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A RETROSPECTIVE COHORT OF VITAMIN D DEFICIENCY ANALYSIS AND GLYCATED HEMOGLOBIN (HBA1C) LEVELS ASSOCIATIONS IN TYPE 2 DIABETES MELLITUS PATIENTS

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Abstract

The prevalence of type II diabetes mellitus (T2DM) is reported to be alarmingly high in Pakistan. According to different reports, hyperglycemia is associated with low vitamin D levels. The main objective of this research is to evaluate the association between vitamin D levels and HbA1c% (glycated hemoglobin) in enrolled participants with T2DM. The current retrospective and cohort study was conducted on 253 T2DM patients aged over 18 years. The proposed questionnaire included attributes like medical records, demographic data, and diagnosis of T2DM. The figures obtained were analyzed using SPSS software (Statistical Package for the Social Sciences). Of enrolled 253 patients, 185 patients aged 45-60 exhibited mean HbA1c% 8.28% (SD value +1.327), and the mean 25-OH vitamin D3 level was less than 20 ng/ml. Our study reported Pearson's correlation coefficient (r = -0.348) between HbA1c% and 25-OH vitamin D3 levels. The findings of this study indicate a negative correlation between vitamin D levels and HbA1c% among patients with T2DM. Using vitamin D supplements in conjunction with diabetes therapy may be an effective preventive strategy to minimize the complications associated with the diabetic condition.

INTRODUCTION

According to past scenarios, Diabetes T2DM incidences are increasing worldwide. A recent report by the International Diabetes Federation (IDF) observed that more than 537 million cases of diabetes were reported across the world. It is estimated that this number will increase to 643 million in the coming years [1]. According to Egyptian manuscripts, the first case of diabetes was reported in Egypt around 3000 years ago [2]. In 1926, diabetes mellitus was divided into two categories type I and type II diabetes mellitus [3]. Type I diabetes, also known as insulin-dependent (DM), is an autoimmune disease that develops when beta cells (make insulin) in the pancreas are destroyed by immune cells. Type II diabetes mellitus, or non-insulin dependent (DM), is characterized by hyperglycemia, insulin deficiency, and insulin resistance. In 1988, T2DM was referred to as a component of metabolic syndrome [4]. Currently, the prevalence of T2DM is rising in Pakistan at an alarming rate. In 2021, the IDF (MENA) reported that the adult population in Pakistan was approximately 123 million, and it was noted that over 26% of this population had T2DM, which caused 32 million cases in Pakistan [5].

The surge in diabetes cases is primarily attributed to environmental and psychological factors. The main factors include sedentary lifestyles, extensive use of electronic gadgets, and an unhealthy diet, which leads to a heightened obesity rate. The prevalence of obesity is 15% among the youth; it is a significant causative factor for the diabetes epidemic in Pakistan [6]. DM disease is characterized by chronic or acute hyperglycemia. There are multiple causes of T2DM mainly, due to insufficient secretion of insulin and insulin resistance, or maybe both obesity, lack of physical activities, age, especially after 45 years, unhealthy diets, and sometimes a genetic mutation [7]. The general signs and symptoms that are highly associated with diabetes mellitus include polyuria, polydipsia, polyphagia, weakness, and emaciation. According to studies, approximately 95% of diabetic patients exhibit one or more of these symptoms. Notably, the above five symptoms are present in around 24% of patients with ketone as compared to 15% of patients who do not have ketosis. Notably, these symptoms are more prevalent in patients under 40 [8].

There are multiple risk factors associated with diabetes mellitus, encompassing obesity, poor diet, genetic predisposition, high cholesterol, high blood pressure, age, gestational, tobacco consumption, etc [9, 10]. Moreover, the association between vitamin D deficiency and T2DM has been frequently reported as a risk factor. However, very few people are aware of this association [11]. Vitamin D is a nutrient required for good health. Vitamin D has many vital roles within the body, such as absorbing calcium, the main building blocks for strong bones, cell proliferation, immune function, and insulin secretion from the pancreas gland [12]. Based on recent studies, a significant portion of the population is diagnosed with inadequate levels of vitamin D, often leading to variant health issues **(as shown in Table 1)** such as rickets (in children), osteoma-acia (in adults), bone weakness, liver and kidney diseases, osteoporosis, and effect insulin secretion (in pancreatic beta-cells) [13].

Vitamin D levels	Condition
Less than 20 ng/mL	Deficiency
20-30 ng/mL	Insufficient
30-50 ng/mL	Sufficient
50-80 ng/mL	Normal
More than 80 ng/mL	Excess or Toxicity

Table 1: Vitamin D levels are associated with health conditions.

Vitamin D is chiefly obtained in two form, D3 (cholecalciferol) and D2 (ergocalciferol), intake of Vitamin D can be acquired through dietary sources and supplements which are derived from animals and plants, also from fortified food. Vitamin D can also be endogenously produced insulin under the influence of UV radiations from sunlight [14]. Moreover, Vitamin D has been found certain potential role in insulin secretion and insulin resistance because of action variations in viatmin D receptor (VDR) and vitamin D binding proteins (DBP) on adipose tissues in human body, as per recent studies [15]. This action of vitamin D is modulating insulin receptor gene expression sensitivity, as they are responsible for the absorption of glucose to the secretion of insulin [16]. This evidence supports the importance of pathogenesis and the risk of developing T2DM. As seen in **Figure 1.** Vitamin D is essential for the body and can be obtained directly from diet or through UVB rays from sunlight that permeate the skin. The substance, 7- Dehydrocholesterol present in the skin, converts into Cholecalciferol (Pre-vitamin D3) by the absorption of UVB radiation [17, 18]. Pre-vitamin D3 is thermodynamically unstable and thermally converted into vitamin D3. Then 25-Hydroxyvitamin D3 (Calcidol) converts into active form 1,25-Dihydroxyvitamin D3. This active form of vitamin D plays a crucial role in bone metabolism, aids in the absorption of calcium (Ca) and phosphorus (P) from the intestine, and is involved in insulin secretion [19].

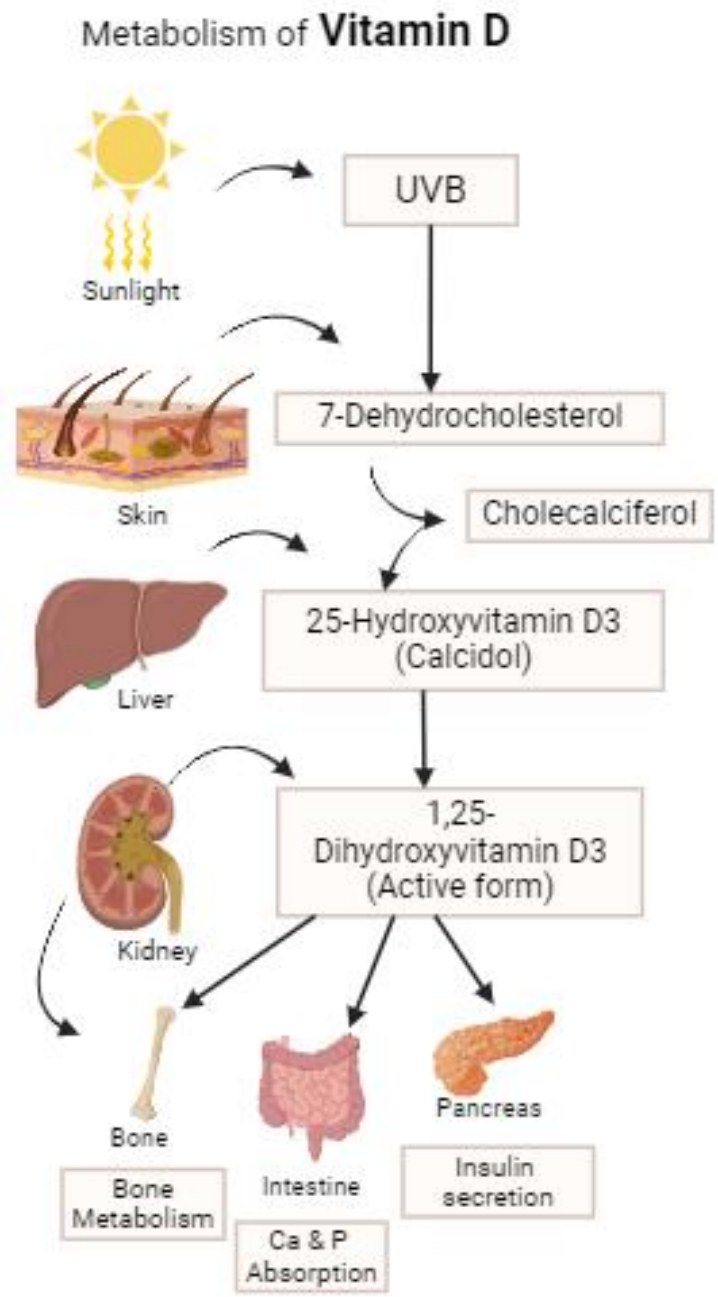

Figure 1: Metabolism of Vitamin D.

2. Material And Methods:

2.1 Study Design:

The current study is a retrospective cohort study conducted to investigate the association between vitamin D levels and the potential for developing type 2 diabetes in 253 patients with T2DM (out of which 68 were excluded depending on standards) in Pakistan (as shown in Figure 2). Our study samples were collected from different cities of Punjab, Pakistan (as shown in Table 2) (as shown in Figure 3).

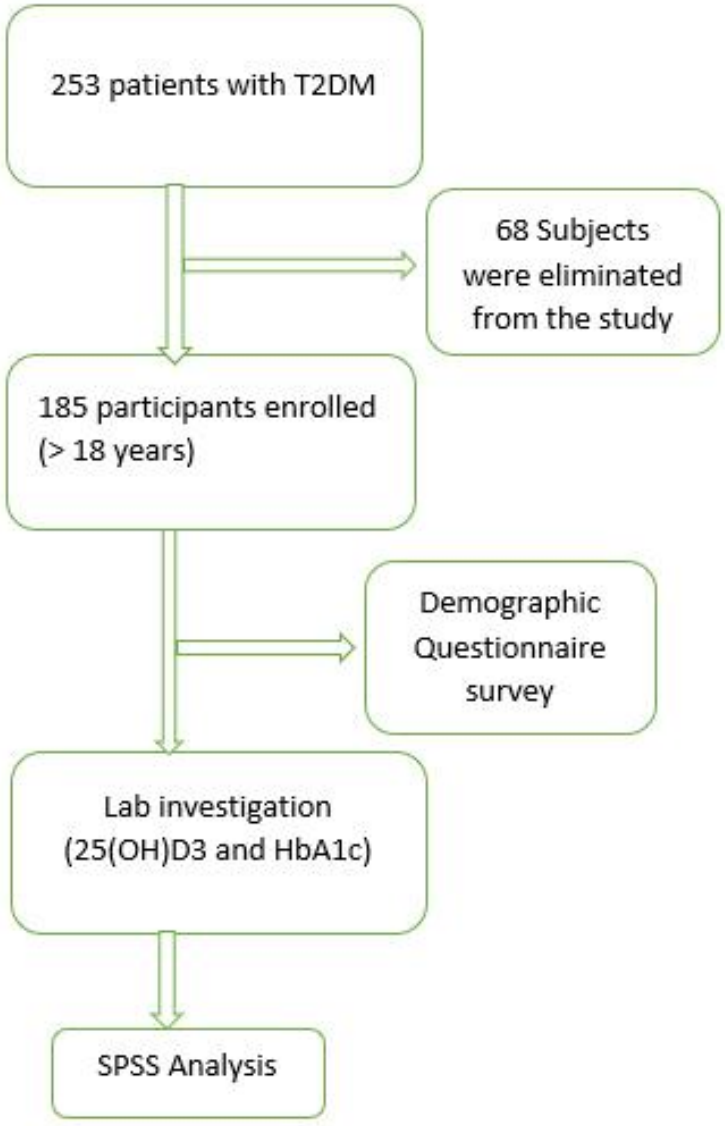

Figure 2. Flowchart of Study Participants.

Table 2. Region of Residence in Punjab.

Cities	Frequency	Percent%
Faisalabad	49	19.4
Lahore	52	20.6
Multan	38	15
Rawalpindi	21	8.3
Sargodha	26	10.3
Chiniot	28	11.1
Bahawalpur	23	9.1
Jhang	2	0.8
Islamabad	2	0.8
Other...	12	4.6
Total	253	100

This table indicates the number of sample collections from different residence regions of Punjab.

2.2 Sample Collection:

Patients with T2DM were identified in different hospitals in Punjab, Pakistan. Demographic Data of all T2DM patients were collected **(as shown in Table 3)**. Two parameters (HbA1c percentages and Vitamin D3) were measured according to standard protocols. HbA1c% of patients were estimated in the lab using BioHermes Device (A1c EZ 2.0 system) [20]. Vitamin D was estimated using Maglumi 800 (Snibe, Shenzhen, China) analyzer, full automation was used for its measurement [21, 22]. The exclusive criteria for the study included patients with type I diabetes and patients aged less than 18. The medical records of the selected patients were reviewed, and the following information was documented: demographic data, diagnosis of T2DM, and any other relevant details.

Table 3. Descriptive Statistics.

Variables	**(n=185)**	**Lab Investigation**	
Demographic Data		25 (OH)Vitamin D3 (ng/ml), Median	< 20 ng/ml
Age (years), Mean	78 (45-60 years)	Vitamin D supplement usage, n %	
Gender, n %		Yes	71 (38.4%)
Male	90 (48%)	No	114 (61.6%)
Female	95 (51.4%)	Vitamin D deficiency symptoms, n %	
Aera, n %		Yes	152 (82.2%)
Urban	128 (69.2%)	No	33 (17.8%)
Rural	57 (30.8%)	(RBS) mg/dl, Mean	220 mg/dl
Occupation, n %			
Students	13 (7%)	**Lifestyle**	
Employed	83 (44.9%)	Frequency of Sunlight exposure, %	
Unemployed	65 (35.1%)	Daily	46.1%
Retired	24 (44.9%)	Occasionally	35.2%
Family history (Diabetic), n %		Rarely	16.8%
Yes	113 (61.1%)	Diet intake, %	
No	57 (30.8%)	Mostly vegetarian	77.3%
Not sure	15 (8.1%)	Mostly non-vegetarian	13%
Treatment		Fast food	2.7%
Oral antidiabetic drugs	65.8%	Fruits and dairy	7%
Insulin only	34.2%	Frequency of Exercise, %	
HbA1c (%), Mean	8.29	Regularly	18.9%
		Occasionally	31.9%
		Rarely	49.2%

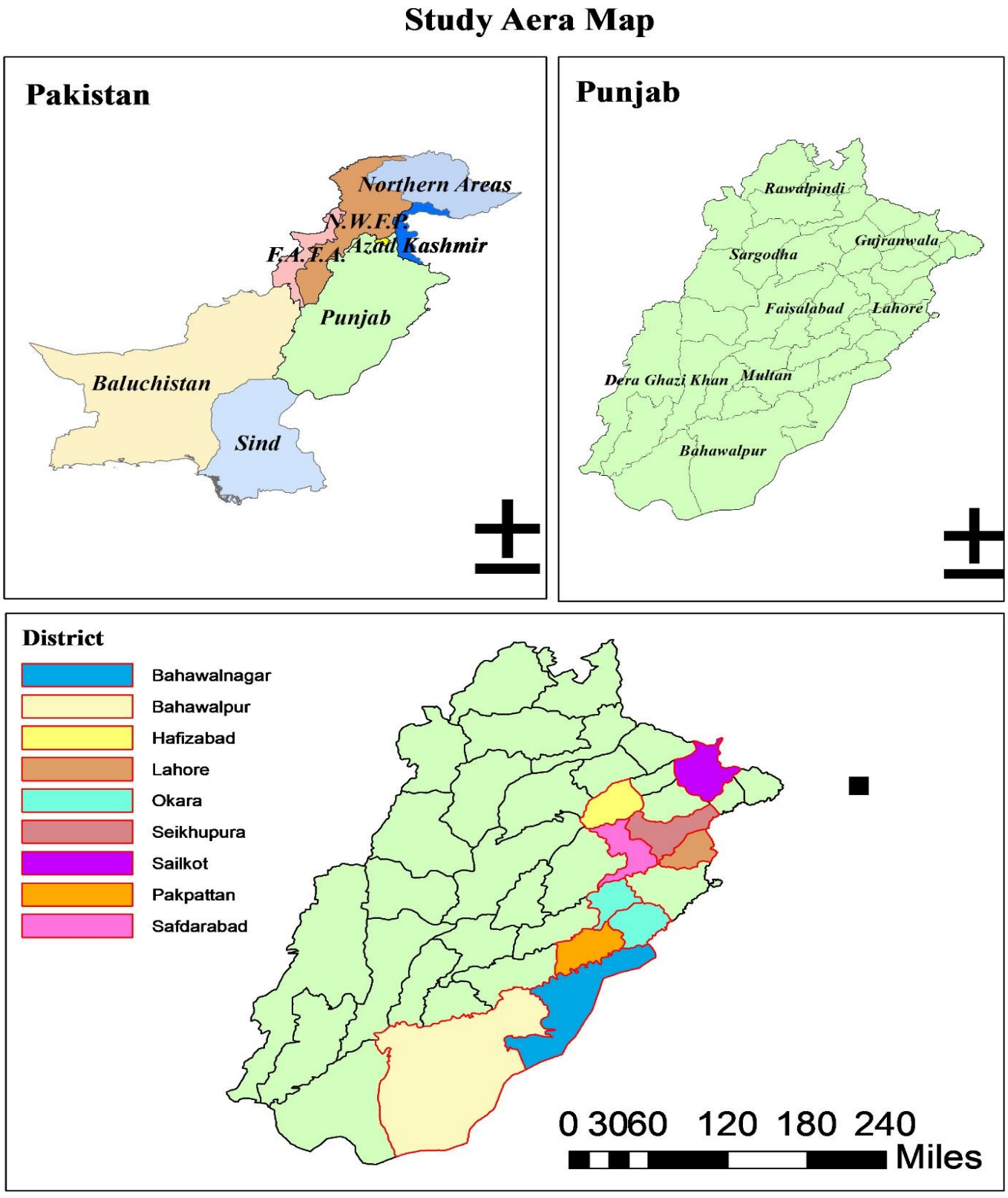

Figure 3. Study Aera Map Punjab, Pakistan.

2.3 Statistical analysis:

Statistical analysis is performed using the licensed SPSS (version 26) as per the method of [23, 24]. Pearson correlation statistics was used to estimate the relation between HbA1c% and serum 25(OH) vitamin D3 levels [25].

3. Results

Among the 185 subjects, 45-60 years was the mean age, the mean HbA1c% observed was 8.29%, and mean 25(OH) Vitamin D3 levels were less than 20 ng/mL among the diabetes mellitus type II patients. While using SPSS, the association between the HbA1c% and 25(OH) vitamin D3 levels among the type II diabetic patients, Pearson's correlation (r = -0.348) shows an inverse relationship between HbA1c% and 25(OH) vitamin D3). In this analysis, the p-value for the correlation coefficient is < 0.001 (0.000), indicating a negative correlation **(as shown in Table 4)**. Descriptives of the data obtained from the diabetes mellitus type II patients **(as shown in Table 5)**.

Table 4. The Pearson Correlation (r) between 25 (OH) Vitamin D3 & HbA1c% levels.

		25 (OH)VITAMIN D3 ng/ml	HbA1c
25 (OH)VITAMIN D3 ng/ml	Pearson Correlation	1	-.348**
	Sig. (2-tailed)		.000
	N	185	185
HbA1c %	Pearson Correlation	-.348**	1
	Sig. (2-tailed)	.000	
	N	185	185
Correlation is significant at the 0.01 level (2-tailed).			

This table indicates the Pearson Correlation (r) between vitamin D and HbA1c%, value is -0.348 that show inverse relationship.

Table 5. Descriptives of the data obtained from the diabetes mellitus type II patients.

	N	Minimum	Maximum	Mean		Std. Deviation	Skewness		Kurtosis	
	Statistic	Statistic	Statistic	Statistic	Std. Error	Statistic	Statistic	Std. Error	Statistic	Std. Error
Age of Patients	185	1 (18-31y)	4 (over 60y)	2.48	.079	1.074	-.003	.179	-1.251	.355
25 (OH)Vitamin D3 (ng/ml)	185	1 (<20 ng/dL)	4 (50-80 ng/dL)	1.68	.061	.829	1.131	.179	.660	.355
HbA1c %	185	6	10	8.29	.098	1.327	-.128	.179	-1.146	.355
Valid N (listwise)	185									

Note:

Variables of Vitamin D levels	Represent	Variables of Age	Represent
1	< 20 ng/mL	1	18-30 years
2	20-30 ng/mL	2	31-45 years
3	30-50 ng/mL	3	46-60 years
4	50-80 ng/mL	4	60+ years

This table indicates the descriptive statistics of selective patients of T2DM with minimum and maximum age, vitamin D levels and HbA1c% respectively.

4. Discussion

This study evaluated the association between vitamin D and T2DM aged 18 years. It was a hospital-based study as well as an environmental-based study, but there were limited resources and period for this research [26]. Diabetes mellitus is a chronic and serious health condition characterized by hyperglycemia, insulin deficiency, and insulin resistance. The key point of this study was to explore how variation in vitamin D levels might increase the risk of development of T2DM. This study could help in early diagnosis and enhance therapy management in T2DM conditions. The risk of T2DM is growing

daily, mainly due to lifestyle factors and genetics. Many lifestyle factors are significant in the development of T2DM, including physical activity, a sedentary lifestyle, smoking, and alcohol consumption. Additionally, obesity has been seen as an essential factor in cases of T2DM, with approximately 55% [27, 28]. The findings of our study demonstrated that individuals with T2DM had reduced vitamin D levels. Furthermore, a substantial statistically inverse correlation existed between HbA1c% and serum vitamin D3 25 (OH). This indicates a positive connection between diabetes control and vitamin D metabolism [29].

There are multiple factors for hyperglycemia in individuals, but decreased levels of vitamin D is a significant factor in all of them [30]. It is believed that action metabolism of vitamin D is involved in diabetes control not only regulate plasma calcium levels. Vitamin D is also directly involved in the function of pancreatic Beta-cells, which influence insulin synthesis and secretion [31]. The presence of (VDR) and (DBP) in pancreatic tissues has played an essential role in glucose metabolism. But sometimes, specific allelic variations in the VDR and DBP genes can cause glucose tolerance and insulin secretion. Moreover, it is stated that decreased level of 1,25-(OH)2D3 inhibits insulin secretion and affects cell growth and VDR levels in the RIN beta-cell line [32]. In scientific investigations on animals, it was found that mice with non-functional VDRs reduced insulin secretion. Moreover, it has also been evidenced in mice tissues where treatment of the pancreas with vitamin D supplements showed improved insulin biosynthesis [33]. The vitamin D and calcium supplement in adults with T2DM potentially improve β cell function and improve insulin secretion. This study was conducted in 16 weeks with randomized trials with 92 adult participants assigned to receive cholecalciferol (vitamin D) or calcium carbonate supplements. The primary outcome was alternation in beta cell functions [34], assessed by IV glucose tolerance test. The secondary outcome includes acute insulin response and insulin sensitivity [35].

It is tough to understand the association between vitamin D and T2DM from a public health perspective. Several limitations and confounders must be alternated in the interpreting data on vitamin D and T2DM. there are significant confounders, including dietary factors, obesity, and genetic predispositions. Vitamin D deficiency is more prevalent in regions with limited sunlight exposure. In such regions, vitamin D supplementation is a cost-effective approach for T2DM prevention [36, 37]. Based on the above discussion, it can be concluded that vitamin D is essential for optimal blood sugar levels and regulating insulin secretion [29]. On the other hand, vitamin D has various potential effects on skeletal and extra-skeletal body tissues; people with diabetes must maintain adequate blood sugar control to achieve optimal vitamin D levels. Based on the findings of the research, it is recommended that all individuals with diabetes undergo regular monitoring of their vitamin D levels and maintain proper control of their blood sugar levels to reduce the risk of complications related to microvascular and macrovascular issues [38, 39].

5. Conclusion:

The findings of this study indicate a significant inverse correlation between vitamin D levels and HbA1c% among patients with T2DM. Vitamin D deficiency is linked to hyperglycemia, and this hyperglycemia leads to vitamin D deficiency by an unknown mechanism. The rising incidence and prevalence of T2DM highlight the importance of modern approaches to management and prevention, which involve the use of vitamin D supplements and diabetes treatment. It is a practical preventive approach to maintain optimal vitamin D levels to reduce complications in diabetic conditions. Glycemic control is also essential for maintaining optimal vitamin D levels, even in patients with T2DM.

Conflict Of Interest: The authors declare no conflict of interest.

Abbreviations:

T2DM = Type 2 diabetes mellitus, DM = Diabetes mellitus, HbA1c = Glycated hemoglobin A1c, IDF = International Diabetes Federation, MENE = Middle East/North Africa, UVB = Ultraviolet B.

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