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

Jiying Wang, Shishi Lv, Guo Chen, Chenlin Gao, Jianhua He, Haihua Zhong, and Yong Xu*

Department of Endocrinology and Metabolism, Affiliated Hospital of Luzhou Medical College, Luzhou 646000, China; E-Mails: wangjiying90@aliyun.com (J.W.); Email: lss219219@163.com (S.L.); Email: terry1210@aliyun.com (G.C.); Email: gaochenlin00@1 Email: hyjx88@163.com (J.H.); Email: zhh-302102@163.com (H.Z.)

*Author to whom correspondence should be addressed; E-Mail: xywyll@aliyun.com; Tel.: +86-139-8025-5895; Fax: +86-830-31653

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Abstract

Although emerging evidence suggests that low levels of vitamin D may contribute to the developm autoimmune disease, the relationship between vitamin D reduction and autoimmune thyroid diseas which includes Graves' disease (GD) and Hashimoto thyroiditis (HT), is still controversial. The ai evaluate the association between vitamin D levels and AITD through systematic literature review. all studies that assessed the association between vitamin D and AITD from PubMed, Embase, CE China National Knowledge Infrastructure (CNKI) databases. We included studies that compared v between AITD cases and controls as well as those that measured the odds of vitamin D deficiency status. We combined the standardized mean differences (SMD) or the odds ratios (OR) in a randon model. Twenty case-control studies provided data for a quantitative meta-analysis. Compared to cc patients had lower levels of 25(OH)D (SMD: −0.99, 95% CI: −1.31, −0.66) and were more likely t in 25(OH)D (OR 2.99, 95% CI: 1.88, 4.74). Furthermore, subgroup analyses result showed that GI patients also had lower 25(OH)D levels and were more likely to have a 25(OH)D deficiency, sugg 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 vitam mainly manifested in the regulation of calcium-phosphorus metabolism, studies in the past 30 year vitamin D may play an important role in the immune system [2,3]. Results show that 1,25-dihydro 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]. Clinic

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 o 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 Hashimoto thyroiditis (HT) and that combining vitamin D with anti-thyroid drugs or thyroid hormo to the treatment of autoimmune thyroid disease (AITD) by suppressing the autoimmune reaction a serum levels of thyroid autoantibodies [10,11]. However, other authors have proposed that vitamin does not increase the risk of AITD and is not associated with early-stage AITD [12,13]. Because th 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 Kno Infrastructure (CNKI) (updated to 20 December 2014) by two investigators (Jiying Wang and Shis the key words "vitamin D", in combination with "autoimmune thyroid disease", "thyroid autoimm "Graves' disease" or "Hashimoto thyroiditis". Articles were only considered if they were in Englis 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 s case group consisted of AITD patients and the control group included healthy individuals; (3) the measures reported quantitative vitamin D levels (mean ± SD) and qualitative vitamin D levels (odd deficiency); (4) the study was a high-quality study (≥7 points according to the Cochrane's Newcas Scale evaluation standard for case-control studies [14]); and (5) was written in English or Chinese. the title and abstract, we excluded a study if it was an animal or *in vitro* experiment, did not contai (e.g., was a medical recapitulate), was not related to AITD, did not contain data on vitamin D, or w control study, case reports, and studies consisting of duplicate data. After reading the full text, we the study if the comparator group did not conform to the requirements (e.g., compared female patie patients), duplicate publication, conference abstracts, no data about vitamin D level (mean ± SD), i data, or it did not refer to AITD. Disagreement was resolved by discussion between the authors (Ji Shishi Lv). If they could not reach a consensus, another investigator (Yong Xu) was consulted reg disagreements.

2.3. Data Extraction

The following information was extracted from each study: the author, publication year, participant (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]), th patients with vitamin D deficiency, the cut-off for defining vitamin D deficiency, *p* value, and stud 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 coml standardized mean differences (SMD) in a random effects model. For studies that reported qualitat levels, we pooled the odds ratios (OR) in a random effects model. We assessed statistical heteroge tests and the I^2 statistic. Publication bias was assessed using Egger's test ($p < 0.1$ was considered t publication bias). All analyses were carried out using the commands metan and metabias in Stata s version 12.0 (Stata Corp).

3. Results

Our search identified 431 unique references, of which 411 did not meet our inclusion criteria. We -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) used to analyze dichotomous data on vitamin D (deficiency or no deficiency) (Table 2).

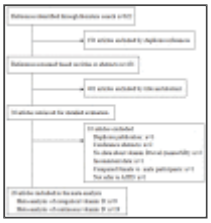

Figure 1
Flow diagram showing study selection.

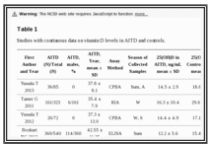

Table 1
Studies with continuous data on vitamin D levels in AITD and controls.

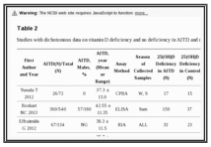

Table 2
Studies with dichotomous data on vitamin D deficiency and no deficiency in AITD and controls.

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

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

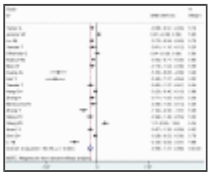

Figure 2
Meta-analysis of studies (chronologically ordered) reporting 25(OH)D levels in autoimmune thyroid disease (AITD) *vs.* controls, standardized mean difference with 95% confidence interval.

For the presence of vitamin D deficiency, nine studies totaling 994 AITD participants and 1035 co included. AITD participants were more likely to be deficient in 25(OH)D (OR 2.99, 95% CI: 1.88,

73.0%, $p < 0.01$) compared to their controls (Figure 3). We found evidence of publication bias as e
Egger's test ($p = 0.056$).

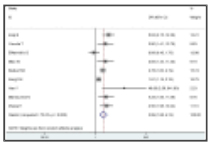

Figure 3
Meta-analysis of studies (chronologically ordered) reporting dichotomous data on 25(OH)D levels in autoimmune thyroid disease (AITD) *vs.* controls and estimated odds ratios (ORs) with 95% confidence interval.

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

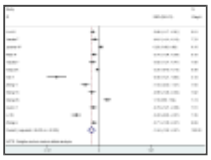

Figure 4
Meta-analysis of studies (chronologically ordered) reporting 25(OH)D levels in Graves's disease *vs.* controls, standardized mean difference with 95% confidence interval.

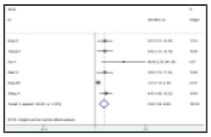

Figure 5
Meta-analysis of studies (chronologically ordered) reporting dichotomous outcomes of 25(OH)D levels in Graves' disease *vs.* controls and estimated ORs with 95% confidence interval.

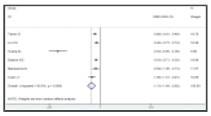

Figure 6
Meta-analysis of studies (chronologically ordered) reporting 25(OH)D levels in Hashimoto thyroiditis *vs.* controls, standardized mean difference with 95% confidence interval.

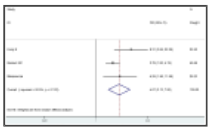

Figure 7
Meta-analysis of studies (chronologically ordered) reporting dichotomous data of 25(OH)D levels in Hashimoto thyroiditis *vs.* controls and estimated ORs with 95% confidence interval.

4. Discussion

The association between low serum vitamin D and autoimmune diseases has been generally accept
researchers. Bellastella G. found that automimmune disease patients showed 25(OH)D levels signi
than healthy controls [33]. A meta-analysis of vitamin D receptor gene polymorphisms and AITD
significant correlation between certain vitamin D receptor gene polymorphisms (such as *Bsm*I and
autoimmune thyroid diseases [34], but no meta-analysis of serum vitamin D levels and AITD has b
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 def
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) Graves' disease occurs when a high proportion of Th2 cells are present and secrete the cytokine IL and a complete lack of IL-4 has been shown to eliminate Graves' disease in animal model [38]. Co Hashimoto thyroiditis patients have a high proportion of Th1 cells, which secrete the cytokine IFN studies showed the secretion of cytokines from Th17 is involved in the development of AITD [40,4 -17A mRNA expression is significantly higher in Hashimoto thyroiditis patients than in healthy co 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 c thyroid gland immune disorder. On the other hand, Graves' disease is an autoimmune thyroid diso thyrotrophin receptor antibody (TRAb) causes hyperthyroidism [48]. Low vitamin D status is asso increased TRAb in this disease [22]. Results also show that levels of 25O (HD) <50 nmol/L are a r positive thyroid autoantibody (Thyroid peroxidase antibody (TPOAb) and thyroglobulin antibodies Thus, this increased thyroid autoantibody in AITD, may be a consequence of the lower levels of vi contributes to AITD.

The levels of vitamin D may dictate the prognosis of Graves' disease [50], and may create an oppo vitamin D supplementation for patients? Research by Kawakami-Tani shows that concomitant adm (such as thyroid hormones or anti-thyroid drugs) of 1α(OH)D3 is useful for treating hyperthyroidis with Graves' disease [51]. Moreover, preliminary results of a small randomized controlled trial als vitamin D treatment significantly decreased TPOAb and TgAb compared with placebo treatment i patients [52]. Current evidence, however, is not definitive, the cost-effectiveness of vitamin D supp AITD patients, as well as its optimal safe doses require further investigation.

To our knowledge, this was the first meta-analysis to investigate the association between vitamin I AITD. The inclusion of Embase, PubMed, CENTRAL, and the CNKI database added strength to o However, our study had some limitations. Firstly, many of the original studies did not adjust for po important confounders, such as season or assay method. The prevalence of vitamin D deficiency a (OH)D levels did not distinctly different between winter and summer weather [53]. Limitations in significant difference may be due to interassay and interlaboratory variability in measurements of the cut-off for defining vitamin D deficiency and the method of AITD diagnosis, which varied acro along with the language differences among the studies and publication bias may have contributed t heterogeneity of our findings. Criterion of vitamin D deficiency include <10 ng/mL, <15 ng/mL a but result showed that cut-points of vitamin D deficiency should be assay specific rather than univ greater consistency between laboratories is required [53]. In the studies, AITD was diagnosed by t test, anti-thyroid antibodies, with or without ultrasonography. Thirdly, due to the nature of the abst control studies in our review, further prospective studies are needed to clarify whether reduced vita a causal factor in the pathogenesis of autoimmune diseases or a consequence of this. Finally, we fo heterogeneity in our analysis. However, we did not find any major clinical heterogeneity and there analysis was appropriate for our study.

5. Conclusions

In conclusion, we have demonstrated that vitamin D deficiency is prevalent in AITD subjects and t subjects have lower levels of serum 25(OH)D, suggesting that lower serum vitamin D is related to deficiency in vitamin D may plays a role in the development of the disease. Large-sample multi-ce

randomized controlled trials will help to consolidate whether there is an association between vitam 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, Jia Yong Xu revised the manuscript and contributed to the discussion. All authors have read and appro manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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