ORIGINAL RESEARCH

Vitamin D deficiency and cardiovascular risk in type 2 diabetes population- A prospective study

[1]Dr. Shreya Nigoskar, [2]Dr. Sonali Kadwe, [3]Shefali Pandey

[1]Professor & Head, [2]Associate Professor, [3]Research Scholar, Department of Biochemistry, Index Medical College, Indore, Madhya Pradesh, India

Corresponding Author
Shefali Pandey
Research Scholar, Department of Biochemistry, Index Medical College, Indore, Madhya Pradesh, India
Email: Biocheminsights@gmail.com

Date of acceptance: 30 March, 2024 Date of Publication: 06 April, 2024

ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) is a global health concern associated with significant morbidity and mortality, particularly due to its cardiovascular complications. Vitamin D deficiency has been implicated in the pathogenesis of T2DM and its related cardiovascular risks, but the relationship remains complex and not fully understood. This study aimed to investigate the association between vitamin D levels, glycemic control, lipid profile, and atherogenic variables in individuals with T2DM. **Methods:** A prospective cohort study was conducted among T2DM patients aged 40 to 60 years without established coronary artery disease. Sociodemographic, anthropometric, biochemical, and atherogenic variables were assessed. Multiple linear regression analysis was performed to examine the relationship between vitamin D and various parameters. **Results:** The study found a high prevalence of vitamin D deficiency (83.3%) among the participants. Poor glycemic control was associated with significantly elevated lipid markers and atherogenic variables. Lower vitamin D levels were correlated with higher HbA1c, fasting plasma glucose, total cholesterol, triglycerides, and non-HDL cholesterol levels. However, no significant association was observed between vitamin D and HDL cholesterol. The study also demonstrated a negative relationship between vitamin D and atherogenic indices, indicating an increased risk of cardiovascular morbidity in individuals with vitamin D deficiency and poorly controlled T2DM. **Conclusion:** The findings suggest a strong inverse association between vitamin D deficiency, glycemic control, and dyslipidemia in T2DM patients. These results underscore the importance of assessing vitamin D status in individuals with poorly controlled T2DM to mitigate the risk of cardiovascular complications. Future research should explore the potential benefits of vitamin D supplementation therapy in this population.

Keywords: Type 2 diabetes mellitus, Vitamin D deficiency, Glycemic control, Dyslipidemia, Cardiovascular disease.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM), also known as "noninsulin-dependent diabetes" or "adult-onset diabetes," is a chronic metabolic disease that is widespread globally. It is characterised by the body's resistance to insulin in the peripheral tissues, along with sub-chronic inflammation, high blood sugar levels, and a relative lack of insulin due to malfunctioning beta cells. [1] The International Diabetes Federation Atlas - 2017 report predicts that by 2045, the global population of individuals aged 20-79 with diabetes would reach 628.6 million. Presently, the global population of individuals with diabetes stands at 424.9 million. Approximately 82 million individuals resided in the South East Asian (SEA) region, accounting for 8.5% of the region's total population. Projections indicate that the Southeast Asia (SEA) region would experience a significant increase in diabetes cases, reaching a total of 151.4 million by the year 2045. This would represent around 11.1% of the adult population in the region. Approximately 48.8% of all adult patients with type 2 diabetes mellitus (T2DM) reside in urban areas. [2] Diabetes accounted for about 4 million adult fatalities worldwide in 2017, or to one fatality occurring every eight seconds. Reports indicate that the worldwide mortality rate for adults with diabetes, regardless of the aetiology, was 10.7%. In 2017, the South East Asian region accounted for 1.1 million fatalities, with over half of these occurring in those below the age of 60. In India, 10.4% of the population has diabetes, with a higher prevalence among urban dwellers from poorer socioeconomic backgrounds. [3] Among individuals in the Indian population who are under the

age of 30, approximately one out of every three, or 33%, are affected by one or more lifestyle diseases, such as diabetes, hypertension, hypercholesterolemia, thyroid disorders, and cancer. The user's text is enclosed in tags. [4]India had the highest number of diabetes-related deaths in the area in 2017, with an estimated one million fatalities. [2] Atherosclerotic cardiovascular disease (ASCVD), encompassing peripheral arterial disease, cerebrovascular disease, and coronary heart disease, is the leading cause of mortality and disability in individuals with diabetes. It also contributes significantly to the financial burden associated with the condition, both directly and indirectly. [5] The aggregate expenditure on healthcare for diabetes was found to be $727 billion in 2017 and is projected to increase to $776 billion by 2045. In 2016, there were 38 million individuals with type 2 diabetes who had a reduced life expectancy, resulting in a total of 2.8 million years of survival lost. [6] Cardiovascular disease (CVD) is the primary cause of death in this group, resulting in a decrease in life expectancy of almost 10 years. [7,8]

Atherosclerosis and endothelial dysfunction are prevalent features of cardiovascular complications associated with diabetes.[9] Both impaired glucose tolerance (IGT) and type 2 diabetes (T2DM) significantly elevate the risk of cardiovascular disease (CVD) by a factor of three to eight. [10] Individuals with diabetes face a much higher risk of developing cardiovascular diseases (CVDs), with an eightfold increase compared to those without diabetes. Moreover, the likelihood of experiencing a heart attack or stroke is two to four times greater for people with diabetes than for those without the condition. [11] The documented factors contributing to the higher occurrence of cardiovascular diseases (CVDs) among Indians encompass a vulnerability to a metabolic syndrome characterised by impaired glucose tolerance (IGT), abnormal lipid levels (dyslipidemia), excessive body weight (obesity), high blood pressure (hypertension), reduced sensitivity to insulin (insulin resistance), and the development of type 2 diabetes. [12] Over a span of ten years, van Hateren et al. [13] documented a steady increase in the hazard ratio for cardiovascular disease (CVD)-related mortality among individuals with type 2 diabetes mellitus (T2DM). This suggests that an upward trajectory in cardiovascular disease (CVD) is likely to occur as the burden of type 2 diabetes mellitus (T2DM) increases. Thus, the primary treatment goals for diabetes care are to reduce the risk of cardiovascular disease (CVD) and achieve tighter control over blood sugar levels to delay the start and slow down the progression of problems associated with type 2 diabetes. [14, 15].

The effect of rigorous glycemic control on the decrease of cardiovascular risk in patients with type 2 diabetes mellitus (T2DM) is a topic of discussion due to contradictory results. The text is encompassed by the tags [16-19]. The United Kingdom Prospective Diabetes Study (UKPDS) showed that effectively controlling elevated blood glucose levels in the first five years of type 2 diabetes mellitus (T2DM) leads to long-term cardiovascular benefits, as opposed to individuals who get standard care. However, the VADT, ADVANCE, and ACCORD trials revealed that a rigorous glycemic control regimen did not yield any cardiovascular benefits. The variability in the outcomes was partly attributed to the clinical characteristics of the population, the duration of diabetes in the people, and the particular form of intensive intervention employed. The results showed that hyperglycemia alone is not enough to cause coronary artery disease (CAD), but it does play a role when combined with other risk factors that increase the susceptibility of patients with type 2 diabetes mellitus (T2DM) to CAD.[20] This emphasises the importance of non-glycemic risk factors in preventing or treating coronary artery disease (CAD) in individuals. Both the American Diabetes Association and the American Heart Association have officially supported the same viewpoint.[21] Hence, it is imperative to assess and handle non-glycemic risk factors, such as high blood pressure, abnormal cholesterol levels, excessive body weight, and inadequate nutritional intake, to avert and regulate cardio-metabolic risk in persons diagnosed with type 2 diabetes mellitus (T2DM). Vitamin D, a crucial lipid-soluble nutrient/steroid hormone, is gaining more recognition for its function in controlling non-skeletal illnesses. Vitamin D is primarily known for its role in regulating the equilibrium of calcium and bone minerals. Over time, it has been associated with several disorders that have no impact on the skeletal system. The extraskeletal phenomenon arises from the presence of vitamin D receptors (VDRs) in almost all cells and the identification of 1-α hydroxylase in organs beyond the kidneys. Over one billion individuals globally are expected to be impacted by a widespread insufficiency of vitamin D, which is strongly associated with elevated rates of obesity, type 2 diabetes mellitus (T2DM), and cardiovascular disease.[22] Over 50% of individuals diagnosed with type 2 diabetes mellitus (T2DM) suffer from vitamin D insufficiency (VDD), indicated by a blood 25 hydroxyvitamin D (25(OH) D) level below 20 ng/mL. [23] The person is experiencing Vitamin D deficiency, with a 25(OH) D level ranging from 21 to 29 ng/mL. This disease is associated with elevated levels of HbA1c, insulin resistance, and systemic inflammation [24]. Observational studies have demonstrated a correlation between vitamin D deficiency (VDD) and the onset and progression of type 2 diabetes mellitus (T2DM), as well as the likelihood of experiencing macrovascular events in the future. [25-27] However, the results of trials investigating the effects of vitamin D administration on insulin resistance have been inconsistent and have sparked discussion. Several investigations have indicated that there is no effect [28,29], whilst others

have showed a positive enhancement [30-33] in insulin action among a wide range of individuals. A randomised clinical trial was conducted to investigate the effect of vitamin D supplementation on persons with type 2 diabetes mellitus (T2DM). The results showed a significant increase in blood vitamin D levels following the administration of vitamin D supplements. Nevertheless, there were no noticeable changes in glycated haemoglobin (HbA1c) levels over the course of the trial. Furthermore, even after accounting for factors such as age, gender, body mass index (BMI), duration of diabetes, baseline HbA1c, lifestyle, homeostasis model assessment - insulin resistance (HOMA-IR), and outdoor physical activity, the levels of 25(OH)D did not have any effect on glycemic management. [34] George et al. [35] conducted a comprehensive review and meta-analysis, which showed that vitamin D supplementation has a limited effect on reducing fasting glucose levels and improving insulin resistance in patients with type 2 diabetes mellitus (T2DM) or impaired glucose tolerance. Nevertheless, individuals with normal glucose tolerance did not have any noteworthy impact on these variables. Li et al. [36] conducted a meta-analysis and discovered that administering oral vitamin D supplements had more beneficial effects on HOMA-IR in individuals with type 2 diabetes mellitus (T2DM) when compared to a placebo. It was found that doses over 2000 IU/day were mostly linked to increased vitamin D levels following the intervention, leading to improved glycemic indices. Nevertheless, there was no discernible effect on fasting blood glucose, HbA1c, and fasting insulin levels. Hypovitaminosis D is proposed as a possible indicator of future macrovascular events in persons diagnosed with type 2 diabetes mellitus (T2DM). [25] The current study was motivated by the conflicting evidence regarding the positive effects of increasing serum vitamin D levels (defined as 25(OH) D level ≥ 30 ng/mL) through vitamin D supplementation on glycemic indices and cardiovascular risk factors in patients with type 2 diabetes mellitus (T2DM). The objective of this study is to assess the biochemical indicators of cardiovascular problems in individuals diagnosed with type 2 diabetes both before to and following vitamin D therapy.

MATERIALS AND METHODS

This prospective cohort study was conducted from January 2020 – December 2023 among type 2 diabetes mellitus (T2DM) patients who visited the outpatient department of Index Medical College, Hospital & Research Centre. (Malwanchal University, Indore, Madhya Pradesh). The biochemical assessments were carried out at the department of Biochemistry, Index Medical College, Hospital & Research Centre.

Type 2 diabetes mellitus (T2DM) individuals of both gender aged between 40 to 60 years with a diabetes duration of one to ten years and no history of established coronary artery disease were included in the study, while T2DM individuals who were on insulin and statin therapy, vitamin D supplementation, subjects with any acute or chronic illness as documented by history and individuals who were diagnosed with thyroid abnormality, cardiac, hepatic and renal dysfunction were excluded.

RESULT

Table 1: Comparison of sociodemographic and anthropometric variables between good and poor glycemic control diabetic population

Variables	Good glycemic control	Poor glycemic control	p
Age (years)	55 (46–64)	57 (48–66)	**0.171[a]**
Sex			
Male	27	28	**0.074[b]**
Female	21	29	
BMI (kg/m^2)	21.02 (18.69–24.29)	21.36 (19.45–24.15)	**0.115[a]**
Duration of diabetes (years)	7 (4–9)	9 (7–13)	**0.002[a]**
Presence of smoking habit	28	37	**0.688[b]**
Presence of hypertension	64	102	**0.024[b]**
Alcohol consumption	**45**	**80**	**0.011[b]**

BMI – body mass index. p-value indicates the level of significance. Non-normally distributed variables are presented as Median (p_{25}–p_{75}), while other variables are presented in numbers. [a]Mann–Whitney U-test to analyze the non-normally distributed variables. [b] Chi-square test used to analyze two categorical variables. Bold values indicates the $p < 0.05$.

Table 2: Comparison of the biochemical parameter and atherogenic variables between good and poor glycemic control diabetic population

Variables	Good glycemic control (n = 48)	Poor glycemic control (n = 57)	p
FPG (mmol/L)	6.806 (6.25–7.44)	7.78 (6.72–9.89)	**<0.001**
Vitamin D (ng/mL)	18.71 (15.40–26.32)	17.89 (12.85–26.57)	**0.031**
TC (mmol/L)	3.85 (3.31–4.58)	4.68 (3.78–5.46)	**<0.001**

TG (mmol/L)	1.52 (1.1–1.99)	1.98 (1.39–2.98)	**<0.001**
HDL-C (mmol/L)	1.08 (1.03–1.19)	1.03 (0.91–1.19)	**0.019**
Non-HDL-C (mmol/L)	2.84 (2.22–3.44)	3.59 (2.77–4.44)	**<0.001**
CRR	3.59 (3.02–4.32)	4.37 (3.62–5.27)	**<0.001**
AC	2.59 (2.02–3.32)	3.37 (2.62–4.27)	**<0.001**
AIP	**0.51 (0.34–0.63)**	**0.63 (0.45–0.85)**	**<0.001**

FPG – fasting plasma glucose; TC – total cholesterol; TG – triglyceride; HDL-C – high-density lipoprotein cholesterol; non-HDL-C – non-high density lipoprotein cholesterol; CRR – cardiac risk ratio; AC – atherogenic coefficient; AIP – atherogenic index plasma. Mann–Whitney U-test has been employed to analyze the non-normally distributed variables. p-value indicates the level of significance. All the variables are presented as Median (p_{25}—p_{75}).

Table 3: Multiple linear regression analysis for vitamin D and lipidprofile

Variable	β-coefficient	p
HbA_1c (%)	−0.097	0.039
FPG (mmol/L)	−0.119	0.011
TC (mmol/L)	−0.160	0.001
TG (mmol/L)	−0.201	<0.001
HDL-C (mmol/L)	0.009	0.577
Non-HDL-C (mmol/L)	−0.166	0.001

FPG – fasting plasma glucose; T C – total cholesterol;TG – triglyceride; HDL-C – high-density lipoprotein cholesterol; non-HDL-C – non-high density lipoprotein cholesterol. p-value indicates the level of significance. Bold values indicate the $p < 0.05$.

DISCUSSION

The study revealed that 83.3% of the patients included in the research exhibited hypovitaminosis D. The research conducted by Bhatta et al. in Nepal documented the frequency of The prevalence of vitamin D deficiency in our study is 73.68%, which is consistent with the findings of study [37]. The previous study conducted in Saudi Arabia found a consistent prevalence of vitamin D deficiency in the diabetic population, which was 76.6% [38]. The Nepalese population has a high incidence of vitamin D deficiency, which can be attributed to a low dietary intake of vitamin D, as well as other risk factors like skin pigmentation, wearing clothes that cover the body well, and lack of awareness about dietary content [39]. In this study, we assessed the relationship between vitamin D levels and glycemic control, lipid profile, and atherogenic variables in the population of Nepalese individuals with type 2 diabetes mellitus. There were no previous investigations conducted on the frequency of hypovitaminosis D in individuals with type 2 diabetes mellitus (T2DM) and its correlation with inadequate glycemic control and cardiovascular risk in Nepal. Our study also revealed that individuals with poor glycemic control exhibited significantly elevated levels of lipid markers compared to those with good glycemic control in the diabetic population. This study has also found that there is a significant association between higher levels of atherogenic variables and poor glycemic control, as indicated by an elevated level of HbA1c. Collectively, the study showed that individuals with inadequate management of diabetes are more likely to develop atherosclerosis and experience cardiovascular morbidity.

Previous studies [40–42] have shown that a higher level of vitamin D is strongly linked to good glycemic control in individuals with diabetes, which aligns with the findings of our study. Our findings indicate that for every decrease of 1 ng/mL in vitamin D levels, there is a corresponding increase of 0.097% in HbA1c and 0.119 mmol/L in FPG. In line with our research, the study conducted by Yang et al. demonstrated a negative correlation with FPG [43]. Unlike our results, the study conducted by Saedisomeolia et al. did not find any significant correlation with the level of HbA1c [44]. Several researchers propose that pancreatic β-cells contain specific vitamin D receptors, which directly influence insulin secretion and regulate glucose homeostasis in type 2 diabetes mellitus (T2DM) [45]. Additionally, a study elucidated that vitamin D improves insulin responsiveness for glucose transport in skeletal muscle through the expression of insulin.

Receptors are present [46]. Furthermore, the activation of the vitamin D response element in the promoter of the human insulin gene is triggered by the active form of vitamin D. This activation is responsible for the expression of insulin, which plays a crucial role in maintaining glucose homeostasis [47]. Our analysis revealed that there is a significant negative relationship between vitamin D and TC (β-coefficient = -0.160) as well as TG (β-coefficient = -0.201) after accounting for other factors that could influence the results. However, a study conducted by Saedisomeolia et al. [44] found a non-significant negative association with TC and TG. In line with our results, Saedisomeolia et al. demonstrated a favorable correlation with HDL-C. The research conducted by Chiu et al. demonstrated a significant correlation between vitamin D and TC (total cholesterol), but no

significant correlation with TG (triglycerides) [48]. The research conducted by Ge et al. in China [49] revealed that vitamin D did not have a significant correlation with TC and TG, but did have a significant correlation with HDL-C. Similarly, the studies conducted by Rolim et al. in Brazil [50] and Yang et al. in China [43] found a significant negative correlation with TC. Additionally, the study conducted by Yu et al. in Korea [41] found a significant correlation with TG. In addition, we conducted a correlation analysis to determine the association between vitamin D levels and lipid markers in populations with both poor and good glycemic control. There was a strong inverse relationship between TC (total cholesterol), TG (triglycerides), and non-HDL-C (non-high-density lipoprotein cholesterol) levels and vitamin D levels in patients with poorly controlled diabetes. Nevertheless, there was no substantial correlation observed between HDL-C and poor glycemic control in the population. Therefore, our results indicate that individuals with a deficiency in vitamin D are more likely to develop dyslipidemia and have poor control of type 2 diabetes mellitus.

While the impact of vitamin D on lipid metabolism is not well comprehended, it has been observed to have positive effects on glycemic control and lipid metabolism . Vitamin D affects the absorption of calcium, which in turn influences the synthesis and release of pancreatic insulin. Previous research indicated that an increased concentration of calcium reduces cholesterol levels through the secretion of bile acids [51]. The level of cholesterol in the bloodstream has an impact on the way vitamin D affects the transcription of the vitamin D receptor and insulin-induced gene-2 (Insig-2).

The enzyme responsible for cholesterol synthesis is downregulated by this process [52]. In individuals with diabetes and low levels of vitamin D, the signals of the vitamin D receptor may be suppressed. This can lead to the formation of foam cells, which in turn increases the level of cholesterol in the blood. These processes contribute to the development of atherosclerosis, which is a major factor in the development of cardiovascular diseases [53]. Furthermore, the elevated calcium levels [54] may lead to a decrease in the production and release of hepatic triglycerides. Vitamin D enhances the activity of lipoprotein lipase, which in turn affects lipid metabolism [55]. Several studies have proposed a hypothesis that vitamin D has an impact on the function of β-cells and insulin sensitivity. This could potentially explain the development of dyslipidemia in individuals with vitamin D deficiency, as dyslipidemia is closely associated with insulin sensitivity [56].

Non-HDL-C encompasses all lipid components in the plasma, such as chylomicron, VLDL-C, IDL-C, and LDL-C, excluding HDL-C. HDL-C is a reliable indicator of the risk of cardiovascular diseases and lipid disorders [57]. The measurement can be taken in both non-fasting patient samples and in patients with elevated levels of triglycerides (>400 mg/dL) [58]. In this study, we discovered a negative association between non-HDL-C and serum vitamin D concentration, with a β-coefficient of -0.166 and a p-value of 0.001. In our study, we observed a significant negative correlation ($r = -0.228$, $p = 0.001$) between non-HDL-C levels in poorly controlled diabetes and vitamin D. This finding is illustrated in Figure 1d. However, there is no significant association between vitamin D and non-HDL-C in this context.

Well-managed diabetes relationship . The research conducted by Sriram et al. in the United States also indicates a negative relationship between vitamin D and non-HDL-C, which aligns with our own findings. The long-term cardiovascular risk in patients with type 2 diabetes mellitus (T2DM) can be predicted by the rising levels of non-HDL cholesterol (non-HDL-C) [58]. Multiple studies indicate that a 1 mg/dL increase in non-HDL-C is associated with a 5% higher risk of cardiovascular morbidity [59]. Consistent with the previous findings, this finding also indicates that individuals with vitamin D deficiency and poorly controlled diabetes are more likely to experience cardiovascular morbidity.

Atherogenic indices serve as predictive indicators for cardiovascular risk. We conducted an analysis to examine the relationship between an atherogenic variable and vitamin D levels in diabetic individuals with both poor and good glycemic control. There is a strong negative correlation between atherogenic variables and vitamin D in individuals with poor glycemic control. This suggests that low levels of vitamin D may be a potential cause of atherosclerosis and the development of cardiovascular diseases. Based on our research, we observed that AIP was significantly higher in individuals with diabetes who were deficient in vitamin D and had poor blood sugar control. Additionally, there was a negative correlation between AIP and serum vitamin D levels ($r = -0.199$, $p = 0.002$) . An elevation in AIP has an impact on the secretion of insulin and the dysfunction of β-cells, leading to inadequate control of blood sugar levels in patients with type 2 diabetes mellitus. The correlation coefficient (r) between CRR and the variable of interest was -0.245, indicating a significant negative relationship ($p < 0.001$).

The correlation between serum vitamin D and both figure 2a and AC ($r = -0.245$, $p < 0.001$) in figure 2b is negative and statistically significant. These factors are important predictors of cardiovascular risk. Nevertheless, this study did not find a significant correlation between vitamin D levels and lipid markers and atherogenic variables in the diabetes population with good glycemic control. The collective evidence strongly indicates that individuals with type 2 diabetes who have poor glycemic control and a deficiency in vitamin D are susceptible to cardiovascular morbidity.

Furthermore, our previous research has yielded additional knowledge regarding the study of hyperglycemia-induced vasculopathy and its prevention strategies. These strategies can be effectively examined by utilizing human endothelial cells and conducting experiments on diabetic mice [60,61]. Therefore, the cellular level and diabetic animal model of poor glycemic control can be utilized to investigate the physiological role and relationship of vitamin D in glucose homeostasis.

CONCLUSION

The results of our study clearly show a strong negative relationship between glycemic control, as measured by HbA1c, and vitamin D levels. Therefore, individuals with poorly controlled type 2 diabetes mellitus (T2DM) and a deficiency of vitamin D are at a higher risk of developing dyslipidemia compared to those with insufficient or sufficient levels of vitamin D. Therefore, it is recommended that patients with type 2 diabetes mellitus (T2DM) who are at risk of developing complications due to poorly controlled blood sugar levels should be advised to undergo vitamin D testing. This may aid in future vitamin D supplementation therapy and an augmentation in sunlight exposure, which may decrease the risk of cardiovascular disease (CVD).

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