

# A Review and Meta-Analysis of The Association Between Vitamin D and Carotid Atherosclerosis in Patients with Type-2 Diabetes

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## Abstract

**Background and aims:** Many scholars have explored the relationship between carotid atherosclerosis and vitamin D in patients with type 2 diabetes. Summarize these studies and draw the conclusions.

**Methodology/Principal Findings:** An electronic search was conducted of several databases, including PubMed, Web of Science, EmBase, Cochrane library, China National Knowledge Infrastructure(CNKI), WANFANG DATA, for papers that describe the association between serum 25-hydroxyvitamin D(25OH-D) related to CAS in patients with type 2 diabetes(T2D).Of these, 6 met our inclusion criteria from which the number of patients.

**Result:** This meta-analysis indicates that serum 25OH-D concentration is negatively related to CAS in patients with T2D(P=0.000). There is heterogeneity among these studies (SMD=0: z=3.82, p=0.000).

**Conclusion:** Using new meta-analysis techniques we determined the risk of CAS in patients with T2D is increased low with low serum 25OH-D.

**Keywords:** Vitamin D; Carotid atherosclerosis; Diabetes; Meta-analysis

## Introduction

Vitamin D represents one of the major driving factors for the development of life on earth and for human evolution. While up to 10-20% of the human organism's requirements in vitamin D can be obtained by the diet (under most living conditions in the USA and Europe), approximately 90% of all needed vitamin D has to be photosynthesized in the skin through the action of the sun (ultraviolet-B (UV-B)) [1]. Vitamin D deficiency is a commonly observed global phenomenon, both in the general population and in hospitalized patients, including critically ill patients. Vitamin D deficiency is associated with multiple adverse health outcomes, including increased morbidity and mortality in the general population and in critically ill patients. Vitamin D is a fat-soluble vitamin that plays an important role in bone metabolism. However, Vitamin D is also a steroid hormone that exerts multiple pleiotropic effects. Vitamin D regulates immunity, inflammation, cell proliferation, differentiation, apoptosis, and angiogenesis [2]. Vitamin D deficiency and diabetes mellitus are two common conditions and they are widely prevalent across all ages, races, geographical regions, and socioeconomic conditions. Epidemiologic studies have shown association of vitamin D deficiency and increased risk of chronic diseases, such as cancer, cardiovascular disease, T2D, and autoimmune diseases, such as multiple sclerosis and type 1 diabetes mellitus(T1D) [3]. Low serum 25OH-D concentrations are associated with an increased risk of macrovascular and microvascular disease events in T2D [4-6]. Diabetes mellitus, T2D patients and patients with cerebrovascular disease (CVD) had a significant reduction in serum 25OH-D concentrations, so ongoing evaluation of the protective role of vitamin D3 supplementation in the development of atherosclerosis is needed [7].

Even though several studies comparing the relationship between serum 25OH-D and CAS in patients with T2D have been reported, most are small series with conflicting results. It is still uncertain whether serum 25OH-D concentration is negatively related to CAS in patients with T2D. We therefore systemically searched and analyzed the available literature to clarify the relationship between the two and provide new ideas for the clinical treatment of CAS with T2D.

## Materials and Methods

### Search strategies

We did our best to include all related studies published until date, regarding the association between serum 25OH-D and CAS in patients with T2D. Eligible studies were found by searching the PubMed, Web of Science, EmBase, Cochrane library, China National Knowledge Infrastructure (CNKI), WANFANG database. We applied no language restrictions. We used the following combined text and MeSH terms: "25-hydroxyvitamin D" and "carotid atherosclerosis" and "type 2 diabetes".

### Inclusion criteria

Two reviewers independently assessed the quality of included studies according to the NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE(NOS). The standard includes selection, comparability and exposure. The overall scores range from 0 to 9. The following criteria were used for a publication to be included in the meta-analysis.

A. Published is about discussing the relationship between serum 25OH-D and CAS in patients with type 2 diabetes.

B. Their grouping is patients with CAS and without CAS, research variables include serum 25OH-D.

C. Their research is a cohort study.

D. Excluded the literature which have the data missing or Different set of control groups.

### Data extraction and quality assessment

Two investigators extracted and tabulated all the relevant data independently, and then cross-checked, to measure the consistency of the observers. Data extracted from each study were as followings: name of the first author, publication year, total number of participants, age, sex, serum 25OH-D level mean and standard deviation, numbers of case and controls.

Two reviewers independently assessed the quality of included studies according to the NOS standards. Scores of between scored 0 and 3 were regarded as low scores, between scored 4 and 6 as moderate quality, between scored 7 and 9 as high quality. Disagreements were also settled down by discussion among authors.

### Statistical Analysis

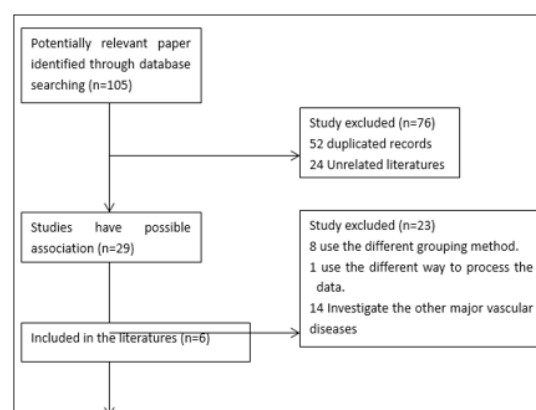
All statistical analyses were performed using Stata11.0 software to extract T2D with carotid atherosclerosis group (CAS group) and T2D without carotid atherosclerosis group (N on-CAS group) and mean serum vitamin D standard deviation. For meta-analysis, the effect of continuous variable analysis using Std mean difference (SMD) summary. The aggregated results and 95% Conf. Interval (CIs) for effect size were calculated using inverse-variance weighted random-effects meta-analysis. I-squared (I<sup>2</sup>) was used to assess heterogeneity across studies, with I<sup>2</sup> values of 0%, 25%, 50% and 75% representing no, low, moderate and high heterogeneity, respectively. Influence analysis was also conducted to determine

whether an individual study affected the aggregate result or not. Egger's linear regression test was done to assess publication bias.

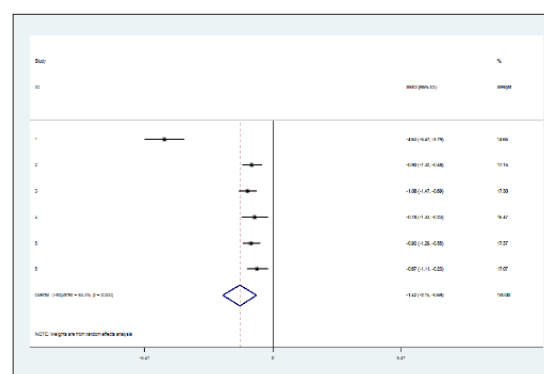
## Result

### Literature search results

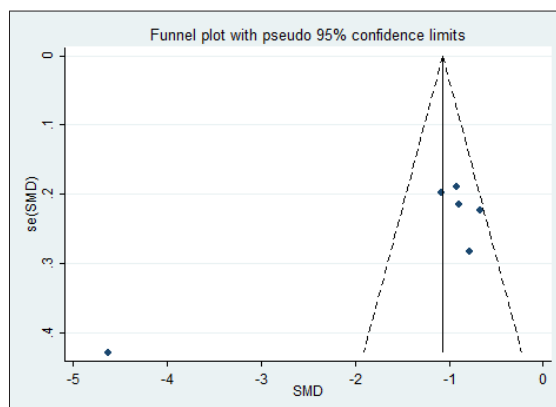
Document retrieval flow chart shown in Figure 1. We searched a total of 105 related articles. Based on the exclusion criteria included above, six studies [8-13] were identified as a correlation between serum 25OH-D concentration and carotid atherosclerosis including 568 A sample All six studies provide enough data to calculate the possible relationship between vitamin D and carotid atherosclerosis. Including 324 people in the CAS group and 244 people in the NCAS group, all of them came from China, the articles' NOS standards scores above 4 points. Research and patient related characteristics After screening the literature, the main functions of the group and the related parameters are listed in the Table 1. This meta-analysis indicates that serum 25OH-D concentration is negatively related to CAS in patients with T2D (95%CI= [-2.151- -0.692],  $p=0.000$ ,  $I^2=93.3\%$ ). There is heterogeneity among these studies (SMD=0:  $z=3.82$   $p=0.000$ ) (Figure 2 & 3). The Begg test did not make sense for a meta-analysis of less than 10 articles, so it did not.



**Figure 1:** Flow diagram of the literature search.



**Figure 2:** Forest plots of association of Vitamin D with carotid atherosclerosis. The squares and horizontal lines correspond to SMD and 95% CI of specific study, and the area of squares reflects study weight. The diamond represents the SMD and 95% CI.



**Figure 3:** Funnel plot of SMD effect and standard error.

**Table 1:** Basic data of included studies concerning serum 25OH-D concentration is negatively related to CAS in patients with T2D.

	Research Sites	Sample Size(C/N)	Men	Age, Years	25-(OH)D, ng/ml
Song [13]	Shan Dong	48/34	28/13	58.68±5.81/57.92±5.10	8.3±1.4/18.0±2.8
Li [12]	He Bei	52/44	-	56.87±10.64/50.84±13.83	4.93±3.49/11.18±9.58
Zhang [9]	Jiang Su	64/54	34/26	47.8±11.4/45.1±10.7	22.7±12.8/35.9±11.5
Ge [10]	He Bei	31/24	13/14	56.55±7.17/53.17±8.38	14.96±5.09/19.17±5.75
Deng	Chong Qing	83/49	31/17	66.99±8.12/62.86±8.16	12.41±6.58/18.13±5.54
Lu [11]	He Bei	46/39	16/3	54.94±7.12/45.38±11.21	12.89±7.07/17.92±8.07

## Discussion

This Meta-analysis shows that the Serum OH25-D in T2D patients with CAS were significantly lower than those without CAS. But the relationship between vitamin D and CAS is not clear yet [14], it is very necessary to explore in depth. Potential mechanism is

A. Vitamin D3 increases the production of PGI<sub>2</sub> through the induction of cyclooxygenase, and that, by modulating prostaglandin metabolism, vitamin D3 may be an important protective factor in the development of atherosclerosis [15].

B. Some studies indicated that 1,25(OH)<sub>2</sub>D<sub>3</sub> suppressed foam cell formation by reducing acetylated or oxidized low-density lipoprotein cholesterol uptake [16].

C. The vitamin D receptor plays a role in immune regulation, inhibition of angiogenesis and vascular smooth muscle cell proliferation, inhibit inflammatory factors and reduce the occurrence of arterial calcification and atherosclerosis [17].

D. Vitamin D exerts a variety of favorable effects on endothelial dysfunction, VSMC proliferation and migration, and calcification, as well as on the inflammatory/immune process of atherosclerosis [18]. This discovery provides us with a new idea for the future prevention of CAS in T2D patients clinically and can prevent medication in patients with vitamin D deficiency.

A Meta-analysis is observational in nature and may suffer from confounding bias. Some of the data is missing when we are screening the literature. In this study, a large collection of literature, according to strict exclusion and inclusion criteria were screened literature, reduce selection bias, to a certain extent to ensure the reliability of the results. Since all the cases in the literature are from China, this is because there is very little research in foreign literature using the grouping criteria when we retrieve articles and the data are not very comprehensive, so this conclusion may have some limitations. In summary, there is a correlation between the serum 25OH-D concentration is negatively related to carotid atherosclerosis in patients with type 2 diabetes. However, this study has high heterogeneity. The reason for the analysis may be that the sample size is too small and needs further well-designed, multicenter, large sample, randomized controlled trials.

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