Meta-Analysis of the Association between Vitamin D and Autoimmune Thyroid Disease

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Abstract

Although emerging evidence suggests that low levels of vitamin D may contribute to the development of autoimmune disease, the relationship between vitamin D reduction and autoimmune thyroid diseases, which includes Graves’ disease (GD) and Hashimoto thyroiditis (HT), is still controversial. The aim was to evaluate the association between vitamin D levels and AITD through systematic literature review. We identified all studies that assessed the association between vitamin D and AITD from PubMed, Embase, CENTRAL, and China National Knowledge Infrastructure (CNKI) databases. We included studies that compared vitamin D levels between AITD cases and controls as well as those that measured the odds of vitamin D deficiency by AITD status. We combined the standardized mean differences (SMD) or the odds ratios (OR) in a random effects model. Twenty case-control studies provided data for a quantitative meta-analysis. Compared to controls, AITD patients had lower levels of 25(OH)D (SMD: −0.99, 95% CI: −1.31, −0.66) and were more likely to be 25(OH)D (OR 2.99, 95% CI: 1.88, 4.74). Furthermore, subgroup analyses result showed that GD and HT patients also had lower 25(OH)D levels and were more likely to have a 25(OH)D deficiency, suggesting that low levels of serum 25(OH)D was related to AITD.

Keywords: vitamin D, autoimmune thyroid disease, Graves’ disease, Hashimoto thyroiditis, meta-

1. Introduction

Because an estimated one billion people worldwide have vitamin D deficiency or insufficiency [1] become an important focus of current medical research. Although the biological activities of vitamin mainly manifest in the regulation of calcium-phosphorus metabolism, studies in the past 30 years concluded that vitamin D may play an important role in the immune system [2,3]. Results show that 1,25-dihydroxyvitamin D3 can either prevent or markedly suppress experimental autoimmune encephalomyelitis, rheumatoid systemic lupus erythematosus, type 1 diabetes, and inflammatory bowel disease [4,5,6,7,8]. Clinical
also shown that vitamin D supplements may reduce the incidence of rheumatoid arthritis, multiple type 1 diabetes in children [1]. In the past two decades, vitamin D receptors have been found not only in kidney, and intestine, but also in the immune system (T and B cells, macrophages, and monocytes) system, endocrine system, muscles, brain, skin, and liver [9], suggesting that the role of vitamin D to the skeletal system.

Recently, many studies have shown that low levels of vitamin D contribute to Graves’ disease (GD) and Hashimoto thyroiditis (HT) and that combining vitamin D with anti-thyroid drugs or thyroid hormone contributes to the treatment of autoimmune thyroid disease (AITD) by suppressing the autoimmune reaction at serum levels of thyroid autoantibodies [10,11]. However, other authors have proposed that vitamin D deficiency does not increase the risk of AITD and is not associated with early-stage AITD [12,13]. Because the association between vitamin D levels and AITD is still controversial, we conducted a systematic review of the studies that investigated the relationship between serum 25(OH)D levels and AITD.

2. Methods

2.1. Bibliographic Search

A bibliographic search was performed on PubMed, Embase, CENTRAL, and China National Knowledge Infrastructure (CNKI) (updated to 20 December 2014) by two investigators (Jiying Wang and Shishi Lv) using the key words “vitamin D”, in combination with “autoimmune thyroid disease”, “thyroid autoimmunity”, “Graves’ disease” or “Hashimoto thyroiditis”. Articles were only considered if they were in English and were not hand-searched.

2.2. Eligibility Criteria and Excluded Studies

Articles were included in this meta-analysis if (1) they described a population-based case-control study; (2) the case group consisted of AITD patients and the control group included healthy individuals; (3) the outcome measures reported quantitative vitamin D levels (mean ± SD) and qualitative vitamin D levels (odds ratio of deficiency); (4) the study was a high-quality study (≥7 points according to the Cochrane’s Newcastle Scale evaluation standard for case-control studies [14]); and (5) was written in English or Chinese. After reading the title and abstract, we excluded a study if it was an animal or in vitro experiment, did not contain original data (e.g., was a medical recapitulate), was not related to AITD, did not contain data on vitamin D, or was a control study, case reports, and studies consisting of duplicate data. After reading the full text, we excluded the study if the comparator group did not conform to the requirements (e.g., compared female patients with male patients, duplicate publication, conference abstracts, no data about vitamin D level (mean ± SD), no vitamin D data, or it did not refer to AITD. Disagreement was resolved by discussion between the authors (Jiying Wang and Shishi Lv). If they could not reach a consensus, another investigator (Yong Xu) was consulted regarding disagreements.

2.3. Data Extraction

The following information was extracted from each study: the author, publication year, participant characteristics (age, gender, number), season, type of serum vitamin D assay, serum vitamin D (reported in ng/mL that reported vitamin D in nmol/L, we converted the values to ng/mL by dividing by 2.496 [15]), the number of patients with vitamin D deficiency, the cut-off for defining vitamin D deficiency, p value, and study quality. Information was independently extracted by Jiying Wang and Guo Chen, and all data were confirm author (Chenlin Gao).
2.4. Statistical Method

For studies that reported quantitative vitamin D levels for AITD participants and controls, we combined the standardized mean differences (SMD) in a random effects model. For studies that reported qualitative levels, we pooled the odds ratios (OR) in a random effects model. We assessed statistical heterogeneity using tests and the $I^2$ statistic. Publication bias was assessed using Egger’s test ($p < 0.1$ was considered to be publication bias). All analyses were carried out using the commands metan and metabias in Stata version 12.0 (Stata Corp).

3. Results

Our search identified 431 unique references, of which 411 did not meet our inclusion criteria. We conducted meta-analyses on the remaining 20 articles [10,11,13,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31]. Of the 20 included articles, 19 were used to analyze continuous data on vitamin D levels (Table 1) and nine were used to analyze dichotomous data on vitamin D (deficiency or no deficiency) (Table 2).

Overall, most studies showed a higher prevalence of vitamin D deficiency and lower vitamin D levels in AITD patients compared with controls.

The meta-analysis of the continuous vitamin D by AITD status included 3603 participants (1782 AITD cases and 1821 controls). On average, AITD patients had lower levels of 25(OH)D compared to controls (SMD: $-1.31$, $95\%$ CI: $-0.66$) ($I^2 = 94.8\%$, $p < 0.01$) (Figure 2). We found evidence of publication bias as evidenced by Egger’s test ($p = 0.009$).

For the presence of vitamin D deficiency, nine studies totaling 994 AITD participants and 1035 controls included. AITD participants were more likely to be deficient in 25(OH)D (OR 2.99, 95\% CI: 1.88, 4.74) (Figure 1).
73.0%, \( p < 0.01 \) compared to their controls (Figure 3). We found evidence of publication bias as evidenced by Egger’s test (\( p = 0.056 \)).

To estimate the association between 25(OH)D and Graves’ disease or Hashimoto thyroiditis, we conducted subgroup analyses: On average, Graves’ disease patients had lower 25(OH)D compared to controls (SMD: –1.04, 95% CI: –1.52, –0.57) (Figure 4), and were more likely to have a 25(OH)D deficiency (OR 3.50, 95% CI: 1.86, 6.56) (Figure 5). Likewise, Hashimoto thyroiditis patients had lower 25(OH)D compared to controls (SMD: –1.13, 95% CI: –1.64, –0.62) (Figure 6), and were more likely to have a 25(OH)D deficiency (OR 4.07, 95% CI: 2.12, 7.82) (Figure 7).

4. Discussion

The association between low serum vitamin D and autoimmune diseases has been generally accepted by researchers. Bellastella G. found that autoimmune disease patients showed 25(OH)D levels significantly lower than healthy controls [33]. A meta-analysis of vitamin D receptor gene polymorphisms and AITD showed significant correlation between certain vitamin D receptor gene polymorphisms (such as BsmI and AITD [34], but no meta-analysis of serum vitamin D levels and AITD has been published to date. In the present study, the serum 25(OH)D was lower in AITD patients compared to healthy individuals, and AITD was more likely to develop in individuals who showed serum 25(OH)D deficiency which suggested that vitamin D deficiency may play a role in the pathological process of AITD.
AITD has been traditionally thought to be related to unbalanced ratio of T helper cell type 1 (Th1) and Th2 cells. Graves’ disease occurs when a high proportion of Th2 cells are present and secrete the cytokine IL-4. A complete lack of IL-4 has been shown to eliminate Graves’ disease in animal model [38]. Conversely, Hashimoto thyroiditis patients have a high proportion of Th1 cells, which secrete the cytokine IFN-γ, IL-4, and IL-17 [40]. -17A mRNA expression is significantly higher in Hashimoto thyroiditis patients than in healthy controls [41]. Interestingly, vitamin D plays an important role in regulating Th1, Th2, and Th17 cells, as well as IFN-γ, IL-4, and IL-17 [44,45,46,47]. These findings may explain why lower levels of vitamin D contribute to thyroid gland immune disorder. On the other hand, Graves’ disease is an autoimmune thyroid disorder in which thyrotrophin receptor antibody (TRAb) causes hyperthyroidism [48]. Low vitamin D status is associated with increased TRAb in this disease [22]. Results also show that levels of 25O (HD) <50 nmol/L are a risk factor for positive thyroid autoantibody (Thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody) [22]. Thus, this increased thyroid autoantibody inAITD, may be a consequence of the lower levels of vitamin D contributes to AITD.

The levels of vitamin D may dictate the prognosis of Graves’ disease [50], and may create an opposite effect. Research by Kawakami-Tani shows that concomitant administration of vitamin D (such as thyroid hormones or anti-thyroid drugs) of 1α(OH)D3 is useful for treating hyperthyroidism with Graves’ disease [51]. Moreover, preliminary results of a small randomized controlled trial show that vitamin D treatment significantly decreased TPOAb and TgAb compared with placebo treatment in patients [52]. Current evidence, however, is not definitive, the cost-effectiveness of vitamin D supplementation for patients requires further investigation.

To our knowledge, this was the first meta-analysis to investigate the association between vitamin D deficiency and AITD. The inclusion of Embase, PubMed, CENTRAL, and the CNKI database added strength to our study. However, our study had some limitations. Firstly, many of the original studies did not adjust for potential confounders, such as season or assay method. The prevalence of vitamin D deficiency at different levels did not distinctly differ between winter and summer weather [53]. Limitations in the cut-off for defining vitamin D deficiency and the method of AITD diagnosis, which varied across the studies and publication bias may have contributed to heterogeneity of our findings. Criterion of vitamin D deficiency include <10 ng/mL, <15 ng/mL or <20 ng/mL, but result showed that cut-points of vitamin D deficiency should be assay specific rather than universal and that greater consistency between laboratories is required [53]. In the studies, AITD was diagnosed by thyroid function test, anti-thyroid antibodies, with or without ultrasonography. Thirdly, due to the nature of the abstracted case control studies in our review, further prospective studies are needed to clarify whether reduced vitamin D is a causal factor in the pathogenesis of autoimmune diseases or a consequence of this. Finally, we found statistical heterogeneity in our analysis. However, we did not find any major clinical heterogeneity and therefore the pooled analysis was appropriate for our study.

5. Conclusions

In conclusion, we have demonstrated that vitamin D deficiency is prevalent in AITD subjects and subjects have lower levels of serum 25(OH)D, suggesting that lower serum vitamin D is related to deficiency in vitamin D may play a role in the development of the disease. Large-sample multi-center...
randomized controlled trials will help to consolidate whether there is an association between vitamin AITD, and consequently give directions as to the beneficial effect of vitamin D supplementation in

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**Author Contributions**

Jiying Wang and Shishi Lv performed bibliographic search; Jiying Wang, Guo Chen and Chenlin C data and performed statistical analyses; Jiying Wang and Haihua Zhong drafted the manuscript, Ji Yong Xu revised the manuscript and contributed to the discussion. All authors have read and approved the final manuscript.

**Conflicts of Interest**

The authors declare no conflict of interest.

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[PMC free article] [PubMed] [Cross Ref]


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