkhwa, Pakistan A Prospective Interventional Multi Center Study.

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ABSTRACT

Vitamin D deficiency is linked to recurring and infectious diseases. Recent research has shown that vitamin D has skeleton-related functions, such as the ability to inhibit the development of cancer and cardio metabolic disorders and to have anti-inflammatory characteristics. Vitamin D insufficiency is relatively widespread and may contribute to the pathophysiology of disorders linked to insulin resistance, such as diabetes and obesity. Possible impacts on Type 2 Diabetes Mellitus (T2DM) patients with asymptomatic vitamin D deficiency's HbA1C levels have been discussed in this study. The study's goal is to find out whether supplementing with vitamin D can lower HbA1C levels in those with T2DM and asymptomatic vitamin D deficiency. To investigate the impact of vitamin D supplementation on HbA1 level in patients with newly diagnosed Type II diabetes who are asymptomatically Vitamin D deficient in northern Khyber Pakhtunkhwa region, Pakistan. The study likely uses a randomized controlled trial (RCT) design, in which two groups of T2DM patients with asymptomatic vitamin D deficiency are given, respectively, placebos and vitamin D supplements. Before and after a predetermined intervention time, the HbA1C levels in both groups are measured. Both the intervention (vitamin D supplementation) and the control (placebo) groups' participant demographic and clinical characteristics, such as age, gender, diabetes duration, baseline HbA1C levels, and vitamin D levels, were described. The main result demonstrated the effect of vitamin D supplementation on HbA1C levels, and differences in HbA1C levels between the two groups were statistically significant after the intervention. This could include modifications to mean HbA1C values and any variations in the proportion.

Keywords: Patients, T2DM, Metformin, HbA1c, Vitamin D supplementation.

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INTRODUCTION

Several studies have demonstrated that vitamin D influences a wide range of biological processes that regulate the metabolism of calcium (Ca) and phosphorus (P), cell division, differentiation, apoptosis, immunological regulation, genome stability, and neurobiology. Recent studies have shown that vitamin D is strongly linked to autoimmune illnesses, cancers, diabetes, and cardiac problems (1, 2). A variety of chronic and infectious disorders are associated with vitamin D insufficiency. Several studies have revealed that this deficiency's prevalence may vary geographically. Although vitamin D deficiency is frequently reported in the South Asian population, the true scope of the illness and the underlying causes are little understood due to the dearth of systematic reviews and meta-analyses (3). With the biological actions of 1, 25(OH)2D3, vitamin D is now widely regarded as a hormone rather than one of the traditional dietary vitamins (4). Diabetes development has been connected to vitamin D deficiency. Recent research has demonstrated that the presence of diabetic mellitus type 2 (T2DM), islet beta cell function, insulin resistance, body fat, and BMI levels are all inversely connected with 25 (OH) D levels (5, 6). In contrast, there was a positive correlation between 25(OH)D levels and insulin sensitivity. People who are 25OHD deficient are more likely to develop type 2 diabetes and insulin resistance (7). 1, 25 (OH) 2 D3 can be coupled with the vitamin D3 receptor on islet cells to enhance their functionality (8). This lessens the process of chronic pancreatic inflammation, improves insulin sensitivity, and inhibits inflammatory factors. It also inhibits the action of the renin-angiotensin system, which promotes insulin secretion (9). The function of islet cells can be enhanced by vitamin D intake (10).According to studies, calcium binding protein that is dependent on vitamin D is present not only in islet cells but also within PP cells and D cells, with islet cells having the highest concentration. Its main function is to control the amount of intracellular calcium through a calcium binding protein that is vitamin D dependent. This has an impact on the endocrine and metabolic functions of the different pancreatic cell types (11). Other research has revealed that islets isolated from mice lacking 25OHD released significantly more glucagon hormone following in vitro stimulation with 10 mol/L arginine or hypoglycemia (blood glucose control is less than 1.7 mol/L) than islets isolated from mice with normal levels of vitamin D. Additionally, supplementing with 1,25 (OH) 2D3 can restore normal glucagon levels. (12). Extensive research have connected 25OHD deficiency to a higher risk of depression (1, 2) , Alzheimer's disease (13), epilepsy (14) and neurocognitive impairment (15, 16). However, not all research was able to demonstrate that 1,25(OH)2D3 might boost calcium binding proteins (17). One way that 1,25(OH)2D3 might work is through raising serotonin levels of brain (18). Additionally, 1,25(OH)2D3 has been shown to promote the phagocytosis and clearance of amyloid- by macrophages in Alzheimer patients (19). This may contribute to the explanation of the link between a high incidence of 25OHD insufficiency (20), and Alzheimer disorders (21).

METHODS

This Prospective interventional Multi-Center study Conducted in Department of Diabetes, Endocrinology

& Metabolic diseases, Hayatabad Medical complex Peshawar Pakistan; Department of Endocrinologist Our Lady Of Lourdes Hospital,Co Louth Ireland; Department of General Medicine & Diabetes South West Acute Hospital 124 Irvine town Road Ennis Killen Bt74 6dn-Uk England from **jan 2023 to jan 2024** Out of 250 men and women were enlisted to participate in the study. Each person was given a simple questionnaire that included a complete past and present medical history as well as details on all drugs. Subjects gave written informed consents before being included into the study. None of the patients analysed in the analysis changed their medication schedule at any point during the study period. Out of 250 participants, 122 were eliminated for various reasons, such as non- compliance, failure to follow up, or possible medication changes. With a final count of 128 patients, 28 male and 36 female patients were divided into Group A (treated with Metformin only at 1000 mg after dinner), while 22 male and 42 female patients were divided into Group B (treated with Metformin same dosage and oral Vitamin D supplementation 200,000 IU/month for 3 months). Patients or attendants gave their informed permission. Patients with type 2 diabetes mellitus who were between the ages of 30 and 60, of either gender (male or female), clinically asymptomatic blood vitamin D levels below 20 mg/ml, and taking metformin for the treatment of type 2 diabetes mellitus with HbA1C levels between 7 and 9.5 were included in the study. 28 males (43.8%) and 36 females (56.2%) made up group A (metformin only), while 22 males (34.3%) and 42 females (65.6%) made up group B (metformin plus oral vitamin D). 26 patients in group A were getting anti-glycemic medication when the experimental trial got underway, and it took an average of 2.63 years for diabetes in group A patients to be diagnosed and begin treatment. It took 3.25 years from the time of diagnosis to the beginning of treatment for the 38 patients in group B receiving anti-glycemic medication. Patients with fasting serum calcium levels above 10.5 mg/dL, known histories of nephrolithiasis, hypercalciuria, malignancy, TB, sarcoidosis, Paget's disease, malabsorption syndromes, and renal insufficiency as shown by renal profile, the presence of proximal myopathy, and pregnant females were all excluded. We collected demographic information like name, age, sex, height, and weight. The height and weight were measured using recognized conventional methods. Body mass index is calculated by dividing weight in kilograms (kg) by height in square meters (m^2) (22). At the beginning of the trial, blood was collected from each patient and sent to the lab for analysis of HbA1c, S-25(OH) D, calcium, phosphorus, alkaline phosphatase, and fasting blood sugar. At the end of the third month (during the first follow-up), HbA1C levels were measured in all patients, but S-25(OH) D levels were only measured in Group-B patients who had received oral vitamin D. No individuals were removed from the study because no one had S-25(OH) D levels exceeding 150 ng/ml at its conclusion. Only in Group-B patients' blood was drawn at the end of the sixth month (at the last check-up) and sent to the lab for HbA1c and S-25(OH)D levels testing. Those who regularly take antacids, use mineral oil products, take cortisone or other steroids, diuretics, weight-loss medications, phenobarbital or phenytoin, have liver or gallbladder disease, have gastrointestinal diseases, or take daily multivitamins with calcium were all excluded from the

study. Other conditions that were disregarded were hyperparathyroidism, renal stone disease, abnormal calcium, phosphorus, and alkaline phosphatase levels, as well as symptoms of metabolic disorders such Paget's disease or osteomalacia.

ETHCIAL APPROVAL STATEMENT

Ethical approval was obtained from the Hospital Ethics Committee/Board & Postgraduate Studies Committee, Hayatabad,Medical,Complex,Peshawar.**(Ref.No.799/ HEC/B&PSC/04/2022,granted-to-Dr.Khalid Usman).** Written informed consent was secured from all participants. Procedures adhered to the Declaration of Helsinki; confidentiality was maintained throughout and data were de-identified before analysis.

STATISTICAL ANALYSIS

The statistical programmed for social sciences (SPSS) version 20 was used to statistically analyse the data that was recorded on pre-defined proforma. Age, height, weight, fasting blood sugar, serum calcium, phosphorus, alkaline phosphate, and S-25(OH)D were among the quantitative variables that underwent measurements for minimum, maximum, range, mean, standard deviation (SD), and kurtosis. Using a frequency table and percentages, the qualitative elements of efficacy and gender were expressed. The HbA1C level in both groups was analyzed using the ANOVA/Fried Man test over the course of the follow-up period. A paired sample t-test and the Wilcoxon signed ranked test were used to compare the HbA1C level before and after therapy. In both treatment groups, the Chi-Square test was performed to gauge the efficacy of the therapy. It was deemed significant at P 0.05.

RESULTS

The overall minimum age of male patients was 30, maximum age of 60, mean age 45 years ±SD 9, skewness 0.427 and kurtosis 0.833. Female patients have minimum age of 30 years and maximum of 59 years with mean age of 42 years ±SD 8, skewness 0.491 and kurtosis 0.953. The mean heights of male participants in group A were 1.67 ± 0.06 m, whereas the mean height of female participants of this group was 1.58 ± 0.05 m. The mean heights of group B male patients were 1.69 ± 0.06 m, whereas the mean height of female patients of this group was 1.64 ± SD 0.06 m. In group A, the mean weight of male participants was 73.04 ±SD10.12 kg, and female patients mean weight was 75.01±SD10.12 kg. while the average weight of the combined group was 70.61 9.65 kg. The mean calculated BMIs of male patients were 26.13 ± SD 2.98 kg/m^2 in group A and 25.67 ± SD 3.14 kg/m^2 for female participants of the group. In group B, mean calculated BMI of male participants in group B was 24.23 ± SD 2.67 kg/m^2, whereas mean BMI of female participants was 23.89 ± SD 3.16 kg/m^2.

RANDOM BLOOD SUGAR (RBS)

The minimum baseline BSR values of 28 male patients were 197.87 mg/dl in the group A, maximum value 234.67, mean 218.94 ± SD 12.36, skewness (-0.695), and kurtosis (-0.25) as shown in Table 1. The RBS of male patients in their first visit ranged from 187.32 – 220.19 with mean 208.00 mg/dl ± SD 11.41. In the second visit, ranged from 179.34 – 212.96 with mean 199.86 mg/dl ± SD 10.31. The minimum baseline BSR values of 36 female patients were 205.85 mg/dl in the group A, maximum value 231.67, mean 220.14 ±

SD 9.06, skewness (-0.582), and kurtosis (-1.23). The RBS of female patients in their first visit ranged from 191.43 – 217.89 with mean 208.00 mg/dl ± SD 8.14. In the second visit, ranged from 187.64 – 203.35 with mean 196.35 mg/dl ± SD 6.17. The difference between the first pair (RBS of male baseline-RBS of first visit) for male patients have mean difference of 10.94 ± SD 3.19 and the difference is significant having P< 0.000. In the second pair of t-test for comparison of mean difference, (RBS of male baseline-RBS of second visit) the mean difference value of 19.08 ± SD 4.97 and the difference is significant having P< 0.000 as shown in Table 2. A significant difference was observed between the pair of male patient in their first visit and second visit having mean value of 8.13 ± SD 2.99. The difference between the first pair (RBS of female baseline-RBS of first visit) for female patients have mean difference of 12.05 ± SD 3.96 and the difference is significant having P< 0.000. In the second pair of t-test for comparison of mean difference, (RBS of female baseline-RBS of second visit) the mean difference value of 23.79 ± SD 4.98 and the difference is significant having P< 0.000. A significant difference was observed between the pair of male patient in their first visit and second visit having mean value of 11.74 ± SD 4.78.

CALCIUM LEVEL

The minimum baseline Ca values of 28 male patients were 8.47 mg/dl in the group A, maximum value 9.76, mean 8.98 ± SD 0.40, skewness (-0.48), and kurtosis (-0.80) as shown in Table 3. The Ca of male patients in their first visit ranged from 8.71 – 9.92 with mean 9.25 mg/dl ± SD 0.42. In the second visit, ranged from 9.12 – 9.99 with mean 9.54 mg/dl ± SD 0.32. The minimum baseline Ca values of 36 female patients were 8.31 mg/dl in the group A, maximum value 9.53, mean 8.96 ± SD 0.43, skewness (-.16), and kurtosis (-1.68). The Ca of female patients in their first visit ranged from 8.09 – 9.42 with mean 8.78 mg/dl ± SD 0.53. In the second visit, ranged from 9.24 – 9.91 with mean 9.53 mg/dl ± SD .20. The minimum baseline Ca values of 28 male patients were 8.37 mg/dl in the group B, maximum value 9.77, mean 9.08 ± SD 0.58, skewness (-0.01), and kurtosis (-2.36). The Ca of male patients in their first visit ranged from 8.37 – 9.72 with mean 9.03 mg/dl ± SD 0.50. In the second visit, ranged from 9.11 – 9.64 with mean 9.36 mg/dl ± SD 0.18. The minimum baseline Ca values of 36 female patients were 8.37 mg/dl in the group B, maximum value 9.54, mean 8.96 ± SD 0.49, skewness (-0.16), and kurtosis (-2.20). The Ca of female patients in their first visit ranged from 8.29 – 9.25 with mean 9.93 mg/dl ± SD 0.49. In the second visit, ranged from 9.17– 9.72 with mean 9.50 mg/dl ± SD 0.16.The difference between the first pair (Ca of male baseline-Ca of first visit) for male patients in group A have mean difference of -0.26 ± SD 0.21 and the difference is significant having P< 0.004. In the second pair of t-test for comparison of mean difference, (Ca of male baseline -Ca of second visit) the mean difference value of -0.55 ± SD 0.24 and the difference is significant having P< 0.000 as shown in Table 4. A significant difference was observed between the pair of male patient in their first visit and second visit having mean value of -0.29 ± SD 0.16. The difference between the first pair (Ca of female baseline -Ca of first visit) for female patients have mean difference of 0.18 ± SD 0.16 and the difference is significant having P< 0.006. In the second pair of t-test for comparison of mean difference,

(Ca of female baseline -Ca of second visit) the mean difference value of -0.56 ± SD 0.36 and the difference is significant having P< 0.001. Significant difference in the pair of Ca of female first visit and Ca of female second visit having mean -0. 74 ± SD 0.45. The difference between the first pair (Ca of male baseline -Ca of first visit) for male patients in group B have mean difference of .05 ± SD .27 and the difference is non-significant having P≥ 0.548. In the second pair of t-test for comparison of mean difference, (Ca of male baseline -Ca of second visit) the mean difference value of -0.27 ± SD 0.48 and the difference is non-significant having P≥ 0.103 as shown in Table. A significant difference was observed between the pair of male patient in their first visit and second visit having mean value of -0.33 ± SD .38. The difference between the first pair (Ca of female baseline -Ca of first visit) for female patients have mean difference of 0.03 ± SD 0.14 and the difference is non-significant having P≥ 0.48. In the second pair of t-test for comparison of mean difference, (Ca of female baseline -Ca of second visit) the mean difference value of -0.53 ± SD 0.47 and the difference is significant having P< 0.007. A significant difference was observed between the pair of female patient in their first visit and second visit having mean value of -0.56± SD -0.45 at P≤ 0.003.

PHOSPHORUS LEVEL

The minimum baseline P values of 28 male patients were 4.01 mg/dl in the group A, maximum value 4.71, mean 4.36 ± SD 0.27, skewness (0.16), and kurtosis (2.02) as shown in Table 5. The P of male patients in their first visit ranged from 4.13 – 4.93 with mean 4.51 mg/dl ± SD 0.26. In the second visit, ranged from 4.11– 4.92 with mean 4.48 mg/dl ± SD 0.26. The minimum baseline P values of 36 female patients were 4.01 mg/dl in the group A, maximum value 4.51, mean 4.26 ± SD 0.15, skewness (0.11), and kurtosis (0.56). The P of female patients in their first visit ranged from 4.02 – 4.54 with mean 4.22 mg/dl ± SD 0.16. In the second visit, ranged from 4.01 – 4.61 with mean 4.34 mg/dl ± SD 0.19. The minimum baseline P values of 22 male patients were 4.12 mg/dl in the group B, maximum value 4.82, mean 4.37 ± SD 0.25, skewness (0.52), and kurtosis (1.05). The P of male patients in their first visit ranged from 4.01– 4.62 with mean 4.30 mg/dl ± SD 0.23. In the second visit, ranged from 4.15– 4.62 with mean 4.38 mg/dl ± SD 0.17. The minimum baseline P values of 42 female patients were 4.12 mg/dl in the group B, maximum value 4.67, mean 4.36 ± SD 0.21, skewness (0.09), and kurtosis (1.81). The P of female patients in their first visit ranged from 4.12 – 4.65 with mean 4.34 mg/dl ± SD 0.22. In the second visit, ranged from 4.13– 4.64 with mean 4.38 mg/dl ± SD 0.20. The difference between the first pair (P of male baseline -P of first visit) for male patients in group A have mean difference of 0.15 ± SD 0.40 and the difference is non-significant having P< 0.26. In the second pair of t-test for comparison of mean difference, (P of male baseline -P of second visit), the mean difference value of 0.13 ± SD 0.37 and the difference is non-significant having P< 0.34 as shown in Table 6. A non-significant difference was observed between the pair of male patient in their first visit and second visit having mean value of 0.04 ± SD 0.27. The difference between the first pair (P of female baseline- P of first visit) for female patients have mean difference of 0.03 ± SD 0.13 and the difference is non-significant having P< 0.40. In the second pair of t-

test for comparison of mean difference, (P of female baseline- P of second visit), the mean difference value of 0.07 ± SD 0.27 and the difference is non-significant having P< 0.38. Significant difference in the pair of P of female first visit and P of female second visit having mean 0. 11 ± SD 0.31. The difference between the first pair (P of male baseline- P of first visit) for male patients in group B have mean difference of .06 ± SD 0.25 and the difference is non-significant having P≥ 0.44. In the second pair of t-test for comparison of mean difference, (P of male baseline- P of second visit), the mean difference value of 0.01 ± SD 0.22 and the difference is non-significant having P≥ 0.88. A non-significant difference was observed between the pair of male patient in their first visit and second visit having mean value of 0.07 ± SD 0.17. The difference between the first pair (P of female baseline- P of first visit) for female patients have mean difference of 0.02 ± SD 0.28 and the difference is non-significant having P≥ 0.81. In the second pair of t-test for comparison of mean difference, (P of female baseline- P of second visit) the mean difference value of 0.01 ± SD 0.30 and the difference is non-significant having P< 0.92. A non-significant difference was observed between the pair of female patient in their first visit and second visit having mean value of 0.03± SD 0.41 at P≤ 0.89.

ALKALINE PHOSPHATASE (AP)

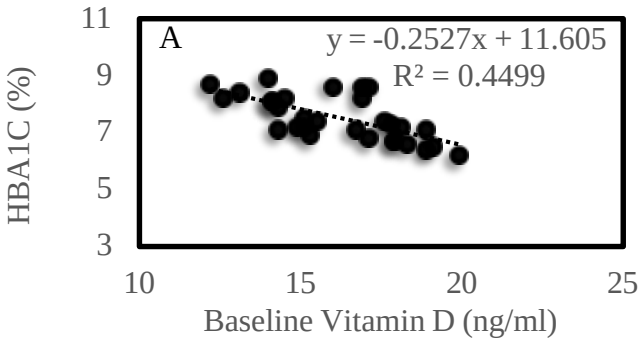
At baseline, in group A, the mean AP was 91.75 mg/dl as shown in Table 7, and no significant differences were observed in the level of AP during first and second visit of the male patients as indicated in Table 8. Similarly, the mean value of AP for female patients at their baseline was 91.93 mg/dl. Non-significant differences in AP levels were observed during first and second visit of female patients.

VITAMIN D

The minimum baseline vitamin D values of 22 male patients were 12.2 ng/ml in the group B, maximum value 19.9, mean 16.14 ± SD 2.08, skewness (-0.09), and kurtosis (-0.98) as shown in Table 9. The vitamin D of male patients in their first visit ranged from 16.1– 23.1 with mean 19.19 ng/ml ± SD 2.12. In the second visit, ranged from 17.2– 23.3 with mean 20.44 ng/ml ± SD 1.56. The minimum baseline vitamin D values of 42 female patients were 16.80 ng/ml in the group B, maximum value 26.80, mean 21.81 ± SD 2.61, skewness (0.18), and kurtosis (-0.74). The vitamin D of female patients in their first visit ranged from 18.20 – 28.30 with mean 23.17 ng/ml ± SD 2.91. In the second visit, ranged from 16.70– 27.80 with mean 21.13 ng/ml ± SD 3.76.

HEMOGLOBIN LEVEL (HBA1C)

The minimum baseline HBA1C values of 22 male patients were 6.2 % in the group B, maximum value 8.9, mean 7.52 % ± SD 0.78, skewness (0.16), and kurtosis (-1.21) as shown in Table 10. The HBA1C of male patients in their first visit ranged from 4.6– 8.1 with mean 6.69 % ± SD 0.79. In the second visit, ranged from 5.4– 7.8 with mean 6.44 % ± SD 0.72. The minimum baseline HBA1C values of 42 female patients were 5.70 % in the group B, maximum value 8.20, mean 7.01 ± SD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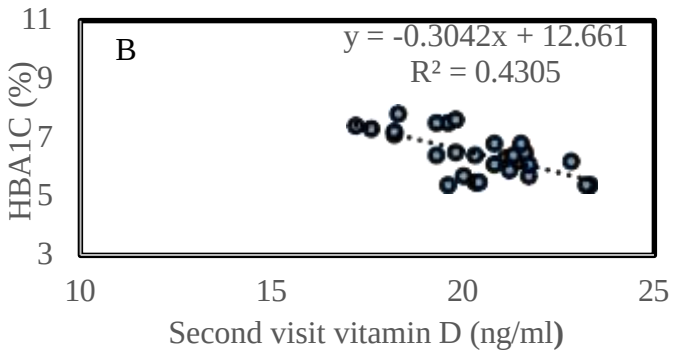
R² = 0.4499
HBA1C (%)
Baseline Vitamin D (ng/ml)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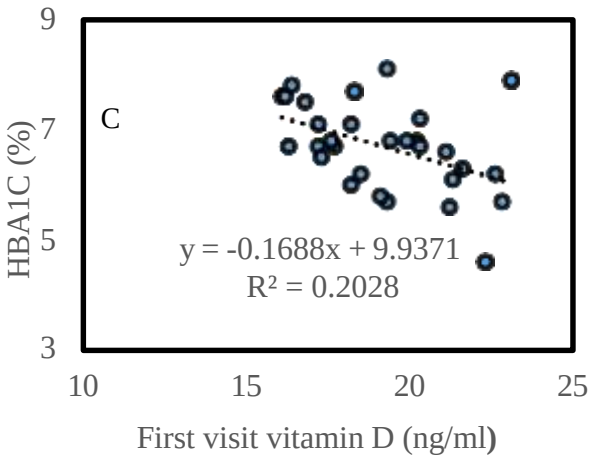
R² = 0.4305
HBA1C (%)
Second visit vitamin D (ng/ml)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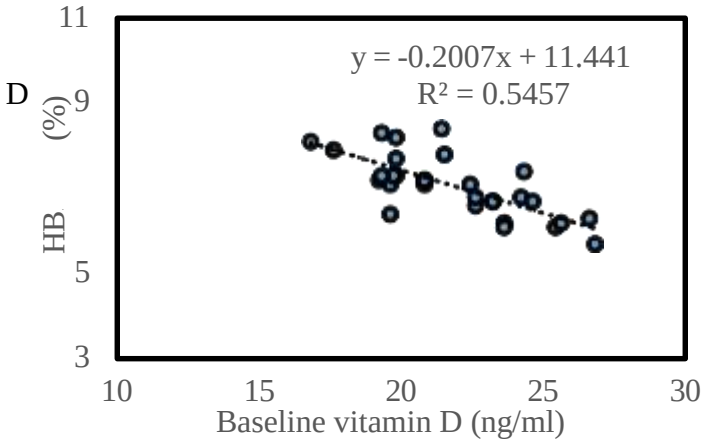
R² = 0.2028
HBA1C (%)
First visit vitamin D (ng/ml)


D
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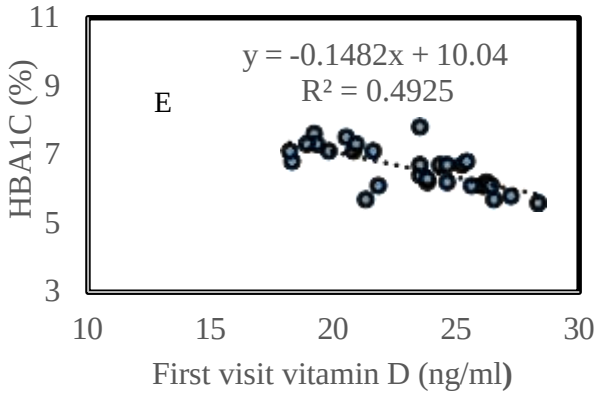
R² = 0.5457
HB (%)
Baseline vitamin D (ng/ml)


E
y = -0.1482x + 10.04
R² = 0.4925
HBA1C (%)
First visit vitamin D (ng/ml)

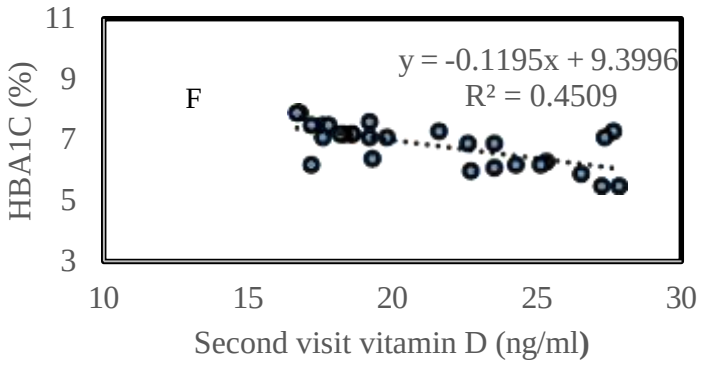

F
y = -0.1195x + 9.3996
R² = 0.4509
HBA1C (%)
Second visit vitamin D (ng/ml)

Table 1. Descriptive statistics for random blood sugar of male and female participants at different visits during study period of six month

Participants, RBS	Range	Minimum	Maximum	Mean	SD	Skewness	Kurtosis
Male baseline	**36.82**	**197.85**	**234.67**	**218.94**	**12.36**	**-.695**	**-0.25**
Male first visit	32.87	187.32	220.19	208.00	11.41	-1.100	0.29
Male second visit	33.62	179.34	212.96	199.86	10.31	-1.145	0.84
Female baseline	25.82	205.85	231.67	220.14	9.06	-.582	-1.23
Female first visit	26.46	191.43	217.89	208.09	8.14	-1.018	0.51
Female second visit	15.71	187.64	203.35	196.35	6.17	-.328	-1.88

Table 2. Paired sample t-test for comparison of random blood sugar of male and female participants in group (A)

Pairs Pair-1 to 3 for male participants Pair-4 to 6 for female participants	Paired differences				t-value	df	P-Value
	Mean	SD	99% confidence interval of differences				
			Lower	Upper			
RBS of male baseline – RBS first visit	10.94	3.19	7.66	14.22	10.84	27	0.00
RBS of male baseline – RBS second visit	19.08	4.97	13.97	24.19	12.13	27	0.00
RBS of male first – RBS of male second	8.13	2.99	5.06	11.21	8.59	27	0.00
RBS of female baseline – RBS first visit	12.05	3.96	7.97	16.12	9.60	35	0.00
RBS of female baseline – RBS second visit	23.79	4.98	18.66	28.91	15.08	35	0.00
RBS of female first – RBS of female second	11.74	4.78	6.82	16.65	7.76	35	0.00

Table 3. Descriptive statistics for calcium of male and female participants of the study groups at different visits

Participants, Ca, Group A (metformin)	Range	Minimum	Maximum	Mean	SD	Skewness	Kurtosis
Male baseline	1.29	8.47	9.76	8.98	0.40	.48	-0.08
Male first visit	1.21	8.71	9.92	9.25	0.42	.41	-1.01
Male second visit	.87	9.12	9.99	9.54	0.32	.15	-1.32
Female baseline	1.22	8.31	9.53	8.96	0.43	-.16	-1.68
Female first visit	1.33	8.09	9.42	8.78	0.53	-.07	-2.21

Female second visit	.67	9.24	9.91	9.53	0.20	.40	-0.14
Group B (metformin + oral vitamin D							
Male baseline	1.40	8.37	9.77	9.08	0.58	-.01	-2.31
Male first visit	1.35	8.37	9.72	9.03	0.50	-.26	-1.78
Male second visit	.53	9.11	9.64	9.36	0.18	.23	-1.18
Female baseline	1.17	8.37	9.54	8.96	0.49	-.06	-2.20
Female first visit	1.23	8.29	9.52	8.93	0.49	-.09	-2.21
Female second visit	.55	9.17	9.72	9.50	0.16	-1.06	0.70

Table 4. Paired sample t-test for comparison of Ca of male and female participants in the two groups (A, B)

Pairs, group A (metformin only) Pair-1 to 3 for male participants Pair-4 to 6 for female participants	Paired differences				t-value	df	P-value
	Mean	SD	99% confidence interval of differences				
			Lower	Upper			
Ca of male baseline – Ca first visit	-0.26	0.21	-0.48	-0.03	-3.81	27	0.00
Ca of male baseline – Ca second visit	-0.55	0.24	-0.80	-0.31	-7.34	27	0.00
Ca of male first – Ca of male second	-0.29	0.16	-0.46	-.13	-5.82	27	0.00
Ca of female baseline – Ca first visit	0.18	0.16	0.01	.34	3.52	35	0.00
Ca of female baseline – Ca second visit	-0.56	0.36	-0.93	-.19	-4.91	35	0.00
Ca of female first – Ca of female second	-0.74	0.45	-1.21	-.28	-5.20	35	0.00
Group B							
Ca of male baseline – Ca first visit	0.05	0.27	-0.23	0.34	0.62	21	0.54
Ca of male baseline – Ca second visit	-0.27	0.48	-0.77	0.22	-1.81	21	0.10
Ca of male first – Ca of male second	-0.33	0.38	-0.72	0.05	-2.77	21	0.02
Ca of female baseline – Ca first visit	0.03	0.14	-0.11	0.18	0.72	41	0.48
Ca of female baseline – Ca second visit	-0.53	0.47	-1.02	-0.04	-3.52	41	0.00
Ca of female first – Ca of female second	-0.56	0.45	-1.03	-.10240	-3.96	41	0.00

Table 5. Descriptive statistics for Phosphorus of male and female participants of the study groups at different visits

Participants, P, Group A (metformin)	Range	Minimum	Maximum	Mean	SD	Skewness	Kurtosis
Male baseline	0.70	4.01	4.71	4.36	0.27	0.16	2.02
Male first visit	0.80	4.13	4.93	4.51	0.26	0.07	1.15
Male second visit	0.81	4.11	4.92	4.48	0.26	0.02	0.91
Female baseline	0.50	4.01	4.51	4.26	0.15	0.11	0.56
Female first visit	0.53	4.02	4.54	4.22	0.16	0.75	0.09
Female second visit	0.59	4.01	4.61	4.34	0.19	0.32	1.14
Group B (metformin + oral vitamin D							
Male baseline	0.70	4.12	4.82	4.37	0.25	0.52	1.05
Male first visit	0.61	4.01	4.62	4.30	0.23	0.25	1.82
Male second visit	0.47	4.15	4.62	4.38	0.17	0.14	1.84
Female baseline	0.55	4.12	4.67	4.36	0.21	0.09	1.87
Female first visit	0.53	4.12	4.65	4.34	0.22	0.46	1.81
Female second visit	0.51	4.13	4.64	4.38	0.20	0.06	1.82

Table 6. Paired sample t-test for comparison of P of male and female participants in the two groups (A, B)

Pairs, group A (metformin only) **Pair-1 to 3 for male participants** **Pair-4 to 6 for female participants**	**Paired differences**				**t-value**	**df**	**P-value**
	Mean	SD	99% confidence interval of differences				
			Lower	Upper			
P of male baseline – P first visit	0.15	0.40	0.57	0.26	1.19	27	0.26
P of male baseline – P second visit	0.13	0.37	0.51	0.27	1.01	27	0.34
P of male first – P of male second	0.04	0.27	0.24	0.31	0.38	27	0.71

P of female baseline – P first visit	0.03	0.13	0.10	0.17	0.87	35	0.40
P of female baseline – P second visit	0.07	0.27	0.35	0.19	0.92	35	0.38
P of female first – P of female second	0.11	0.31	0.43	0.20	1.18	35	0.26
Group B							
P of male baseline – P first visit	0.06	0.25	0.19	0.32	0.80	21	0.44
P of male baseline – P second visit	0.01	0.22	0.24	0.22	0.15	21	0.88
			0.25	0.10	1.36	21	
P of female baseline – P first visit	0.02	0.28	0.26	0.31	0.24	41	0.81
P of female baseline – P second visit	0.01	0.30	0.38	0.30	0.36	41	0.92
P of female first – P of female second	0.03	0.41	0.46	0.43	0.14	41	0.89

Table 7. Descriptive statistics for calcium of male and female participants of the study groups at different visits

Participants, AP, Group A (metformin)	Range	Minimum	Maximum	Mean	SD	Skewness	Kurtosis
Male baseline	4.22	90.10	94.32	91.75	1.49	0.46	-1.26
Male first visit	4.41	90.00	94.41	92.05	1.75	0.22	-1.51
Male second visit	5.00	90.01	95.01	92.31	1.83	0.14	-1.67
Female baseline	3.38	90.01	93.39	91.93	1.23	-0.39	-1.44
Female first visit	4.29	90.10	94.30	91.74	1.44	0.21	-0.58
Female second visit	4.26	90.13	94.39	92.53	1.33	-0.60	-0.60
Group B (metformin + oral vitamin D							

Male baseline	5.22	90.18	95.40	92.66	1.69	0.17	-0.98
Male first visit	4.91	92.58	97.49	94.87	1.57	0.21	-0.99
Male second visit	6.29	91.39	97.68	94.82	1.81	-0.29	0.38
Female baseline	5.19	93.35	98.54	95.41	1.73	0.72	-0.45
Female first visit	3.59	94.43	98.02	96.21	1.31	-0.00	-1.49
Female second visit	6.00	91.39	97.34	94.84	1.90	-0.54	-0.12

Table 8. Paired sample t-test for comparison of AP of male and female participants in the two groups (A, B)

Pairs, group A (metformin only) **Pair-1 to 3 for male participants** **Pair-4 to 6 for female participants**	**Paired differences**				**t-value**	**df**	**P-value**
	Mean	SD	99% confidence interval of differences				
			Lower	Upper			
AP of male baseline – AP first visit	-0.30	2.37	-2.73	2.13	-0.40	27	0.69
AP of male baseline – AP second visit	-0.56	2.33	-2.96	1.83	-0.76	27	0.46
AP of male first – AP of male second	-0.25	2.78	-3.12	2.60	-0.29	27	0.77
AP of female baseline – AP first visit	0.19	2.25	-2.11	2.51	0.27	35	0.78
AP of female baseline – AP second visit	-0.59	1.75	-2.39	1.20	-1.06	35	0.31
AP of female first – AP of female second	-0.78	1.27	-2.09	0.52	-1.95	35	0.08
Group B							
AP of male baseline – AP first visit	-2.20	2.00	-4.26	-0.14	-3.48	21	0.01
AP of male baseline – AP second visit	-2.15	2.66	-4.89	0.58	-2.56	21	0.03
AP of male first – AP of male second	0.05	2.78	-2.80	2.91	0.06	21	0.95
AP of female baseline – AP first visit	-0.79	2.27	-3.13	1.54	-1.10	41	0.29
AP of female baseline – AP second visit	0.57	1.94	-1.42	2.57	0.93	41	0.37
AP of female first – AP of female second	1.37	2.20	-.89	3.63	1.97	41	0.08

Table 9. Descriptive statistics for HBA1C and Vitamin D of male and female participants of the study group B at different visits

Participants, HBA1C, Group B (metformin + Oral Vitamin D)	Range	Minimum	Maximum	Mean	SD	Skewness	Kurtosis
HBA1C							
Male baseline	2.7	6.2	8.9	7.52	0.78	0.16	-1.21
Male first visit	3.5	4.6	8.1	6.69	0.79	-0.36	0.24
Male second visit	2.4	5.4	7.8	6.44	0.72	0.26	-0.94
Female baseline	2.50	5.70	8.20	7.01	0.65	-0.08	-0.77
Female first visit	2.20	5.60	7.80	6.64	0.59	0.12	-0.90
Female second visit	2.40	5.50	7.90	6.80	0.71	-0.40	-0.95
Vitamin D							
Male baseline	7.7	12.2	19.9	16.14	2.08	-0.09	-0.98
Male first visit	7.0	16.1	23.1	19.19	2.12	0.26	-1.04
Male second visit	6.1	17.2	23.3	20.44	1.56	-0.25	-0.32
Female baseline	10.00	16.80	26.80	21.81	2.61	0.18	-0.74
Female first visit	10.10	18.20	28.30	23.17	2.91	-0.21	-1.13
Female second visit	11.10	16.70	27.80	21.13	3.76	0.57	-1.20

Linear regression analysis of HBA1C and 25-hydroxyvitamin D in male patients from (A to C) (A) baseline vitamin D with HBA1C, (B) first visit vitamin D with HBA1C, (C) second visit vitamin D with HBA1C. In female patients, (D) baseline vitamin D with HBA1C, (E) first visit vitamin D with HBA1C, (F) second visit vitamin D with HBA1C.

DISCUSSION

The information is meaningless, and there aren't many controlled research in this area despite the significance of vitamin D in avoiding diabetes, cardiovascular disease, or its risk factors. Both male and female patients in the current study had lower vitamin D levels, and intriguingly, there was an inverse correlation between vitamin D levels and glycosylated haemoglobin across the board. It seems that vitamin D may be connected to glucose regulation in type 2 diabetes mellitus. The findings of this analysis were considerably dissimilar from those of other studies. The fact that the HbA1c in the combination group was significantly higher than in the metformin alone group at the end of the follow-up period may assist to explain why the mean HbA1c in the metformin group alone was also low. Among its many advantages, vitamin D helps in regulating haemoglobin A1c (HbA1c). It promotes insulin sensitivity and secretion. (23). The levels of vitamin D2 were higher in those with diabetes and in women; all of the individuals had been given a weekly prescription for 50,000 units of vitamin D2. (24). Diabetes mellitus (DM) is a severe metabolic illness characterized by numerous

harmful molecular pathways, cellular abnormalities, and disruption of the biologic milieu. Its prevalence is currently a global health problem, particularly among younger persons. The management of diabetes has an unmet need for new therapeutic targets. As vitamin D deficiency is more prevalent in diabetic patients than in the general population, vitamin D is a viable target in the pathophysiology of DM. The particular pathophysiological mechanism is yet unknown, despite evidence that it can considerably increase peripheral insulin sensitivity and glucose metabolism (25). With relation to their glycemic status, people with lower vitamin D concentrations—as determined by 25-hydroxyvitamin D—might have different risk profiles. Due to the low incidence of diabetes in our study's population but high relationships with incident prediabetes, more research is needed. Increasing vitamin D status could considerably lower diabetes if done at the population level. (26). Alone supplementation with 1000 IU of vitamin D3 for nine months was linked to a lower MetS risk profile in postmenopausal women with VD insufficiency. MetS, hypertriglyceridemia, and hyperglycemia were all less common in women taking VD supplements. (27). The continuous release of insulin requires calcium (Ca2+) influx, which also results in a high rate of energy consumption. (28). Patients with Type 1 diabetes and diabetic nephropathy receiving paricalcitol medication did not experience any change in plasma N-terminal proprion natriuretic peptide levels, although there was a substantial decrease in urine albumin excretion rate. (29). Many chronic diseases have been connected by epidemiological research to vitamin D levels. (30). Our results indicate that despite the fact that vitamin D deficiency is common in both T2DM and non-diabetic participants, its impact on insulin resistance and haemoglobin glycation could not be confirmed (31). The percentage of T2DM cases and control subjects with vitamin D deficiency was 91.4% and 93.0%, respectively. In T2DM cases ($p = 0.057$ & $p = 0.257$ respectively) and in control subjects ($p = 0.675$ & $p = 0.647$ respectively), there was no correlation between serum 25OHD deficit and HbA1c or HOMA-IR.(32). Across all racial and cultural groupings and in all age categories, vitamin D insufficiency is a common ailment that affects between 30 and 50 percent of the population. In addition to vitamin D's well-known function in calcium homeostasis, a new risk factor for cardiovascular disease is developing from vitamin D deficiency (CVD). Low vitamin D levels have been linked to major CVDs such coronary artery disease, heart failure, and atrial fibrillation, according to multiple epidemiological and clinical investigations in particular. (33). Yet, there is conflicting evidence from interventional trials investigating the effectiveness of vitamin D supplementation for the population's prevention of diabetes. (34). Observational studies have shown an inverse relationship between the incidence of type 2 diabetes mellitus (T2DM) and low serum 25-hydroxy vitamin D (25(OH)D) (35). Several interventional and clinical trial investigations have also shown considerable improvements in the metabolic state of DMT2 patients as a result of

vitamin D treatment with regard to glucose homeostasis, while positive effects on vascular function were insufficient. The moderate effects of vitamin D on glycemic management and insulin resistance in a few randomised controlled studies, according to a new analysis by Pilz and colleagues, are not enough to suggest vitamin D therapy for DMT2 patients. (36). Insulin resistance starts to develop when diabetes first appears. By releasing more insulin, the beta-cells can overcome this resistance and avoid hyperglycemia. Yet, as this hyperactivity increases, the β-cells suffer excessive Ca2+ and reactive oxygen species (ROS) signalling that results in cell death and the onset of diabetes. Both the initial development of insulin resistance and the subsequent onset of diabetes brought on by -cell death are influenced by vitamin D insufficiency. Insulin resistance is largely caused by inflammation; which vitamin D works to diminish. The natural resting levels of Ca2+ and ROS, which are increased in the -cells during diabetes, are preserved by vitamin D. The epigenome is maintained in a considerable part by vitamin D. Many diabetes-related genes are rendered inactive by hypermethylation as a result of epigenetic changes. By enhancing the expression of DNA demethylases, which prevent hypermethylation of several gene promoter regions of many genes associated to diabetes, vitamin D prevents such hypermethylation (37-38).

LIMITATIONS OF THE STUDY

In contrast to other trials where patients were taking different drugs, including insulin, all of the patients in the present investigation were on a single pharmaceutical regimen. Additionally, the vitamin D dosage was monthly, which could assist to explain the study's subpar findings because the patients' levels of absorption may vary depending on the adverse effects of their diabetes, such as autonomic neuropathy, which was not assessed in this trial. However, its unfavorable results at least provide insight into the fact that giving vitamin D to diabetic patients for blood sugar control should be opposed until compelling study data are widely available. Before an opinion can be reached, it appears that more studies must be done using alternative methodologies and inclusion and exclusion criteria in order to have a better understanding of the role that vitamin D plays in the glycemic management of diabetes patients.

CONCLUSION

Vitamin D supplementation shown to significantly lower HbA1C levels in these patients, it may be offered as a novel supplementary strategy for treating T2DM. Since addressing both conditions at once may improve glucose control, this may be especially crucial for patients who also have vitamin D

deficiency. Future study directions could be suggested by the researchers, including more extensive and long-term trials, mechanistic studies, or research into particular subgroups that might gain more from vitamin D supplementation. clinical repercussions, discussion points could include for the findings' potential therapeutic ramifications, such as whether vitamin D supplementation for T2DM patients with asymptomatic vitamin D deficiency should be considered as an additional therapy. It is significant to emphasize that the specifics of the study, its methodology, and the data gathered would determine the actual results and debate. To fully comprehend the results and consequences of the study, read the entire results and discussion parts of the full manuscript if you have access to it.

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All authors contributed significantly to the study's conception, data collection, analysis,

Manuscript writing, and final approval of the manuscript as per **ICMJE criteria.**

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