Review

Vitamin D Deficiency Increases the Risk of Diabetic Retinopathy: A Meta-Analysis of Observational Studies

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Abstract: Background: Diabetic retinopathy (DR) is one of the most prominent pathological microvascular complications in diabetes. A series of studies reported that vitamin D deficiency was associated with increased prevalence of retinopathy in diabetic patients but the results were inconsistent. In this study we focused on evaluating the relationship between vitamin D deficiency and DR by conducting a meta-analysis of observational studies. **Methods:** Systematic computerized searches were performed in PubMed, MEDLINE, and the Cochrane Library for relevant original articles till November 20, 2016. The pooled odds ratios (ORs) with corresponding confidence intervals (CIs) were calculated to assess the associated value of vitamin D deficiency to the risk of DR. 9 studies including 6332 participants were subjected to final analysis. **Results:** The results indicated that vitamin D deficiency increases the risk of DR (OR = 1.57, 95% CI 1.32-1.87) with a little heterogeneity ($I^2 = 23\%$). In addition, the subgroup analysis demonstrated that there were obvious heterogeneities in T2DM ($I^2 = 47.8\%$). Sensitivity analysis showed that the results were relatively stable and reliable. **Conclusion:** our meta-analysis demonstrated that vitamin D deficiency could increase the risk of DR.

Keywords: vitamin D deficiency; diabetic retinopathy; meta-analysis.

1. Introduction

Vitamin D plays an important role in human health, especially in bone metabolism[1]. In addition to its calciotropic function, the vitamin D has potent nonclassical pleiotropic effects, including immunomodulatory, anti-inflammatory, antioxidant, anti-angiogenic, and anti-proliferative properties[2-8]. Vitamin D appears to have important effects on glucose homeostasis via actions on insulin synthesis, secretion, and inflammation[2,9]. Multiple studies have previously shown that vitamin D deficiency is highly prevalent in type 1 and type 2 diabetes[10,11]. Additionally, there is a growing interest in the potential role of vitamin D in the development of diabetic micro- and macro-angiopathic complications[12]. Several clinical and experimental observations has reported that vitamin D deficiency is involved in several patho-physiological processes, such as inflammation, endothelial dysfunction, and up-regulation of the renin-angiotensin-angiotensin-aldosterone system (RAAS)[13,14], which have associated with the development of complications of diabetes[15]. Furthermore, the potential role of vitamin D in the development of diabetic retinopathy (DR) has been a matter of specific interest in recent years[16-20].

Diabetic retinopathy (DR) is regarded as the leading cause of legal blindness in adults worldwide. As one of the most prominent pathological microvascular complications in diabetes, the prevalence of DR in diabetes patients has attached more and more attention from public[12]. In the United States, among individuals with diabetes it has direct influences on quality of life and functional independence of aging, affecting about 28.5% of people with more than 40 years[21].

Modifiable nutritional factors may influence risk for DR, but they have been relatively understudied in epidemiologic investigations[22,23]. Accumulating evidence from some epidemiologic studies suggest that vitamin D status may be a novel modifiable risk factor for DR[6,7,24-26]. There is some experimental evidence on the preventive effect of vitamin D in the development of DR in a rodent model, In vitro and in vivo studies suggested that vitamin D affects blood pressure and blood glucose control, which are the strong risk factors for DR[5]. Vitamin D status could protect against development of DR via its anti-inflammatory and anti-angiogenic properties[2-5]. However, the evidence behind the involvement of vitamin D is really scarce. There are additionally epidemiologic studies implied that there was no significance between vitamin D status and the development of DR. To clarify the correlation between insufficiency vitamin D and the risk of DR, a meta-analysis of observational studies was conducted in this study.

2. Materials and Methods

2.1. Publication searches and selection Criteria

The studies that investigated the correlation between vitamin D insufficiency and the risk of DR were conducted through a systemic search in PubMed, MEDLINE and the Cochrane Library till November 20, 2016. The strategies included the keywords 'vitamin D' or '25-hydroxyvitamin D', and 'Diabetic retinopathy' or 'DR'. A comprehensive search of reference lists of all review articles and original studies matching the eligibility criteria were retrieved to identify all potential studies. After reviewing the abstracts, studies potentially eligible for inclusion were further assessed by reading full-texts. Two investigators independently assessed all papers and collected data.

2.2. Inclusion criteria

The inclusion criteria in the meta-analysis were as follows: (a) Both cross-section study and case-control studies were included. (b) The study should assess the association between vitamin D and DR risk. (c) The study reported the level of vitamin D in serum. (d) OR estimates with corresponding 95% CIs (or can be calculated on associated data) had to be reported. (e) Studies published in English were considered. (f) Vitamin D deficiency was regarded as the concentration of vitamin D in serum less than 30 ng/ml.

2.3. Data extraction

A standardized protocol for data collection was used for data extraction. For each study analyzed, the follow information was extracted: the first author's name, year of publication, study design, number of participants, number of cases, type of diabetes, country or area of origin, OR estimates and their corresponding 95% CIs. Data extraction was performed independently by two investigators, and any independently by two investigators initial disagreement was resolved by consensus after further review of the studies.

2.4. Statistical analysis

The ORs with 95% CIs were used to assess DR risk. If those variables were not offered, those data were conduct by a 2 x 2 table using the number of vitamin D deficiency cases in the DR and control group compare with the total number of participants in both group. For ORs and 95% CI, some studies compared high level vitamin D with DR, we transformed into comparing low level of VD with DR. *Forest plots* were used to visually assess pooled estimates and corresponding 95% CIs. The possible heterogeneity across included studies was assessed by the *Cochrane Q test* and *I²* statistic[27]; $p < 0.1$ for the *Q test* or $I^2 > 50\%$ was considered as significant heterogeneity. In the presence of significant heterogeneity, a random-effects model was used to calculate the pooled effect size; otherwise, a fixed-effects model was applied[28]. In addition, we performed a sensitivity analysis to investigate the influence of single study on the pooled estimate by omitting one study by turns. Furthermore, *Begg funnel* plots and *Egger's* regression test were applied to assessthe publication bias

of this meta-analysis at the $p < 0.10$ [29]. We also conducted subgroup analysis to explore the possible explanations for the heterogeneity. All the data were analyzed by the STATA version 12.0 software.

3. Results

3.1. Selected Articles

A total of 147 relevant articles were found in initial search from PubMed, MEDLINE and the Cochrane Library till November 20, 2016 for cross-section study and case-control studies, and then 108 articles were excluded after reviewing the titles and abstracts. Furthermore, we reviewed full-text for the final selection and excluded 18 papers in which the association could not evaluated, we further excluded 2 cohort studies and 2 reviews. In addition, 8 articles were excluded for insufficient data. In total, 9 papers were selected for the final analysis. A flow chart shows the process of selecting articles (Figure 1). According to the quality scale, 9 studies had 7 or more scores with high quality.

Figure1. Flow chart of article and study selection.

3.2. Description of the studies

The characteristics of the studies are listed in Table 1. Those studies were published from 2011 to 2016, in which two studies were conducted in North America, four studies were conducted in Asia, two studies were conducted in Europe and one studies conducted in Australia. Five studies assessed the association between serum vitamin D and DR in T2DM, two studies described this association in T1DM. The participants of other studies suffered from diabetic mellitus, but they did not report the type of DM. Among 9 studies, 4 of them showed a significant association between vitamin D deficiency and the risk of DR, others were not significant. This meta-analysis reported that compared with control group, vitamin D deficiency in diabetic patients were prone to get DR (OR = 1.57, 95% CI 1.32 - 1.87) on a fixed-effects model, and there was little heterogeneity across studies ($I^2 = 23\%$, $p = 0.239$), which indicated vitamin D deficiency increased the risk of DR (Figure 2).

Table 1. Characteristics of observational study included in the meta-analysis.

Author	Year	Location	Study design	Type of diabetic	Participants(N)	Case(N)	OR	LCI	UCI	Significant
Amy	2016	American	Population-Based prospective	T2DM	1399	277	1.07	0.76	2.22	No
Dong hyun	2014	Korea	Cross-Sectional	NR	2113	375	1.52	0.88	2.63	No
Bhanuprakash	2015	India	Case-Control	T2DM	164	82	0.9	0.47	1.7	No
R. He	2014	China	Cross-Sectional	T2DM	1520	865	1.63	1.23	2.15	Yes
H ARLEEN	2011	Australia	Cross-Sectional	T1DM	495	80	2.12	1.03	4.33	Yes
Nuria	2015	Spanish	Case-Control	T1DM	283	139	1.57	0.98	2.53	No
John F	2012	American	Cross-Sectional	NR	133	82	1.44	0.63	3.3	No
Naoki	2014	Japan	Cross-Sectional	T1DM	75	21	3.45	1.11	10.6	Yes
Hala	2013	Republic of Lebanon	Cross-Sectional	T2DM	210	136	2.8	2.1	8	Yes

NR: not report ; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetic mellitus.

Figure 2. Forest plot showing an association between vitamin D deficient and DR.

3.3. Subgroup analysis

We further respectively conducted subgroup analyses of all included studies based on location, source of controls and the type of diabetic mellitus to determine the influencing factors that may impact the overall result. The result of the Q -test was $p = 0.187$, $I^2 = 37.6\%$ in the Eastern country (Figure 3), and $p = 0.14$, $I^2 = 44.6\%$ in the hospital of control subgroup (Figure 4) and $p = 0.11$, $I^2 = 47.8\%$ in the T2DM subgroup (Figure 5). Thus these subgroups were used the fixed-effects models. The subgroup analysis based on location showed no significant associations between western country and eastern country. And there were no associations in different sources of controls and the type of diabetic mellitus as well (Table 2).

Table 2. Subgroup analysis of DR in control group and case group.

Subgroup	No. of study	OR [95%CL]	P	I ² (%)
Location				
Western country	5	1.62 (1.23-2.12)	0.24	27.4
Eastern country	4	1.54 (1.23-1.93)	0.19	37.6
Source of country				
Population –based	5	1.58 (1.29-1.95)	0.29	19.3
Hospital –based	4	1.55 (1.12-2.14)	0.14	44.6
Type of DM				
T1D	2	2.44 (1.33-4.47)	0	48
T2D	5	1.51 (1.24-1.85)	0.11	48

Figure 3. Forest plot showing the association of Eastern country and Western country with risk of DR. **Figure 4.** Forest plot showing the association of population-based and hospital-based with risk of DR.

Figure 5. Forest plot showing the association of T1DM and T2DM with risk of DR.

3.4. Publication bias

No sign of publication was find by examining *funnel plots*. The results of *Begg’s test* ($p = 0.75$ for OR) and *Egger’s test* ($p = 0.64$ for OR) indicated there was no obvious publication bias (Figure 6).

Figure 6. Funnel plot for the assessment of publication bias in the meta-analysis.

3.5. Sensitivity

We found that no individual publication was significantly bias in the results. The sensitivity analyses showed that the cumulative results were stable (Figure 7).

Figure 7. The plot showing the sensitive in the meta-analysis.

4. Discussion

Vitamin D deficiency has been reported to be associated with a series of diseases such as diabetes, inflammation, and cancer[30-32]. Moreover, low level of vitamin D has been approved to increase the risk of diabetic complications such as diabetic nephropathy, and diabetic foot[33,34]. Recently, there has been a rapidly grown interest in the associate between vitamin D status and the risk of DR. But the conclusion is still not clarified. Therefore, we performed a meta-analysis of 9 studies involving a total of 6332 individuals, which provided a comprehensive assessment of the protection of vitamin D against DR. This meta-analysis indicated that low level of vitamin D was associated with the increase risk of DR. Furthermore, the subgroup analyses were conducted according to location, source of controls and the type of DM to determine the factors that maybe affect the final result. There was no significant difference in the subgroup analyses of location and source of controls. In addition, we observed low heterogeneity, which maybe resulted from type of diabetes (T1DM $I^2 = 0$, T2DM $I^2 = 47.8\%$). Based on the conclusion, it would be necessary to inspect the level of serum glucose and retina in the people with low level of vitamin D.

The potential mechanisms of vitamin D against DR are still not clarified. Vitamin D has a series of potent nonclassical pleiotropic effects, including immunomodulatory, anti-inflammatory, antioxidant, anti-angiogenic, and anti-proliferative properties when recognized with vitamin D receptor[35,36]. Vitamin D receptor is widely expressed in most of the tissues, including retina[37,38]. It has been reported that the disruption of glucose metabolism caused microvascular disease, especially in retina. And vitamin D could stable the glucose metabolism by up-regulating insulin secretion, and protecting against β -islet cells damage in the pancreas[39,40]. *In vitro and in vivo* studies suggested that low level of chronic inflammation played an important role in the development of DR, which could induce the vascular endothelial cell damage[41,42]. Vitamin D has been reported that it could defend against vascular endothelial cells damage by the suppressing of inflammatory factors (MCP-1 and TNF- α)[37,43]. Since the characteristic of DR is vascular proliferation[44]. Vitamin D inhibited angiogenesis by reducing the expression of vascular endothelial growth factor and decreasing the proliferation of endothelial cell[4,5,45]. In conclusion, vitamin D can prevent DR by anti-inflammatory, anti-angiogenic, anti-proliferative and stabilizing the glucose metabolism.

Currently only a few of prospective cohort studies indicated that the level of vitamin D negatively associated with the risk of DR[20]. But there is still not enough evidence from clinical trials to prove that vitamin D supplementation could successfully treat DR. And also there are no uniform standards of the adequate dosages and duration of vitamin D supplementation. Therefore, further clinical trials are needed to confirm whether vitamin D supplementation can prevent DR and assess the effects of vitamin D supplementation in the patients with low level of vitamin D. At the same time, more clinical trial should be conducted to evaluate the benefits and disadvantage with long duration and high dose of vitamin D treatment.

Several limitations of this meta-analysis should be acknowledged. First, some inevitable bias may exist in our study, for example we only focused on papers published in English. It would miss some eligible studies that were not reported or published in other languages. Second, there may be some other factors affect the observed associations between vitamin D level and the risk of DR, such as BMI and duration of diabetic, which cannot be identified from the extracted data. It has been reported that the increase of BMI is along with risk of vitamin D deficiency[46]. Besides, we did not perform a subgroup analysis of the DR severity (no proliferation diabetic retinopathy or proliferation diabetic retinopathy) due to inadequately material.

5. Conclusion

This meta-analysis suggests that vitamin D deficiency increase the risk of DR. Further studies are needed to investigate the association between vitamin D deficiency and the risk of DR in type of DM and evaluate whether vitamin D supplementation can prevent DR.

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Abbreviations

DR	diabetic retinopathy
DM	diabetes mellitus
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetic mellitus

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