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THE RELATIONSHIP BETWEEN VITAMIN D DEFICIENCY AND DIABETIC RETINOPATHY: A CROSS-SECTIONAL STUDY

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ABSTRACT

Introduction: Diabetic Retinopathy (DR) is the most common cause of legal blindness among the working-age group. To date, its relationship with vitamin D deficiency remains ambiguous in the literature. This study aimed to fill this gap by further assessing the association between vitamin D deficiency and DR.
Materials and Methods: A cross-sectional study was conducted at a diabetes center in Tabuk City, Saudi Arabia, from April 2019 to March 2020. A structured questionnaire was used to collect data regarding patient demography, the duration of diabetes, and any chronic diseases. It also included a series of direct interview questions for the participants regarding vitamin D supplementation and its related factors. Data related to DR were also reported. Furthermore, a blood sample was taken to measure the vitamin D levels of the participants.
Results and Discussion: Out of the 174 participants with the diagnosis of diabetes mellitus (49.4% women) within the age range of 25–94 years (mean age 49.80±13.45) who participated in this study, retinopathy was found in 31%, and vitamin-D deficiency was reported in 36.8% of the participants. No relationship was established between DR and vitamin D deficiency (P-value 0.084), nor between retinopathy, Body Mass Index (BMI), and gender (P-values 0.117 and 0.637 respectively). However, DR was found to be associated with the duration of diabetes (P-value 0.004).
Conclusion: There was no evidence of a relationship between DR and vitamin D deficiency, and retinopathy was found to be not associated with BMI or gender. However, DR was found to be associated with the duration of the disorder.

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Introduction

With 350 million people currently suffering from the disease and with the number expected to double worldwide by the year 2030, diabetes mellitus has become an epidemic [1]. Nearly a quarter of Saudi Arabia's population is suffering from diabetes mellitus (23.1%) [2]. Diabetic complications such as Diabetic Retinopathy (DR) have become a major challenge for the healthcare system [3]. Furthermore, DR is becoming the leading cause of blindness among the working-age group, which is responsible for the considerable growth of adult work disability. [4]

It should be noted that the degree of prevalence of DR varies from region to region in Saudi Arabia. According to a registry-based study, an overall prevalence of 19.7% and the age and duration of diabetes are the most common risk factors of developing any degree of DR. [5] Another study [6] reported a prevalence of 36.4%, while other studies from Saudi Arabia reported a prevalence of 44.7%. [7] Therefore, based on these studies, it can be concluded that DR is the common complication experienced by diabetic patients in Saudi Arabia.

On the other hand, a high prevalence of vitamin D deficiency has also been reported in Saudi Arabia and all over the globe. It is estimated that 60% of the Saudi population has some degree of vitamin D deficiency. [8]

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Vitamin D receptors are found in various organs including the retina. [9, 10] Whether vitamin D might prevent the development and progression of DR due to its anti-inflammatory and antiangiogenic properties is a controversial topic. This hypothesis has gained importance due to the presence of some previous evidence. [11] Moreover, some hypotheses have associated vitamin D with diabetes mellitus in general due to its ability to positively regulate systemic hypertension [12] and control blood glucose, [13] both of which are well known for increasing the risks of DR. [14, 15] These adjustable nutritional factors may influence the incidence and progression of DR, but they have been understudied in epidemiological implementation. Furthermore, the number of epidemiologic studies evaluating the possible relationship between vitamin D and DR is limited, with this relationship being proposed in only some studies. [16]

A multicenter study conducted with 4767 patients in China showed that patients whose vitamin D level was in a lower quartile had a higher prevalence of DR compared to their counterparts in the first quartile. [17] Mutlu et al., Zoppini et al., and Bajaj et al. supported the above findings. [18-20] Nadri et al. found that a vitamin D level of ≤ 18.6 ng/mL is associated with proliferative DR, [21] a finding that is supported by Yuan et al. [22] who conducted a case-control study and found that vitamin D deficiency is associated with the onset of type 2 diabetes mellitus and its vascular complications such as DR. [23] Another study established that vitamin D deficiency places diabetic patients at risk of developing DR and loss of hearing. [24] A study conducted in India highlighted the association of vitamin D deficiency with the severity of DR. [25] Similarly, a meta-analysis study underlined a significant association between vitamin D deficiency and DR. [26] Other similar studies also found an association between vitamin-D deficiency and the presence and severity of DR in patients with type 2 diabetes, [27] wherein a vitamin D level of more than 75 ng/mL implied a lower risk of developing DR. [28] Conversely, many studies have also denied the possibility of any relationship between a vitamin-D deficiency and DR prevalence or severity. [29-31] A study conducted in China found that vitamin D deficiency was associated with retinopathy only among patients with a well-controlled blood sugar level. [32] Vitamin-D deficiency was not found to be related to Body Mass Index (BMI), age, or DR, but it was found to be associated with the duration of diabetes. [33] Engelen et al. [34] reported similar findings. Alam et al., however, in another study did not find any association between vitamin D in serum and the presence or severity of DR. [35] In hindsight, it can be concluded that the relationship between vitamin D and DR is a hot topic of discussion, and thus, more studies are required to establish a relationship between the towns, if there is a possibility of any. For this and other reasons, this study assesses the relationship between vitamin D deficiency and DR in Tabuk City, Saudi Arabia.

Methods:

This is a cross-sectional study that was conducted with 174 diabetes mellitus patients who visited the diabetes center in Tabuk City, Saudi Arabia, from April 2019 to March 2020. This is the only diabetic center in Tabuk. The center serves almost 12,000 people. The patients were known cases of diabetes as per the American Diabetes Association and were visiting the center for regular checkups. A face-to-face interview was carried out using a structured questionnaire. The information gathered was: patient demography, the duration of diabetes, and the habits of naturally acquired vitamin D such as through sun exposure (15 minutes daily), milk consumption, and daily physical activity of 30 minutes at least five times/week. Furthermore, an expert ophthalmologist conducted a retinal examination after pupillary dilatation. The following were reported: microaneurysms, blot or flame-shaped hemorrhages, hard exudates, cotton-wool spots, Neovascularization of Disc (NVD), Neovascularization of Elsewhere (NVE), and Neovascularization of Iris (NVI) or evidence of laser treatment for DR. Furthermore, the presence of chronic diseases such as hypertension, dyslipidemia, liver cirrhosis, renal failure, and mal-absorption was also identified. Family history of diabetes, vitamin D supplementation, and medications, including antihypertensive, lipid-lowering, and diabetes medications were also reported and collected from the patient files. Furthermore, a blood sample was taken from the patients to determine their vitamin D level. Chemiluminescence immunoassay was used to estimate the level of 25(OH)-vitamin D [36], wherein a level of≤20 ng/mL is considered deficient [37].

The BMI was calculated from the weight and height (BMI ≥30, 25–29, and 18–25 were considered obese, overweight, and normal, respectively). HbA1c was collected from the patients' medical records.

All participants signed a written consent form, and the ethical committee of the University of Tabuk, Saudi Arabia approved the research.

Statistical Analysis:

The Statistical Package for Social Sciences (SPSS, version 20, New York) was used during the analysis of the collected data. Descriptive and summary statistics were performed to describe the study participants according to their different characteristics. Additionally, a binary logistic regression analysis was conducted to test the relationship between DR and vitamin D deficiency. A-P value of<0.05 was considered to be significant.

Results:

Out of the 174 participants with diabetes mellitus (49.4% of whom were women) (Figure 1) who were within the age range of 25–94 with a mean value of 49.80±13.45 years and who had been diagnosed with diabetes for 9.36±6.56 years, 75.9% were found to be exposed to sunlight for more than 15 minutes daily, and 13.7% were found to consume 3 cups of milk/day.

This implies that the milk consumption of the group was inadequate. Renal impairment, hypertension, dyslipidemia, and coronary artery disease were reported in 1.1%, 23%, 5.7%, and 4.6% of the participants, respectively. DR (either Non-proliferative Diabetic Retinopathy (NON-PDR) and/or Proliferative Diabetic Retinopathy [PDR]) was found in 31% of the participants. As shown in Figure (2), 48.3% of the patients were on vitamin D supplements, and nearly half (49.4%) were adhering to exercising. It should be noted that 71.3 percent of them had a family history of diabetes, and the mean of their BMI was 26.96±4.51, their glycated hemoglobin was 8.50±1.60, and their vitamin D level was 26.37±13.76. Vitamin-D deficiency was reported in 36.8% of the participants. In this study, 37% of the patients were on hypertension medications, 23% on lipid-lowering drugs, 35.6% on oral hypoglycemic medications, 12.6% on insulin, and 51.7 percentage were using insulin as well as oral drugs (Table 1).

This study found no evidence of a relationship between DR and vitamin D deficiency (Wald 2.994, P-value 0.084, CI 0.841–16.264), nor could DR be associated with BMI and gender (Wald 2.459, P-value 0.117, CI 0.776–1.029 and Wald 0.223, P-value 0.637, CI 0.369–5.092, respectively). However, DR was found to be associated with the duration of diabetes (Wald 8.095, P-value 0.004, 95% CI 0.766–0.952) (Table 2).

Table 1. Basic Characteristics of the Study Group

Age (25–94)	49.80±13.45
Sex	
Males	88 (50.6%)
Females	86 (49.4%)
Duration since the Diagnosis of Diabetes	9.36±6.56
Adequate Sun Exposure	132 (75.9%)
Adequate Milk Consumption	24 (13.7%)
Renal Failure	2 (1.1%)
Hypertension	40 (23%)
History of Coronary Artery Disease	8 (4.6%)
Dyslipidemia	10 (5.7%)
Retinopathy	254(31%)
On vitamin-D	84 (48.3%)
Exercise	86 (49.4%)
Family History of Diabetes	124 (71.3%)
Body Mass Index	26.96±4.51
Vitamin-D Level (ng/ml)	26.37±13.76
vitamin-D deficiency	64 (36.8%)
The Glycated Hemoglobin	8.50±1.60
Antihypertensive Drugs	66 (37.9%)
On Statins	40 (23%)
Hypoglycemic Drugs	
Oral	62 (35.6%)
Insulin	22 (12.6%)
Both Oral Hypoglycemic Drugs and Insulin	90 (51.7%)

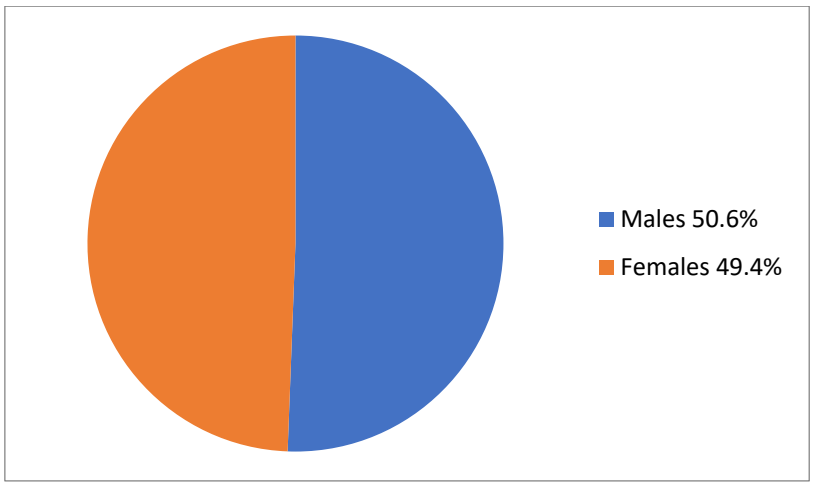

Figure 1: Gender Distribution of the Sample

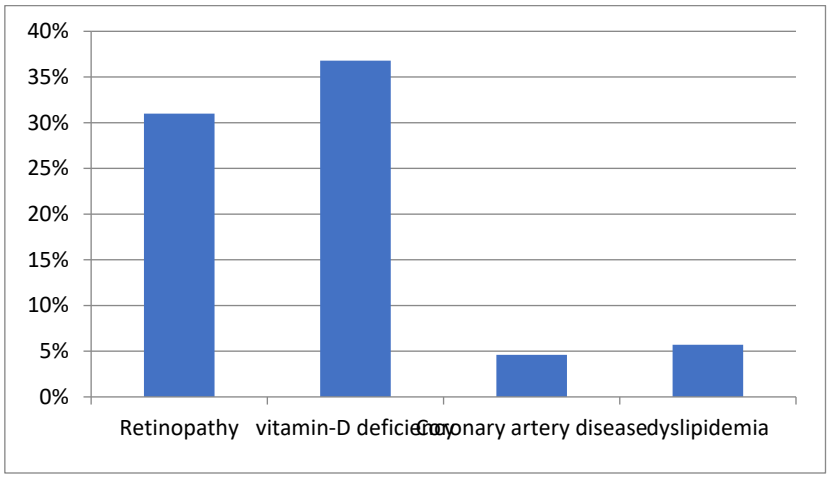

Figure 2: Retinopathy, Vitamin-D Deficieny, and others among the Sample

Table 2. The Association between DR, Vitamin-D deficiency, BMI, duration of Diabetes Mellitus, Vitamin D Supplementation, and Gender

Character	Wald	P-value	95% CI
Vitamin-D Deficiency	2.994	0.084	0.841–16.264
Vitamin-D Level	0.798	0.372	0.434–9.336
BMI	2.459	0.117	0.776–1.029
Duration of Diabetes	8.095	0.004	0.766–0.952
Gender	0.223	0.637	0.369–5.092
Constant	4.691	0.030	

Discussion:

In this study, DR was reported in nearly one-third of the participants. This finding is consistent with that of previous studies from Saudi Arabia. [7] The data obtained from this study revealed a vitamin D deficiency in 36.8% of the participants even though the majority of them were receiving adequate sun exposure and nearly half of them were on vitamin D supplementation (10000–50000 IU/month). The findings of this study are, therefore, in line with Ahmed et al.'s findings. [6] These findings can be explained by the idea that genetic factors play a role or that different methods of assessment reveal varying vitamin D levels. Previous literature has shown that vitamin D supplementation has immunomodulatory effects on patients with DR. [38] A high BMI and a lack of physical activity are reflected in the poor glycemic control that was observed in the current sample following previous findings. [39] In the current survey, no association was found between vitamin D deficiency and retinopathy, which contradicts previous observations. [8, 40] The reasons for this inconsistency are not clear. However, a possible explanation can be that this discrepancy resulted from a variation in the definition of vitamin D deficiency or the cutoff level for vitamin-D deficiency. In the present study, a level of ≤20 ng/mL was considered indicative of deficiency, which is virtually in agreement with most studies, although many studies consider a vitamin D serum level of less than 10 ng/ml to define vitamin D deficiency. [41] Another possible explanation for the present study not finding a relationship between DR and vitamin D deficiency, which contradicts the result of many observational studies that found a connection, is the great extent of vitamin D deficiency among the Saudi population, which is even seen in 60% of the population in some studies. Therefore, no relationship between the two could be adequately detected [42]. Conversely, some other studies also found no association between the two, which is in line with our findings. [43, 44] Many previous studies found no association between obesity and DR either, [8, 40] supporting the current findings in which no association was identified between DR and BMI. In the present study, DR was found to be associated with the duration for which the participants had diabetes, similar to some previous observations. [45, 46] A study published in Hong Kong [47] found no association between gender and DR, which is consistent with the observations of the current study.
The current study was limited by the small-sized study sample and the fact that the study was conducted at a single tertiary center. The latter meant that the study could not control for the various risk factors associated with retinopathy.

Conclusion:

DR and vitamin D deficiency were common among patients with diabetes mellitus in Tabuk City, Saudi Arabia. However, no association was discovered between DR, vitamin D deficiency, BMI, and gender. Retinopathy, instead, was found to be associated with the time elapsed since the diagnosis of diabetes mellitus.

Abbreviations:
DR: Diabetic Retinopathy
BMI: Body Mass Index
NVD: Neovascularization Disc
NVE: Neovascularization Elsewhere
NVI: Neovascularization Iris
SPSS: The Statistical Package for Social Sciences

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Conflicts of Interest
None

Availability of Data:
All the data presented in this manuscript are available on request.

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