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Effect Of Vitamin D Supplements In Improving Glycemic Control In Type 2 Diabetes Mellitus

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Abstract

Objective: To evaluate the efficacy of Vitamin D supplements in improving glycemic control in Type 2 Diabetic patients
It was a Quasi-Experimental trial conducted at the Department of Chemical Pathology of Fauji Foundation Hospital Rawalpindi, from Sep 2019 to December 2019.
Method: 100 patients between the ages of 20-65 years with serum 25(OH)D conc <25nmol/L and HbA1c >8.0% were given 200000 IU of vitamin D for 3 months and then their Vitamin D and hbA1c levels were compared with the baseline.
Results: The average alterations in HbA1c associated with initial Vitamin D levels of ≤ 40 nmol/L were 8.440 ± 1.787, subsequently reducing to 7.373 ± 1.093 after three months, demonstrating a statistically significant p-value of 0.000. Similarly, for individuals with initial Vitamin D levels > 40 nmol/L, the mean changes in HbA1c were 8.644 ± 1.928 initially, transforming to 7.551 ± 1.047 after three months, with a statistically significant p-value of 0.000.
Conclusion: The inclusion of Vitamin D supplements in conjunction with conventional anti-diabetic medications and exogenous insulin demonstrates an improvement the glycemic status of diabetic patients, as indicated by a reduction in HbA1c levels.
Keywords: HbA1c, glycemic control, Vitamin D.

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1. Introduction

The escalating prevalence of non-communicable diseases globally, including in Pakistan, has led to an increasing threat, with diabetes emerging as a highly prevalent condition among NCDs.[1] According to an estimate, the number of diabetes cases by 2045 will be increased to 693 million from 451 and between 2010 and 2030, developing nations are projected to have 69 percent more adults with diabetes than developed countries (20%).To adequately improve insulin resistance has a strong emphasis on the treatment of type 2 diabetes mellitus.

Vitamin D (serum level of 25(OH)D < 20 ng/ml) deficiency has affected various populations and has been considered an important public health issue globally due to a decline in outdoor activities, environmental pollution, sun protection measures, and obesity prevalence.[2] K. Iqbal and colleagues reported that in Pakistan, 58.7% of diabetic patients were suffering from vitamin D deficiency, further deteriorating their HBA1c status.[3]

Vitamin D has a major role in glucose homeostasis as its receptors are present on the beta cell of the pancreas Islet of Langerhans and deficiency of vitamin D is strongly related to the development of diabetes mellitus. The potential role of vitamin D deficiency in insulin resistance has been proposed to be associated with inherited gene polymorphisms including vitamin D-binding protein, vitamin D receptor, and vitamin D 1 alpha-hydroxylase gene. Other roles have been proposed to involve immunoregulatory function by activating innate and adaptive immunity and cytokine release, activating inflammation by upregulation of nuclear factor and inducing tumour necrosis factor α, and other molecular actions to maintain glucose homeostasis and mediate insulin sensitivity by a low calcium status, obesity, or by elevating serum levels of parathyroid hormone. As the major regulator for calcium homeostasis, vitamin D directly and or indirectly improves insulin exocytosis via activating calcium-dependent endopeptidases.

Mounting evidence revealed that Vitamin D has a major role in glucose homeostasis as its receptors are present on the beta cell of the pancreas Islet of Langerhans.[4] Findings from meta-analysis and a cohort study revealed that individuals having hydroxyvitamin D levels < 20 ng/ml were at higher risk of developing Type 2 Diabetes mellitus as compared to those individuals with 25(OH)D levels ≥ 20 ng/ml.[5] While current epidemiological studies have mainly focused on vitamin D supplementation and its effects on HbA1c in individuals with type 2 diabetes

in non-Asian regions, it is crucial to assess the influence of vitamin D on insulin resistance specifically in the Asian region. In a randomized controlled trial spanning six months and involving 275 patients, it was observed that individuals with vitamin D levels below 20 ng/mL did not exhibit HbA1c improvement despite receiving vitamin D supplementation at a monthly dosage of 50,000 IU. Similar results were corroborated in 86 German patients who received a daily dose of 1904 IU over six months.[7] On the contrary, epidemiological research involving South Asian females who were vitamin D-deficient residing in New Zealand might considerably lower their HOMA-IR levels with regular vitamin D supplementation after 6 months.[8] The differences may be partially attributed to the considerable ethnicity-linked disparities in Insulin sensitivity.[9] Epidemiological research on the relationship between vitamin D status and the risk of insulin resistance or hyperglycemia has so far shown suggestive but inconclusive outcomes.[10-12] While there is limited evidence indicating an impact of vitamin D deficiency on postprandial glycaemia and insulin response, supplementation could potentially aid in optimizing these mechanisms. However, this aspect has not been thoroughly documented. On the contrary, vitamin D supplementation appears to have some positive impact on the incidence and control of diabetes but whether Vitamin D affects metabolic regulations in diabetic patients has not been well studied. However, it is an area of great importance due to vitamin D insufficiency in diabetic individuals. It is postulated that improving glycemic control by Vitamin D supplementation will result in reduced diabetic complications and lowered economic burden. Furthermore convincing and long-term comparative trials are needed for making stronger evidence on the beneficial impact of vitamin D treatment on T2DM.

In summary, the objectives of our study were to assess the average change in HbA1c levels in individuals with diabetes mellitus who had both vitamin D deficiency and poor glycemic control, with a focus on investigating the impact of vitamin D supplementation on these parameters.

2. Materials & Methods

The study is a quasi-experimental trial with a 3-month follow-up period evaluating the effect of vitamin D supplementation in Type 2 diabetes mellitus patients Department of Pathology, Fauji Foundation Hospital in Rawalpindi. 100 Patients between the ages of 20 and 65 with serum 25(OH)D concentrations < 20 ng/mL were enrolled through the nonconsecutive probability sampling method.

Eligible participants for the research included individuals with type 2 diabetes who met the specified inclusion criteria, newly diagnosed cases of type 2 diabetes within the past year were considered. Inclusion criteria encompassed patients with HbA1c levels at or exceeding 8.0% over the last three months. Participants intending to discontinue hypoglycemic medication in the future were eligible for inclusion. Individuals who had not used calcium supplements and/or vitamin D in the past year were included. The patients who had not adhered to the current National Physical Activity guidelines in the last year were also included.

The patients with gestational diabetics, Individuals with diabetic nephropathy, Type 1 diabetics, Prediabetes, Pregnant or lactating mothers, anaemia, Hemoglobinopathy, Participants with chronic diseases including renal insufficiency (glomerular filtration rate 5 times upper reference limit, tuberculosis, diarrheal, or malabsorption state were excluded from the study. Following the receipt of ethical clearance from the Ethical Review Committee, individuals meeting the operational definitions and inclusion criteria were recruited into the study, with each subject providing informed consent before enrollment.

Particulars of all patients recorded in Performa (Annexure A) as 58 required, by the trainee researcher conducting the study. History was taken to rule out any past or chronic illnesses, pregnancy or lactation including the patient's drug history. After that patients were asked to give their fasting blood samples. A fasting blood sample of 10cc was taken from every patient & collected in EDTA and sodium fluoride tubes respectively for determination of HbA1c, plasma glucose & blood CP. Plain tubes were used for the analysis of serum vitamin D. All the vitamin D insufficient patients were given 200,000 IU vitamin D in divided doses for three months and then again, their serum fasting plasma glucose, serum vitamin D and HbA1c were tested. Biochemical Analysis of Samples: Laboratory investigations were carried out in the Pathology department of a tertiary care hospital in Rawalpindi. HbA1c was measured by "Turbidimetric Inhibition Immunoassay" (TINIA) on Siemens

Dimension RXL Next. Plasma glucose was measured by the hexokinase method on Siemens Dimension RXL Next. Serum vitamin D levels by immunoassay on Elecsys.

Utilizing Epi Info, the sample size was determined to be 100, considering a population mean change of HbA1c between baseline and after three months' treatment of vitamin D insufficiency as 0.6610, with a standard deviation of 0.2. The calculation was performed at a 5% level of significance and a precision of 4%. The data were entered and analyzed using SPSS version 20 for Windows. Frequency and percentage were computed for qualitative variables, totalling 59 in number. For the quantitative variables like age, weight, height, serum fasting glucose and serum vitamin D mean ±SD, the difference in hbA1c before and after three months was calculated. The paired sample t-test was employed to compare the mean changes in HbA1c before and after the treatment of vitamin D. The resulting p-value provides a measure of statistical significance. Effect modifiers like age and baseline vitamin D levels will be controlled by stratification, and post-stratification paired sample t-test will be applied.

3. Results

There were 100 female patients included in this study who were previously diagnosed diabetic patients according to the American Diabetes Association (ADA) criteria. The average age was 53.70 ± 8.913 years with the mean height of the patients being 1.65 ± 0.087 meters. The mean weight of patients was 73.83 ± 9.85 kg (Table 3) with a mean BMI of 27.18 ± 4.2 SD. The mean systolic blood pressure of the patients was 122.7 mmHg ± 5.9 as shown in Table 1.

Table 1: Descriptive Statistics of Participant Characteristics

Variables	Mean	SD
Age	53.70	8.913
Height(Meters)	1.65	0.087
Weight	73.8	9.85
BMI	27.18	4.27
Systolic BP(mm Hg)	122.7	5.919
Diastolic BP(mm Hg)	80.10	3.407

The mean fasting blood glucose before taking Vitamin D supplements was 9.44 mmol/l ± 2.28 SD and it decreased to a mean value of 8.02 mmol/l, ±1.66SD (described in Table 2) after three months of taking vitamin D orally. The mean HbA1c before QED was 8.5% ±1.86 SD which declined to 7.4% ± 1.06 SD described in (Table 2). In the context of age stratification, for females aged 50 years or younger, their average HbA1c level before treatment was 8.085 ± 1.670.

Table No. 2: Changes in Fasting Blood Glucose, HbA1C, and Vitamin D Levels Over 3 Months

Variables		Mean	SD	P-Value
Fasting Blood Glucose (mmol/l)	Baseline	9.44	2.28	<0.001
	After 3 Months	8.02	1.667	
HBA1C (%)	Baseline	8.5	1.86	<0.001
	After 3 Months	7.48	1.06	
Vitamin D (nmol/l)	Baseline	24.80	9.45	<0.001
	After 3 Months	119.88	39.05	

Table 3: Impact of Effect Modifiers on HbA1C Levels

Effect Modifier	Pre HBA1C	Post HBA1C	P-value
Age			
≤50 years	8.085±1.670	7.2971 ± 0.97513	0.001
>50 years	8.0292±1.93	7.5862± 1.1014	0.001
Baseline Vitamin D levels			
≤40nmol/L	8.4404±1.787	7.373±1.093	0.001
>40nmol/L	8.644±1.928	7.5508±1.047	0.001

Following the treatment, this mean HbA1c changed to 7.2971 ± 0.975, and the observed difference was statistically significant with a p-value of 0.001. The average HbA1c for females aged over 50 years was 8.029 ± 1.930 initially, and after the treatment, it changed to 7.580 ± 1.010, demonstrating a statistically significant p-value of 0.000, as indicated in Table 3. In terms of baseline Vitamin D levels, the mean changes in HbA1c for individuals with ≤ 40 nmol/L were 8.440 ± 1.787 at the beginning, which subsequently decreased to 7.373 ± 1.093 after three months, with a statistically significant p-value of 0.000. Similarly, for those with baseline Vitamin D levels > 40 nmol/L, the mean changes in HbA1c were 8.644 ± 1.928 initially, which reduced to 7.551 ± 1.047 after three months, with a statistically significant p-value of 0.000, as depicted in Table 3. Seventy-four out of 100 female patients were using exogenous insulin.

4. Discussion

Attaining effective glycemic control stands as a crucial factor in mitigating issues associated with diabetes mellitus Vitamin D has various other skeletal roles, including its involvement in type 2 diabetes, in addition to its function in maintaining calcium homeostasis. Hypovitaminosis D has been suggested to be a possible risk factor for type 2 diabetes onset.

In this quasi-experimental investigation, we assessed the impact of a 3-month oral vitamin D3 supplementation on glycemic control in individuals with type 2 diabetes. Notably, a significant influence of vitamin D supplementation was identified within the entire study population. Furthermore, a notable association between vitamin D supplementation and HbA1c levels was observed after 3 months, specifically among patients aged less than 50 and those aged greater than 50 who had vitamin D deficiency. This study commenced with the hypothesis that vitamin D supplements could enhance overall glycemic control in individuals with type 2 diabetes. The research uncovered several significant findings: firstly, a majority of diabetic individuals with inadequate glycemic control, evidenced by elevated levels of Fasting Plasma Glucose (FPG) and HbA1c, exhibited insufficient or deficient serum levels of vitamin D. Secondly, elevating vitamin D levels from a baseline of 24 nmol/l to 119 nmol/l led to a notable decrease in Fasting Plasma Glucose and HbA1c, key indicators of glycemic control in diabetic individuals. Thirdly, diabetic patients relying on exogenous insulin also showed significant improvements in FPG and HbA1c when supplemented with vitamin D.

Various hypotheses have highlighted the association between vitamin D insufficiency and type 2 diabetes. Epidemiological studies have demonstrated that vitamin D has a substantial impact on both insulin resistance and decreased beta cell function, which are fundamental issues in type 2 diabetes.

This was demonstrated by Chiu et al. in 126 glucose-tolerant participants in his research, disproving the earlier hypothesis that glucose tolerance might negatively impair insulin sensitivity and beta-cell function. (13-15)Numerous factors contributed to vitamin D deficiency and poor glycemic control in our research. Initially, individuals predominantly stayed indoors for extended periods due to the excessively hot weather. Moreover, they participated less in outdoor activities, particularly during the summer season. Glycemic regulation subsequently deteriorates, and sun exposure is also decreased. Second, little is known about the significant role that insulin resistance plays in the development of Type 1 diabetes mellitus. A preceding illness and/or the beginning of puberty, both of which are linked to insulin resistance, frequently signal the development of T1D.[16] Findings from our study showed a significant association between Vitamin D level and age group. Age is likely to be linked with vitamin D levels as older age groups are less capable of making Vitamin D from sunlight compared to younger individuals and elderly individual's kidneys are less capable of converting vitamin D into its active form.[17] Our findings imply that low vitamin D levels (inadequate and deficient) were much more common in female patients. This may be because of societal customs and religious requirements that require women to cover their whole bodies with clothing and wear a headscarf while they are outside. The major barrier preventing 25(OH) D synthesis and status is clothing. Even if they reside in a sunny region, women wearing hijabs cannot synthesize enough vitamin D from sunlight exposure to their exposed hands and faces. This outcome was consistent with the findings that many other studies had documented.[18,19] The current study has investigated a higher mean HbA1c value among patients with diabetes. Consistent with our findings, a study done by Desy Wulandari et al.[20] showed a significant difference in HbA1c levels due to vitamin D supplements. Two epidemiological researches have revealed that low vitamin D levels were responsible for improper metabolic control among diabetic patients.[21,22] Similarly, Sakineh et al. reported that vitamin D can affect glycemic control in diabetic patients as vitamin D3 supplementation improves HbA1C in all glycemic patients. Additionally, the association between HbA1c and vitamin D may exist as a result of how vitamin D affects insulin production from beta cells, systemic inflammation, and insulin effects. As a result, it is reported that vitamin D and diabetes mellitus are related. In this study, participants demonstrated a notable impact of vitamin D on their HbA1c levels.[23]

5. Conclusion

In a nutshell, Vitamin D supplementation along with conventional antidiabetic medicines and exogenous insulin improves the glycemic status of Type 2 Diabetes Mellitus patients as evidenced by a reduction in HbA1c levels and fasting plasma glucose.

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Y.J - Conception of study
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References

1. Uphoff EP, Newbould L, Walker I, Ashraf N, Chaturvedi S, Kandasamy A, et al. A systematic review and meta-analysis of the prevalence of common mental disorders in people with non-communicable diseases in Bangladesh, India, and Pakistan. J Glob Health. 2019;9(2). https://doi.org/10.7189/jogh.09.020417
2. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357(3):266-81. https://doi.org/10.1056/nejmra070553
3. Iqbal K, Islam N, Mehboobali N, Asghar A, Iqbal MP. Association of vitamin D deficiency with poor glycaemic control in diabetic patients. J Pak Med Assoc. 2016;66(12):1562-5.
4. Mitri J, Pittas AG. Vitamin D and diabetes. Endocrinol Metab Clin North Am. 2014;43(1):205-32. https://doi.org/10.1016/j.ecl.2013.09.010
5. Afzal S, Bojesen SE, Nordestgaard BG. Low 25-hydroxyvitamin D and risk of type 2 diabetes: a prospective cohort study and meta-analysis. Clin Chem. 2013;59(2):381-91. https://doi.org/10.1373/clinchem.2012.193003
6. Kovatchev B, Cobelli C. Glucose variability: timing, risk analysis, and relationship to hypoglycemia in diabetes. Diabetes Care. 2016;39(4):502-10. https://doi.org/10.2337/dc15-2035
7. Strobel F, Reusch J, Penna-Martinez M, Ramos-Lopez E, Klahold E, Klepzig C, et al. Effect of a randomised controlled vitamin D trial on insulin resistance and glucose metabolism in patients with type 2 diabetes mellitus. Horm Metab Res. 2014;46(01):54-8. https://doi.org/10.1055/s-0033-1358453
8. Von Hurst PR, Stonehouse W, Coad J. Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient–a randomised, placebo-controlled trial. Br J Nutr.2010;103(4):549-55. https://doi.org/10.1017/s0007114509992017
9. Sun X, Cao Z-B, Tanisawa K, Ito T, Oshima S, Higuchi M. Vitamin D supplementation reduces insulin resistance in Japanese adults: a secondary analysis of a double-blind, randomized, placebo-controlled trial. Nutr Res. 2016;36(10):1121-9. https://doi.org/10.1016/j.nutres.2016.07.006
10. Qu G-B, Wang L-L, Tang X, Wu W, Sun Y-H. The association between vitamin D level and diabetic peripheral neuropathy in patients with type 2 diabetes mellitus: An updated systematic review and meta-analysis. J Clin Transl Endocrinol. 2017;9:25-31. https://doi.org/10.1016/j.jcte.2017.04.001
11. Zhang Q, Cheng Y, He M, Li T, Ma Z, Cheng H. Effect of various doses of vitamin D supplementation on pregnant women with gestational diabetes mellitus: a randomized controlled trial. Exp Ther Med. 2016;12(3):1889-95. https://doi.org/10.3892/etm.2016.3515
12. Barbarawi M, Zayed Y, Barbarawi O, Bala A, Alabdouh A, Gakhal I, et al. Effect of vitamin D supplementation on the incidence of diabetes mellitus. J Clin Endocrinol Metab. 2020;105(8):2857-68. https://doi.org/10.1210/clinem/dgaa335
13. Chiu KC, Chu A, Go VLW, Saad MF. Hypovitaminosis D is associated with insulin resistance and β cell dysfunction. Am J Clin Nutr. 2004;79(5):820-5. https://doi.org/10.1093/ajcn/79.5.820
14. Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of β-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. Diabetes Care. 2006;29(5):1130-9. https://doi.org/10.2337/dc05-2179
15. Rossetti L, Giaccari A, DeFronzo RA. Glucose toxicity. Diabetes Care. 1990;13(6):610-30. https://doi.org/10.2337/diacare.13.6.610
16. Greenbaum CJ. Insulin resistance in type 1 diabetes. Diabetes Metab Res Rev. 2002;18(3):192-200. https://doi.org/10.1002/dmrr.291
17. Salih YA, Rasool MT, Ahmed IH, Mohammed AA. Impact of vitamin D level on glycemic control in diabetes mellitus type 2 in Duhok. Ann Med Surg. 2021;64:102208. https://doi.org/10.1016/j.amsu.2021.102208
18. Miettinen ME, Kinnunen L, Leiviskä J, Keinänen-Kiukaanniemi S, Korpi-Hyövälti E, Niskanen L, et al. Association of serum 25-hydroxyvitamin D with lifestyle factors and metabolic and cardiovascular disease markers: population-based cross-sectional study (FIN-D2D). PLoS One. 2014;9(7):e100235. https://doi.org/10.1371/journal.pone.0100235
19. Najeeb HA, Othman R, Salih SF, Mohammed AA, Al Ismaeel Q. Vitamin D level and endogenous DNA damage in patients with cancers in Duhok city, KRG-Iraq. Ann Med Surg. 2020;60:462-7. https://doi.org/10.1016/j.amsu.2020.10.065
20. Wulandari D, Cahyono HA, Widjajanto E, Puryatni A. Low levels of vitamin D correlate with haemoglobin A1c and interleukin-10 levels in pediatric type 1 diabetes mellitus patients. J Trop Life Sci. 2014;4(3):182-6. https://doi.org/10.11594/jtls.04.03.04
21. Svoren BM, Volkening LK, Wood JR, Laffel LM. Significant vitamin D deficiency in youth with type 1 diabetes mellitus. J Pediatr. 2009;154(1):132-4. https://doi.org/10.1016/j.jpeds.2008.07.015
22. Elsayed AM, Mohamed GA. Vitamin D deficiency and its correlation to hemoglobin A1C in adolescent and young adult type 1 diabetes mellitus patients. Al-Azhar Assiut Med J. 2016;14(2):76-80. https://doi.org/10.4103/1687-1693.192643
23. Berridge MJ. Vitamin D deficiency and diabetes. Biochem J. 2017;474(8):1321-32. https://doi.org/10.1042/bcj20170042