Article published online: 2020-05-09

Ann Natl Acad Med Sci (India), **53(3):** 156-165, 2017

Association of Vitamin D and Diabetic Retinopathy in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Objective: To assess the association of vitamin D (VD) and diabetic retinopathy (DR) in patients with type 2 diabetes mellitus (T2DM).

Method: Literature search was conducted for studies assessing the association of VD and DR. Total 9 studies have a sum total of 1741 patients were included for final analysis.

Results: The concentration of VD in controls ranged from 17.5±3.6 to 31.9±12.9 ng/ml, while for T2DM patients without retinopathy it ranged from 11.94±4.21 to 23.10±6.12 ng/ml. T2DM patients with retinopathy had the lowest concentration, ranging from 10.02±5.61 to 19.25±7.86 ng/ml. A higher percentage of T2DM patients without (50.7% to 68.80%) and with (31.2% to 79.63%) retinopathy had VD deficiency (VDD).

Discussion: An inverse association between VD levels and DR was observed. The concentration of VD decreases as the stage of DR advances. VD seems to be an easily modifiable risk factor for DR. Thus, VD supplementation should be encouraged in population at higher risk for diabetic complications.

Keywords: Vitamin D, cholecalciferol, retinopathy, vitamin D deficiency, diabetic retinopathy, diabetic complications, type 2 diabetes, systematic review.

Introduction

With the rapid increase in the incidence of diabetes mellitus (DM) in recent years, the complications related to diabetes have become a larger health problem. Inadequately controlled diabetes precipitates various long-term microvascular (blindness, neuropathy and nephropathy) and macrovascular (cardiovascular and stroke) complications (1, 2) which form the leading cause of morbidity and mortality in diabetic patients worldwide (1). Diabetic retinopathy (DR) being one of the most prevalent complication of diabetes, is considered as a major culprit of blindness globally (1, 3). DR is also the most common cause of non-traumatic visual loss in the working-age population. It has been estimated that the worldwide prevalence of DR was 93 million (35%) and the prevalence of vision-

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threatening DR was 28 million (10.2%) among diabetic patients in 2010 (4). World Health Organization estimates that throughout the time DR accounts for approximately 5% of the worldwide prevalence of blindness, the prevalence rises sharply to 15-17% in developed countries (3).

There are various risk factors that have been suspected in the pathogenesis of DR, like hypertension and hyperglycemia. Although, hypertension and hyperglycemia have demonstrated strongest association, interventions directed at improving these factors have shown moderate success. Thus, the interactions among neural and retinal vascular dysfunction and the mechanisms leading to retinal pathology including neovascularisation have been questioned recently (3).

In addition to the classical role in skeleton and bone health, vitamin D (VD) has been identified to exert non-classical pleiotropic effects such as anti-inflammatory, antiangiogenic, antiproliferative, and immunomodulatory properties (5). It is also considered to positively regulate hypertension and blood glucose levels (6). Moreover, it has been established that maintaining VD at adequate levels can be a useful technique to prevent type 2 diabetes mellitus (T2DM) (7). T2DM and VD deficiency (VDD) have been considered as pandemic diseases with a number of health consequences. Furthermore, VDD is known to be more common in patients with diabetes (5). VDD has an established role in developing the risk of diabetic complications as VD is considered to affect the risk for retinopathy, due to its immunomodulatory properties (3). However, the effect of low levels of VD on causation of type 1 DM (T1DM) is well established, the association between VDD and T2DM is not consistent. Evidences collected from many epidemiological studies, indicate that most of the T2DM cases are attributable to manageable habits and lifestyle changes. Therefore, the identification of easily modifiable risk factors is crucial for the prevention of diabetes and its complications (1). Since, the evidence regarding the association of vitamin is limited (8), and, the prevalence of VDD is contentious in T2DM patients (9), this systematic review has been conducted to establish or refute the association between VD and DR.

A recent PubMed search (till March 31, 2017), with the use of terms “vitamin D” and “retinopathy,” yielded only 159 publications. Thus, few studies have addressed the question of the potential implication of VD in the pathogenesis of DR. Among these studies there were only 9 publications that met the inclusion criteria. The aim of this study was to collect available evidence on the association between VD and DR, and to summarize the results by performing a systematic review of published studies according to Meta-analysis of Observational Studies in Epidemiology (MOOSE) group recommendations (10). The primary objective of this review is to assess whether there is an association between VD status and DR in T2DM.

Methods

Criteria for Considering Studies for the Analysis

All the studies which were retrieved from different search sources based on search terms were screened according to the predefined inclusion and exclusion criteria. Cohort/cross-sectional/case control studies assessing the association between VD and retinopathy in T2DM patients were included in this systematic review. Studies on T1DM, not related to DR, not assessing VD levels, pediatric studies, retrospective studies, studies reporting combined result on both T1DM and T2DM, studies reporting combined data on complications of diabetes and studies with insufficient data were excluded.

Data sources and searches

We conducted an electronic literature search strategy for different PUBMED (till September 2016) for English language to identify studies on retinopathy. We further searched for additional trials in http://www.clinicaltrials.gov and http://ctri.nic.in. The search terms used were vitamin D and retinopathy. Full-text articles were retrieved and reviewed for performing systematic review.

Data extraction and analysis

Data extraction from the selected studies was conducted. Standard Excel spreadsheets were used for the data extraction. The following data were collected from the included studies: first author, year of publication, number of participants, mean age, duration of diabetes, HbA1c levels, body mass index, insulin therapy, total cholesterol, triglycerides, high density lipoprotein and low density lipoprotein.

Results

Search Results

The literature search results are summarized in the flowchart below (Fig. 1). After application of the inclusion and exclusion criteria, predefined in the study protocol, a total of 9 randomized controlled trials (RCTs) were included in the final systematic analysis. Amongst the nine studies included in the systematic review, six studies compared the VD levels in controls and in T2DM patients with DR

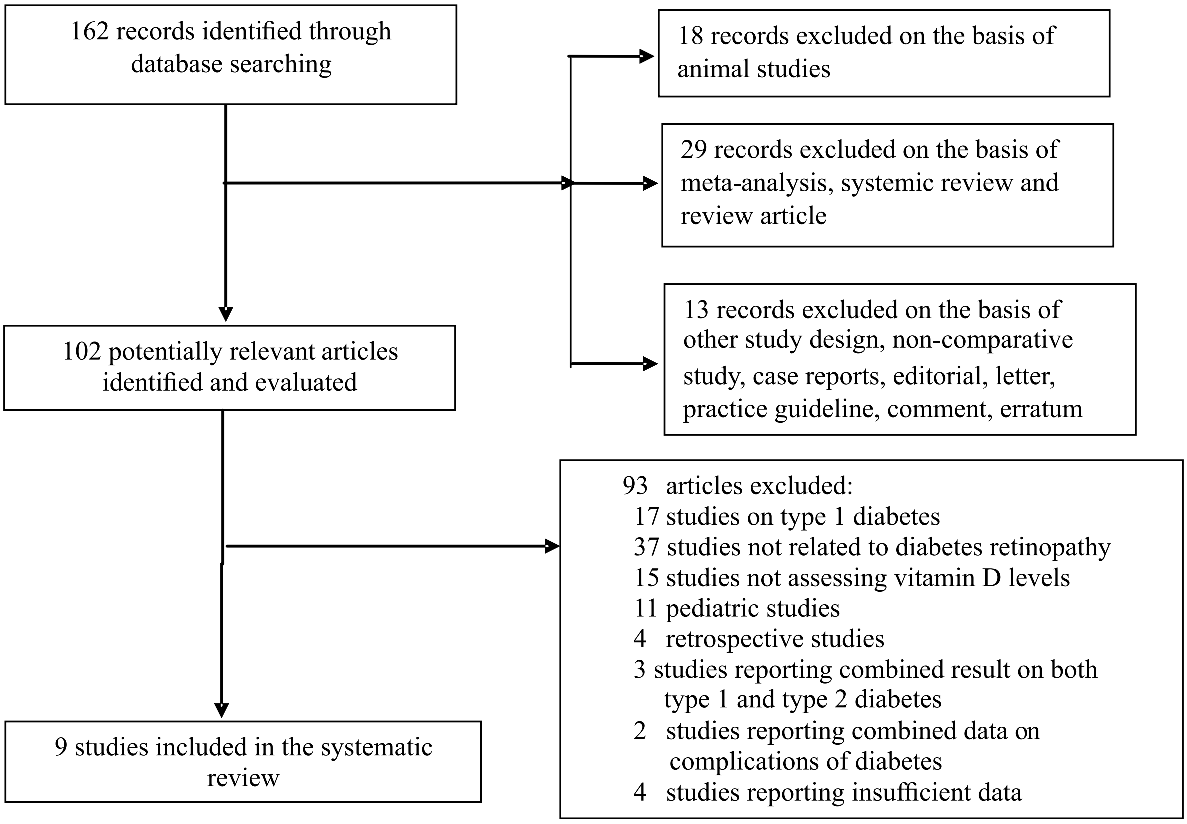
162 records identified through database searching
18 records excluded on the basis of animal studies
29 records excluded on the basis of meta-analysis, systemic review and review article
13 records excluded on the basis of other study design, non-comparative study, case reports, editorial, letter, practice guideline, comment, erratum
102 potentially relevant articles identified and evaluated
93 articles excluded:
17 studies on type 1 diabetes
37 studies not related to diabetes retinopathy
15 studies not assessing vitamin D levels
11 pediatric studies
4 retrospective studies
3 studies reporting combined result on both type 1 and type 2 diabetes
2 studies reporting combined data on complications of diabetes
4 studies reporting insufficient data
9 studies included in the systematic review

Fig. 1: Flow diagram of the literature search strategy. Number of studies identified and rejected at each stage are described.

(1, 9, 11-14), and 4 studies demonstrated the difference between controls and T2DM patients without DR (1, 11-13), one study demonstrated the difference in the levels in T2DM patients with or without DR, and further with Grade 1 or Grade 2-4 DR (8), one study compared the VD levels in patients without DR with non-sight threatening DR (NSTDR) and sight threatening DR(STDR) (15), two studies demonstrated the difference between control, T2DM patients with proliferative DR(PDR) (9, 14) and one study compared the VD levels in controls, T2DM with PDR and non-proliferative DR (NPDR) (16).

Clinical Characteristics of Study Participants

A total of 9 studies were included, analyzing 1,741 diabetic patients. The mean age of controls ranged from 50.7±13 to 60.1±10.9 years, for diabetics without retinopathy the age ranged from 53.22±0.867 to 58.28±11.39 years, while for diabetics it ranged from 52.85±8.26 to 61.6±11.5 years. Mean duration of diabetes in diabetics without retinopathy ranged from 7.2±5.5 to 11.24±5.34 years, whereas, for diabetics with retinopathy the duration ranged from 5.34±3.09 to 13.9±7.3 years. In the diabetics without retinopathy the HbA1c levels ranged from 7.3±1.2% to 10.36±0.65%. However, in diabetics with retinopathy the levels ranged from 7.7±1.4% to 10.88±0.55%. The mean duration of diabetes in patients with PDR was 22.0±10.5 years, while for NPDR it was 18.9±11.1 years. For patients with NSTDR and STDR, the mean duration of diabetes was 10.31±7.05 and 11.68±7.26 years, respectively, while the HbA1c level was 8.94±2.17% and 8.95±2.30% for patients with NSTDR and STDR, respectively (Table 1).

Vitamin D Concentration and Diabetic Retinopathy

The mean concentration of VD in controls ranged from 17.5±3.6 to 31.9±12.9 ng/ml, while the mean concentration of VD for T2DM patients without retinopathy ranged from 11.94±4.21 to 23.10±6.12 ng/ml. T2DM patients with retinopathy had the lowest concentration, ranging from 10.02±5.61 to 19.25±7.86 ng/ml. The VD level in T2DM patients with NPDR was 23.6±10.3, whereas, for PDR the concentration ranged from 11.62±5.69 to 21.10±10.5 ng/ml. Patients without DR had the highest levels (20.5±8.1 ng/ml) as compared to patients with Grade 1 (20±9 ng/ml) and Grade 2-4 DR (18.6±11 ng/ml). Similarly, patients without DR had the highest levels (18.86±7.12 ng/ml) as compared to patients with NSTDR (17.44±6.19 ng/ml) and STDR (15.36±4.81 ng/ml) (Table 2).

Prevalence of Vitamin D Deficiency and Diabetic Retinopathy

Prevalence of VDD ranged from 34.61% to 53% in controls. A higher percentage of T2DM patients without retinopathy and with retinopathy had VDD, which was in the range of 50.7% to 68.80% in the former and 31.2% to 79.63% in the latter, respectively. Twenty-one percent T2DM patients with PDR had VDD, whereas, 18.5% T2DM patients with simple retinopathy had VDD. Percentage of T2DM patients having VDD was higher in Grade 2-4 DR (67.1%) vs 55.6% with Grade 1 DR. Prevalence of VDD was higher in patients with STDR (85.24%) as compared to NSTDR (70.18%)(Table 3).

Discussion

DM being the most common endocrine disorder with its increasing prevalence every year needs to be addressed urgently (17), as the complications of diabetes may become larger health problem. As evident by many epidemiologic studies, most T2DM cases are attributable to modifiable habits and lifestyle factors. Thus, the recognition of easily malleable risk factors is crucial for the prevention of diabetes and its complications (1).

Inadequately controlled DM precipitates various long-term microvascular (blindness, nephropathy, and neuropathy) and macrovascular (cardiovascular and stroke) complications (1, 2), which forms the leading cause of morbidity and mortality in patients of

Table 1 : Clinical characteristics of study participants

First author	Study design	Groups	N	Male %	Female %	Age (yrs)	Duration of diabetes (yrs)	HbA1c level (%)	BMI (kg/m^2)	Insulin therapy (%)	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)
Reddy *et al*, 2015* (1)	Cross-sectional case control	NDC	99	55	45	54.26± 0.743	NA	5.77± 0.20	25.02 ±5.16	NA	151.72 ±10.90	153.81 ±17.54	31.76 ±2.20	104.51 ±5.23
		DR	82	58	42	57.46± 0.913	10.69± 6.10	10.88± 0.55	24.39 ±4.51	NA	182.73 ±10.77	169.36 ±13.12	27.99 ±1.29	120.26 ±6.20
		DNR	82	57	43	53.22± 0.867	11.24± 5.34	10.36± 0.65	24.14 ±4.34	NA	171.47 ±15.24	185.94 ±17.22	26.02 ±1.68	121.16 ±4.90
Ahmadieh *et al*, 2013 (11)	Cross-sectional	Cases	136	38.7	61.3	59.2± 11.4	8.6±7	7.9±1.6	30.9± 5.2	NA	NA	NA	NA	NA
		Controls	NA	39.2	60.8	60.1± 10.9	NA	NA	28.8± 4.5	NA	NA	NA	NA	NA
Alcubierre *et al*, 2015 (8)	Observational case control	NR	144	51.38	48.62	58.1± 10.3	7.2±5.5	7.3±1.2	31.2± 5.2	NA	181.6± 37	137.4± 82.4	48.6± 10.9	111.6± 30.9
		R	139	51.08	48.92	60.3± 8.9	13.9±7.3	8.3±8.4	31.8± 5.4	NA	185.1± 36.5	140.5± 122.7	52.2± 15.6	106.4± 30.2
He *et al*, 2014 (15)	Cross-sectional	NDR	625	50.72	49.28	58.28± 11.39	8.29± 6.92	8.85± 2.69	24.28 ±3.52	NA	4.72± 1.01	1.71± 1.39	1.08± 0.29	2.79± 0.83
		NSTDR	562	50.88	49.11	58.90± 11.42	10.31± 7.05	8.94± 2.17	24.44 ±3.54	NA	4.83±1.28	1.85±1.95	1.09± 0.27	2.79± 0.87
		STDR	333	51.05	48.95	60.66± 12.47	11.68± 7.26	8.95± 2.30	24.24 ±3.52	NA	4.68± 1.26	1.62± 1.42	1.11± 0.31	2.71± 0.83
Bajaj *et al*, 2014 (12)	Cross-sectional case control	Cases	158	60.12	39.88	52.85± 8.26	5.34± 3.09	NA	NA	NA	NA	NA	NA	NA
		Controls	130	61.25	38.75	51.87 ± 6.43	NA	NA	NA	NA	NA	NA	NA	NA
Longo-Mbenza *et al,* 2014 (13)	Case control	NDNR	45	21	53.3	50.7± 13	NA	5±0.6	22.4± 2.9	NA	174.2± 141	75.6± 7.4	56.3± 14.5	63.1± 27
		All T2DM	150	65	56.7	55.2± 13	NA	9.3±4.1	25.8± 5.0	NA	203.2± 56.2	131.8± 45.5	45.3± 27.5	86.7± 45.7
		T2DM without DR		39	53.6	56.6± 12.4	NA	9.8±4.3	26.3± 5.0	58.3	205.1± 54.6	125.2± 45.6	46.6± 118.8	86.2± 42.8
		T2DM with DR		26	66.6	53.4± 13.6	NA	9.8±4.3	25.2± 5	59.1	200.8± 58.6	137± 45.1	43.5± 35.8	47.3± 49.5
Aksoy *et al*, 2000 (14)	Cross-sectional	Controls	20	40	60	56.6± 5.14	NA	NA	NA	NA	NA	NA	NA	NA
		NDR	20	60	40	57.1± 9.41	4.3±5.17	NA	NA	NA	NA	NA	NA	NA
		BDR	15	46.66	53.33	56.9± 9.83	7.4±6.20	NA	NA	NA	NA	NA	NA	NA
		PrePDR	14	50	50	57.1± 5.81	9.7±4.54	NA	NA	NA	NA	NA	NA	NA
		PDR	17	52.94	47.05	58.8± 6.07	12.1± 4.62	NA	NA	NA	NA	NA	NA	NA
Suzuki *et al*, 2006 (9)	Case control	Cases	581	54.56	45.43	61.6± 11.5	11.8±8.6	7.7±1.4	24± 3.9	NA	NA	NA	NA	NA
		Controls	51	49.01	50.98	58.2± 10.6	NA	4.8±0.6	22.0± 2.8	NA	NA	NA	NA	NA

Payne *et al*, 2012 (16)	Cross section-al	ND or OD	NA	53	NA	62.0± 11.6	NA	5.8±0.5	27.9± 6.1	NA	NA	NA	NA	NA
		ND and OD	NA	45	NA	59.8± 13.3	NA	5.8±0.3	28.7± 8.0	NA	NA	NA	NA	NA
		No BDR	NA	51	NA	62.4± 11.3	7.4±7.8	7.5±2.0	31.7± 9.8	24	NA	NA	NA	NA
		NPDR	NA	53	NA	68.3± 10.0	18.9± 11.1	7.4±1.2	31.2± 6.7	73	NA	NA	NA	NA
		PDR	NA	50	NA	59.8± 12.0	22.0± 10.5	8.1±1.9	33.1± 6.7	74	NA	NA	NA	NA

Data are mean±standard deviation.

*Data in mean±standard error.

DR: diabetic retinopathy, DNR: diabetic without retinopathy, NDC: non-diabetic controls, ND: non-diabetic, OD: ocular disease, NR: non-retinopathy, R: retinopathy, NDR: no diabetic retinopathy, NSTDR: non-sight threatening diabetic retinopathy, STDR: sight threatening diabetic retinopathy, BDR: background diabetic retinopathy, NA: not available, BMI: body mass index, LDL: low-density lipoprotein, TC: total cholesterol, TG: triglycerides, HDL: high-density lipoprotein.

Table 2 : Vitamin D concentration and diabetic retinopathy

Author	Vitamin D levels (ng/ml)										P value
	Controls	T2DM with DR	T2DM without DR	T2DM with PDR	T2DM with NPDR	T2DM with simple DR	Grade 1 DR	Grade 2-4 DR	NSTDR	STDR	
Reddy *et al*, 2015 (1)	23.25±61.03	17.12±1.05	16.71±0.97	NA	NA	NA	NA	NA	NA	NA	<0.05*
Ahmadieh *et al*, 2013 (11)	22.5±12	21.8±13.7	12.3±5.5	NA	NA	NA	NA	NA	NA	NA	<0.001*
Alcubierre *et al*, 2015 (8)	NA	19.2±10.1	20.5±8.1	NA	NA	NA	20±9	18.6±11	NA	NA	<0.05**
He *et al*, 2014 (15)	NA	NA	18.86±7.12	NA	NA	NA	NA	NA	17.44±6.19	15.36±4.81	< 0.01#
Bajaj *et al*, 2014 (12)	27.19±9.36	23.10±6.12	19.25±7.86	NA	NA	NA	NA	NA	NA	NA	=0.0001*
Longo-Mbenza *et al*, 2014 (13)	30.85±6.81	15.22±4.4	10.02±5.61	NA	NA	NA	NA	NA	NA	NA	<0.0001*
Aksoy *et al*, 2000 (14)	24.28±6.71	11.94±4.21	NA	11.62±5.69	NA	NA	NA	NA	NA	NA	<0.001*
Suzuki *et al*, 2006 (9)	17.5±3.6	17.6±6.6	NA	15.1±8.0	NA	16.5±6.4	NA	NA	NA	NA	<0.05##
Payne *et al*, 2012 (16)	31.9±12.9	NA	NA	21.1±10.5	23.6±10.3	NA	NA	NA	NA	NA	<0.001*

Data are mean±standard deviation.

T2DM: type 2 diabetes mellitus, DR: diabetic retinopathy, PDR: proliferative diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy, NSTDR: non-sight-threatening diabetic retinopathy, STDR: sight-threatening diabetic retinopathy, NA: not available.

* cases vs control.

** grade 2-4 retinopathy vs no retinopathy.

# NSTDR and STDR vs without DR.

## PDR vs no DR.

Table 3 : Prevalence of vitamin D deficiency and diabetic retinopathy

First Author	Prevalence of VDD (%)										P value
	Controls	DM without retinopathy	DM with retinopathy	DM with PDR	T2DM with simple DR	T2DM with NPDR	Grade 1 DR	Grade 2-4 DR	NSTDR	STDR	
Reddy *et al*, 2015 (1)	45	66	63	NA	NA	NA	NA	NA	NA	NA	<0.05*
Ahmadieh *et al*, 2013 (11)	53	68.8	31.2	NA	NA	NA	NA	NA	NA	NA	NA
Alcubierre *et al*, 2015 (8)	NA	50.7	61.9	NA	NA	NA	55.6	67.1	NA	NA	<0.05**
He *et al*, 2014 (15)	NA	63.61	NA	NA	NA	NA	NA	NA	70.18	85.24	<0.01#
Bajaj *et al*, 2014 (12)	34.61	NA	79.63	NA	NA	NA	NA	NA	NA	NA	=0.0001
Suzuki *et al*, 2006 (9)	NA	60.3	NA	21.0	18.5	NA	NA	NA	NA	NA	NA

Data are mean±standard deviation.
T2DM: type 2 diabetes mellitus, DR: diabetic retinopathy, PDR: proliferative diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy, NSTDR: non-sight-threatening diabetic retinopathy, STDR: sight-threatening diabetic retinopathy, NA: not available.
* cases vs control.
** grade 2-4 retinopathy vs no retinopathy.
# NSTDR and STDR vs without DR.

diabetes worldwide (1). DR being one of the most prevalent microvascular complications is considered as a major culprit of blindness globally (1, 3). Various risk factors have been implicated in the pathogenesis of DR. Although, hypertension and hyperglycemia have demonstrated strongest association with the DR, interventions directed at improving these have shown moderate success. Thus, the interactions among neural and retinal vascular dysfunction and the mechanisms leading to retinal pathology including neovascularisation have been questioned recently (3).

VDD has been associated with increased risk of chronic diseases, such as cancer, T2DM, cardiovascular disease, and autoimmune diseases including T1DM and multiple sclerosis, as evident from epidemiologic studies (1, 8, 18). Moreover, a wide prevalence of VDD and DM has been observed across all ages, socioeconomic conditions, races, and geographic regions. Despite, the well-established effect of hypovitaminosis D on causation of T1DM, the relationship between VD insufficiency and T2DM is inconsistent (1).

Nutritional status, particularly micronutrients, might influence the risk for DR by affecting the biochemical mechanisms underlying DR (1, 3). Moreover, studies have suggested that VD might influence the risk for diabetes and its complications (1). VD has shown pleiotropic effects such as, suppression of cell-mediated immunity, regulation of cell proliferation, stimulation of neurotropic factors like nerve growth factor, glial cell line-derived neurotrophic factor, neurotropin, suppression of renin–angiotensin–aldosterone system, reduction of albuminuria, immunomodulatory effects (12), anti-inflammatory effects, anti-angiogenic, and anti-fibrotic properties (12, 19) and therefore all these VD effects may provide a potential link between VDD and diabetic complications (3) including DR, as there are rising evidences that, inflammation and angiogenesis are involved in the initiation and propagation of DR (19). Findings from some recent studies show a significant inverse association between 25-hydroxyvitamin D [25 (OH)D] levels and the prevalence of diabetic microangiopathy, thus suggesting that VD and microvascular complications are strictly inter-related. Nonetheless, whether lower levels of VD are the cause or result of the microvascular complications are currently unknown (2). Moreover, the possible role of vitamins in the pathogenesis of diabetic complications is of much interest (8).

In a study conducted on T2DM patients low blood VD concentrations were found to be associated with an increased risk of macro- and microvascular disease events (18). Additionally, a study found an inverse relationship between 25(OH)D and the severity of DR, thus concluding that, lower 25 (OH)D status strongly correlates with a higher prevalence of microvascular complications in T2DM patients (2). Another study including both T1DM and T2DM patients, showed an association between the severity of DR and prevalence of VDD (20). An inverse association of 25 (OH)D levels with DR was demonstrated only in men. However, the sex-related variation in the relationship between 25 (OH)D levels and DR is uncertain (19). Furthermore, a meta-analysis demonstrated that VDD is more prevalent in diabetic patients, and that VD supplementation may delay or prevent diabetic complications (21).

In contrast to most reports, serum 25-OH VD concentrations did not differ between subjects with or without diabetes in a retrospective study (21). Another study conducted retrospectively including both T1DM and T2DM patients, found no association between serum 25(OH)D and the presence and severity of DR (3). Thus, the evidence behind the association between VD and retinopathy is non-confirmatory, hence, this systematic review was performed.

The VD levels were found to be inversely associated with the presence of DR. The controls had the highest levels as compared to T2DM patients with or without DR. Additionally, T2DM patients without DR had higher levels than the patients with DR. Moreover, VDD has been found to be associated not only with the presence of DR but also with severity of DR. The concentration of VD decreased at advanced stages. Patients with Grade 2-4 DR had the lower concentration as compared to Grade 1, whereas, patients without DR had higher levels than Grade 1 patients. Similarly, patients with STDR had lower concentration than patients with NSTDR, while patients without DR had highest concentration. Controls had highest concentration as compared to T2DM patients with simple PDR, NPDR and PDR, with PDR patients having the least concentration. All the studies included in this systematic review showed a significant association between the VD levels and DR.

VDD was highly prevalent in the T2DM patients. However, two studies demonstrated that, the prevalence of VDD was higher in patients without DR than in patients with DR (1, 11), suggesting the prevalence of VDD irrespective of the presence of DR, whereas, one study demonstrated a higher prevalence of VDD in T2DM patients with retinopathy as compared to without retinopathy (8). An increased prevalence of VDD was observed in advanced stages of DR. The prevalence of VDD was higher in patients with PDR as compared to simple DR (9). A higher percentage of patients with Grade 2-4 had VDD that patients with Grade 1 DR. Prevalence of VDD was higher in patients with STDR than in NSTDR (15).

Despite, the scarce evidence behind the association of VD and DR, this systematic review suggests an inverse association between the two. However, the question on the potential role of VD in the pathogenesis of diabetic retinopathy is yet to be answered (8). Given previous research indicating possible anti-inflammatory and antiangiogenic properties of VD, the connection between VD and DR warrants further studies (20).

Conclusion

Through this systemic review, it was observed that there is an inverse association between the VD levels and DR. Additionally, the concentration of VD decreases as the stage of DR advances. Moreover, the prevalence of VDD is higher in T2DM patients as compared to controls, which further increases in the advanced stages of DR. Based on the results, it is advisable that VD levels should be routinely monitored in T2DM patients, as VD seems to be an easily modifiable risk factor for DR. VD supplementation should be encouraged in population at higher risk for the diabetic complications.

Funding Details

This paper was not funded.

Financial and Competing Interests' Disclosure

The author's report no conflicts of interest.

References

1. Reddy G, Sivaprasad M, Shalini T, *et al* (2015). Plasma vitamin D status in patients with type 2 diabetes with and without retinopathy. *Nutrition* **31(7-8)**:959-963.

2. Zoppini G, Galletti A, Targher G, *et al* (2015). Lower levels of 25-hydroxyvitamin D3 are associated with a higher prevalence of microvascular complications in patients with type 2 diabetes. *BMJ Open Diab Res Care* **3(1)**: e000058.

3. Alam U, Amjad Y, Chan AW, Asghar O, Petropoulos IN, Malik RA (2016). Vitamin D deficiency is not associated with diabetic retinopathy or maculopathy. *J Diabetes Res* **2016**:1-7.

4. Yun J-S, Lim T-S, Cha S-A, *et al* (2016). Clinical course and risk factors of diabetic retinopathy in patients with type 2 diabetes mellitus in Korea. *Diabetes Metab J* **40(6)**: 482-493.

5. Jung C, Kim K, Kim B, Kim C, Kang S, Mok J (2016). Relationship between vitamin D status and vascular complications in patients with type 2 diabetes mellitus. *Nutr Res* **36(2)**:117-124.

6. Millen A, Sahli M, Nie J, *et al* (2016). Adequate vitamin D status is associated with the reduced odds of prevalent diabetic retinopathy in African Americans and Caucasians. *Cardiovasc Diabetol* **15**: 128.

7. Papandreou D, Hamid Z (2015). The Role of vitamin D in diabetes and cardiovascular disease: an updated review of the literature. *Disease Markers* **2015**:1-15.

8. Alcubierre N, Valls J, Rubinat E, *et al* (2015). Vitamin D deficiency is associated with the presence and severity of diabetic retinopathy in type 2 diabetes mellitus. *J Diabetes Res* **2015**:1-7.

9. Suzuki A, Kotake M, Ono Y, *et al* (2006). Hypovitaminosis D in type 2 diabetes mellitus: association with microvascular complications and type of treatment. *Endocr J* **53(4)**:503-510.

10. Stroup D, Berlin J, Morton S, *et al* (2000). Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* **283(15)**: 2008-2012.

11. Ahmadieh H, Azar ST, Lakkis N, Arabi A (2013). Hypovitaminosis D in patients with type 2 diabetes mellitus: a relation to disease control and complications. *ISRN Endocrinol* **2013** : 1-7.

12. Bajaj S, Singh RP, Dwivedi NC, Singh K, Gupta A, Mathur M (2014). Vitamin D levels and microvascular complications in type 2 diabetes. *Indian J Endocrinol Metabol* **18(4)**: 537-541.

13. Longo-Mbenza B, Muaka MM, Masamba W, *et al* (2014). Retinopathy in non diabetics, diabetic retinopathy and oxidative stress: a new phenotype in Central Africa? *Int J Ophthalmol* **7(2)**:293-301.

14. Aksoy H, Akçay F, Kurtul N, Baykal O, Avci B (2000). Serum 1,25 dihydroxy vitamin D (1,25(OH)2D3), 25 hydroxy vitamin D (25(OH)D) and parathormone levels in diabetic retinopathy. *Clin Biochem* **33(1)**: 47-51.

15. He R, Shen J, Liu F, *et al* (2014). Vitamin D deficiency increases the risk of retinopathy in Chinese patients with type 2 diabetes. *Diabet Med* **31(12)**: 1657-1664.

16. Payne J, Ray R, Watson DG, *et al* (2012). Vitamin D insufficiency in diabetic retinopathy. *Endocr Pract* **18(2)**: 185-193.

17. Parveen R, Agarwal NB, Kaushal N, Mali G, Raisuddin S (2016). Efficacy and safety of canagliflozin in type 2 diabetes mellitus: systematic review of randomized controlled trials. *Expert Opin Pharmacother* **17(1)**: 105-115.

18. Herrmann M, Sullivan DR, Veillard A, *et al* (2015). Serum 25-Hydroxyvitamin D: a predictor of macrovascular and microvascular complications in patients with type 2 diabetes. *Diabetes Care* **38(3)**: 521-528.

19. Jee D, Han K, Kim E (2014). Inverse association between high blood 25-hydroxyvitamin D levels and diabetic retinopathy in a representative Korean population. *PLoS ONE* **9(12)**: e115199.

20. Patrick PA, Visintainer PF, Shi Q, Weiss IA, Brand DA (2012). Vitamin D and retinopathy in adults with diabetes mellitus. *Arch Ophthalmol* **130(6)**:756-760.

21. Usluogullari CA, Balkan F, Caner S, *et al* (2015). The relationship between microvascular complications and vitamin D deficiency in type 2 diabetes mellitus. *BMC Endocr Disord* **15(1)**: 33.