ISSN 2706-6819 Vol.4, Issue 4: 28-33, DOI: 10.25236/IJFM.2022.040406

A Meta-Analysis of Serum Vitamin D Deficiency in Graves' Ophthalmopathy

Shipeng Wang[1,*], Yongwei Yu[2], Jinze Yang[3]

[1]Capital Medical University Forth Clinical School, Beijing, 100176, China
[2]School of Electronic, Information and Electrical Engineering, Shanghai Jiao Tong University, Shanghai, 200241, China
[3]College of Electronic and Information Engineering, Tongji University, Shanghai, 201804, China
**Corresponding author*

Abstract: *Objective: to systematically evaluate the status of serum vitamin D deficiency in patients with Graves' ophthalmopathy (GO). Methods: the case-control studies, cohort studies and randomized controlled trials associated with Graves' ophthalmopathy were searched in PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science. The literatures were screened according to inclusion, exclusion criteria and quality evaluation, and the extracted data were analyzed by Meta with ReviewManager5.4 software. Results: 5 studies were included, and the number of cases included in the study was 887. The results of Meta-analysis showed that compared with the control group, the level of vitamin D in the Graves' ophthalmopathy group was lower than that in the control group (MD=-8.22, 95%CI: -15.75~-11.45, P < 0.001). Conclusion: the decrease of serum vitamin D level is related to the diagnosis of GO. Assessment and supplementation of vitamin D levels may be an important supplement for early treatment of GD patients. Future studies should include longitudinal studies and prospective clinical trials to further explore the mechanisms of observed associations. In view of the small number of included studies, the above conclusions need to be confirmed by more high-quality randomized studies.*

Keywords: *Graves' ophthalmopathy; Vitamin D; Meta-analysis*

1. Introduction

Hyperthyroidism (GD) is an autoimmune disease with diffuse toxic goiter [1-4]. When a patient's immune system attacks his or her eyes, it is often characterized by Graves' ophthalmopathy (GO) [5-7] . The disease incidence in women is much higher than that in men, and it mostly stays in the mild stage (the continued development rate is 5%-6%)[4, 8, 9]. However, mild GO is still a major obstacle to the normal life of patients [5, 10-12], which also increases the pressure on public health [13]. In recent years, the role of vitamin D (VD) in many autoimmune diseases has been gradually discovered, including GD. For example, Kriegel et al. [14] suggest the role of vitamin D deficiency in various autoimmune diseases such as multiple sclerosis, systemic lupus erythematosus and rheumatoid arthritis, while similar mechanisms may play a role in GO. Although the results of the above studies are significant, the relationship between vitamin D deficiency and GO is still well established. Therefore, this study uses Meta-analysis method to systematically evaluate the association between vitamin D deficiency and GO in order to provide reliable evidence for the prevention of GO.

2. Materials and methods

Bibliography retrieval of the literature was performed in databases including Chinese and English databases such as PubMed, EMBASE, CENTRAL and Web of Science, and we searched all published articles related to vitamin D levels and GO from December 2, 2021 to December 2, 2021. Search keywords include: [("Graves Ophthalmopathy" [Mesh] OR "thyroid-associated ophthalmopathy" [tiab] OR "thyroid eye disease" [tiab] OR "Graves' ophthalmopathy" [tiab] OR "Graves' orbitopathy" [tiab] OR "endocrine ophthalmopathy" [tiab] OR "endocrine orbitopathy" [tiab] OR "thyroid associated orbitopathy" [tiab]) AND Vitamin D*].

Inclusion criteria: The types of included studies were case-control study and cohort study; the subjects were ≥ 18 years old and met the diagnostic criteria of Graves ophthalmopathy [4]; the exposure factor was

ISSN 2706-6819 Vol.4, Issue 4: 28-33, DOI: 10.25236/IJFM.2022.040406

the level of serum vitamin D; and the outcome index was GD with GO.

Exclusion criteria: research subjects have malignant tumors or abnormal organ functions such as heart, liver, kidney, etc.; history of infection or use of various immune preparations for treatment within 1 month before the study and other health issues; duplicate publications; conference abstracts, lectures, reviews, and systematic reviews; literature with incomplete or unavailable information.

Quality evaluation standard: the biased risk assessment tool provided by ReviewManager5.4 software was used to evaluate the literature quality.

Diagnostic criteria: the ocular signs of Graves' disease are as follows: 0) no signs and symptoms; 1) one eyelid contracture, blink reduction, Joffory sign, but no symptoms; 2) While there are signs and symptoms, the soft tissue of the orbit is involved; 3) exophthalmos (f > 18mm): 4) corneal involvement; 5) extraocular muscle involvement; 6) loss of visual acuity. Level 2 and above diagnosed as GO [10].

Data extraction: the literature was screened and searched independently by two researchers. The third assistant researcher discussed the divergent literature and confirmed whether the literature was included after consensus. The extracted data included first author, year of publication, type of study, sample size, GO diagnostic criteria, vitamin D level determination method, vitamin D deficiency baseline data and outcome indicators. The whole process has always been carried out on the basis of unanimous agreement in the discussion.

Statistical Analysis: Meta-analysis was performed using ReviewManager5.4 software. The Mean Difference (MD) and 95% Confidence Interval (CI) were used to express the vitamin D level of patients. The heterogeneity test of the included studies was calculated by the Q statistic and the I^2 test. If I^2<50%, a fixed effect model was used for analysis; when I^2>50%, there was evidence of heterogeneity, and a random effects model was used to estimate the effect size. P<0.05 means the difference is statistically significant. The results of the meta-analysis were displayed using forest plots, and the publication bias analysis was using funnel plots.

3. Results

Literature search results According to the above search strategy, a total of 76 related literatures were retrieved in the electronic database, but no related literatures were found in manual search. Among them, 13 were repeated, and 56 were excluded after reading the title and abstract. After reading the full text, 2 articles were excluded because 1 article had no specific data, and only the cut-off value of vitamin D level was given; 1 article did not specifically discuss the relationship between vitamin D level and GO in patients with GD and GO. Therefore, 5 studies were finally included in the analysis[15-19]. The specific process is shown in Figure 1.

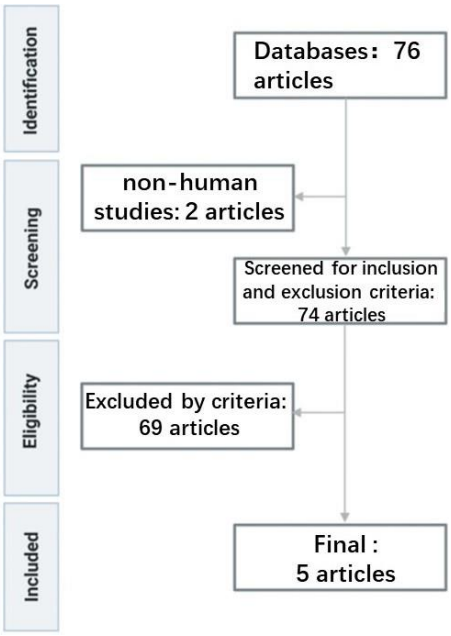

Figure 1: Flowchart of literature screening

ISSN 2706-6819 Vol.4, Issue 4: 28-33, DOI: 10.25236/IJFM.2022.040406

Risk assessment of the included studies All the 5 articles included were studies with a total sample size of 887, including 578 in the control group and 309 in the experimental group. The baseline data of the selected literatures were the same, and the serum vitamin D levels were measured after fasting blood collection. Chemiluminescence method was used in 4 literatures, and the measurement method was not specified in 1 paper. One article defined the cutoff value of vitamin D deficiency (≤ 30ng/ml). In terms of quality assessment, all the included literature showed low risk in the aspects of incomplete outcome data (attrition bias) and selective reporting (reporting bias) and other bias. All the included literature data were complete and not selectively published. The risk assessment of the above study is shown in figure 2 and figure 3.

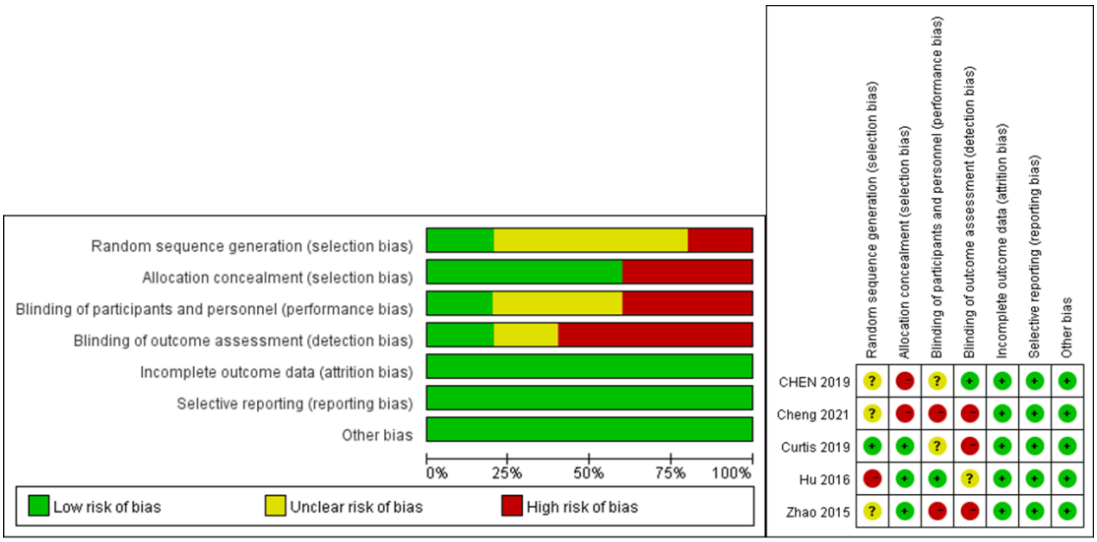

Figure 2: Assessment of risk of bias in included studies

Meta-analysis of vitamin D levels and GO associations A total of 5 articles were included for independent meta-analysis. In all samples, the ratio between the experimental group and the control group was about 0.53. the results of heterogeneity test showed that there was heterogeneity (I2% 96% P < 0.001). The random effect model was used to combine the effect value. The results showed that the level of vitamin D in the GO group was significantly lower than that in the control group (MD=-8.22, 95%CI: -15.75~-11.45, P < 0.001), indicating that the serum vitamin D level in patients with GO was significantly lower than that in the normal control group (figure 3).

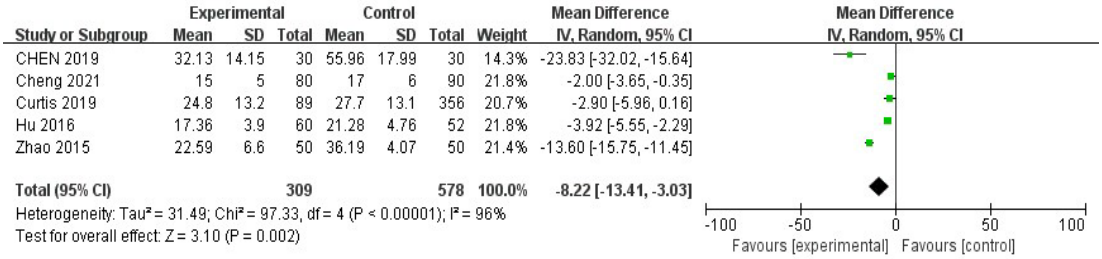

Figure 3: Mean difference forest plot of 25(OH)D.

4. Discussion

At present, the association between vitamin D levels and the risk of GO is still unclear. Studies have shown that GO patients have a higher vitamin D deficiency rate, suggesting that further reductions in serum vitamin D levels are closely related to the occurrence of GD-related complications [18]. For example, Lower VD levels in patients with GD have been supported in previous studies [20]. However, other studies have concluded that the serum VD level is not linked to GD complicated with GO [21]. The results of our meta-analysis showed that the vitamin D level in the GD with GO group was significantly lower than that in the control group, suggesting that there was a statistical correlation between the vitamin D level and GO, and the lower vitamin D level indicated that the body was at risk of developing GO. As a major serious complication of GD, GO involves many factors such as autoimmune system, environment and even genetics. Some studies believe that GO occurs because the immune system damages the thyroid-

ISSN 2706-6819 Vol.4, Issue 4: 28-33, DOI: 10.25236/IJFM.2022.040406

stimulating hormone receptor (TSH-R) [4], and the periorbital tissue is dominated by lymphocyte infiltration, and then a series of inflammatory reactions occur. Cells synthesize a large number of cytokines , it can be seen that the pathogenesis of GO is closely related to the autoimmune response mechanism at the molecular level, belonging to the category of organ-specific autoimmune diseases, with cellular immunity as the main and humoral immunity as the auxiliary effect [22], to maintain the balance between helper T cells type 1/2 (Th1/Th2) and related cytokines. At the same time, a large number of cytokines are released into tissues, which directly cause glycosaminoglycan synthesis and fibroblast proliferation [23, 24] . As a result, a series of clinical symptoms of eye damage appear, such as proptosis, eye movement disorders, and obstructed blood supply, leading to conjunctival hyperemia and edema, eyelid retraction, diplopia, pain, and even optic nerve damage [25, 26]. Daroszewski et al. [27] first proposed that the severity of GO is related to the increase of soluble CTLA-4 concentration. They also used a cohort test to compare the level of soluble CTLA-4 in the blood of normal people and GO patients to reach the above conclusion; Khalilzadeh et al. [28] also found that the incidence of GO was related to gene polymorphisms of anti-inflammatory cytokines such as IFN-γ, IL-2, and TNF-α. Vitamin D is involved in the abovementioned metabolic pathways, and plays an irreplaceable role in calcium and phosphorus homeostasis in regulating bone metabolism, inflammation and immune responses [29]. Thus, a lack of vitamin D naturally predisposes the body to autoimmune diseases, malignant tumors and infections [30, 31]. At the same time, many studies have shown that VD deficiency can lead to the occurrence of other eye diseases, such as diabetic retinopathy [32-34]. In the current study, the serum VD level of each experimental group (GO group) was lower than that of the control group, so It is inferred that the relationship between GO and VD levels may be closer, and the further mechanism may be that the reduction of VD leads to the secondary increase of cytokines, which will lead to the imbalance between Th1/Th2 cells and promote the generation of Th1 cells, while vitamin D deficiency affects the transformation of TH1 cells to Th2, the enhanced function of plasma cells and B cells, and the production of a large number of antibodies. This causes a series of inflammatory and immune responses, and increase the susceptibility to infection and autoimmune responses [35-37]. To our knowledge, this study is the first meta-analysis of GO and vitamin D levels, but more clinical data and trials are still needed.

This study still had limitations. Due to the small amount of literature retrieved, the final number of literatures for meta-analysis is small, and the heterogeneity between studies is large, which reduces the reliability of the results to a certain extent. The included studies were limited to no history of immunotherapy treatment within the past one month, so whether serum VD level can be used as a predictor of GO recurrence after treatment in patients requires more rigorous clinical testing. In addition, all the studies that have been collected that deal with this issue belong to the horizontal comparison in terms of design and conduct, that is, the control group with healthy or without GO, so the direct correlation between the level of VD and the pathogenesis or sequelae of the disease is Impossible. Thus, further and more prospective studies were required to evaluate the role of VD deficiency in GO patients, which may provide more powerful guidance for subsequent clinical diagnosis and treatment.

5. Conclusion

The decrease of serum vitamin D level is related to the diagnosis of GO. Assessment and supplementation of vitamin D levels may be important for early treatment of GD patients.

References

[1] ANDERSEN S L, KNøSGAARD L. Management of thyrotoxicosis during pregnancy [J]. Best Pract Res Clin Endocrinol Metab, 2020, 34(4): 101414.
[2] BARCZYŃSKI M. Current approach to surgical management of hyperthyroidism [J]. Q J Nucl Med Mol Imaging, 2021, 65(2): 124-31.
[3] BOELAERT K, VISSER W E, TAYLOR P N, et al. ENDOCRINOLOGY IN THE TIME OF COVID-19: Management of hyperthyroidism and hypothyroidism [J]. Eur J Endocrinol, 2020, 183(1): G33-g9.
[4] KAHALY G J. Management of Graves Thyroidal and Extrathyroidal Disease: An Update [J]. J Clin Endocrinol Metab, 2020, 105(12): 3704-20.
[5] ANTONELLI A, FALLAHI P, ELIA G, et al. Graves' disease: Clinical manifestations, immune pathogenesis (cytokines and chemokines) and therapy [J]. Best Pract Res Clin Endocrinol Metab, 2020, 34(1): 101388.
[6] GONZáLEZ-GARCíA A, SALES-SANZ M. Treatment of Graves' ophthalmopathy [J]. Med Clin (Barc), 2021, 156(4): 180-6.

ISSN 2706-6819 Vol.4, Issue 4: 28-33, DOI: 10.25236/IJFM.2022.040406

[7] SUBEKTI I, SOEWONDO P, SOEBARDI S, et al. Practical Guidelines Management of Graves Ophthalmopathy [J]. Acta Med Indones, 2019, 51(4): 364-71.
[8] BARTALENA L, PIANTANIDA E, GALLO D, et al. Epidemiology, Natural History, Risk Factors, and Prevention of Graves' Orbitopathy [J]. Front Endocrinol (Lausanne), 2020, 11: 615993.
[9] PERROS P, ŽARKOVIĆ M, AZZOLINI C, et al. PREGO (presentation of Graves' orbitopathy) study: changes in referral patterns to European Group on Graves' Orbitopathy (EUGOGO) centres over the period from 2000 to 2012 [J]. Br J Ophthalmol, 2015, 99(11): 1531-5.
[10] BARTALENA L, KAHALY G J, BALDESCHI L, et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy [J]. Eur J Endocrinol, 2021, 185(4): G43-g67.
[11] KOTWAL A, STAN M. Current and Future Treatments for Graves' Disease and Graves' Ophthalmopathy [J]. Horm Metab Res, 2018, 50(12): 871-86.
[12] ŁACHETA D, MIŚKIEWICZ P, GŁUSZKO A, et al. Immunological Aspects of Graves' Ophthalmopathy [J]. Biomed Res Int, 2019, 2019: 7453260.
[13] PONTO K A, MERKESDAL S, HOMMEL G, et al. Public health relevance of Graves' orbitopathy [J]. J Clin Endocrinol Metab, 2013, 98(1): 145-52.
[14] KRIEGEL M A, MANSON J E, COSTENBADER K H. Does vitamin D affect risk of developing autoimmune disease?: a systematic review [J]. Semin Arthritis Rheum, 2011, 40(6): 512-31.e8.
[15] Y C. Clinical study on the level of serum vitamin D in patients with hyperthyroidism and exophthalmos [J]. Medical Equipment, 2019, 32(23): 48-9.
[16] CHENG X, JIANG T, HU A. Expression and Significance of Fibrous Growth Factor 23 and Klotho Protein in Serum of Patients with Graves Ophthalmopathy [J]. Chinese And Foreign Medical Research, 2021, 19(7): 87-9.
[17] HU Y, SUN L, XIE S, et al. Analysis of bone metabolism in patients with Graves' orbitopathy [J]. Jiangsu Med, 2016, 42(17): 1875-7.
[18] C Z. The study on correlation between serum 25-hydroxyvitamin Dconcentration and Graves disease&its complications [D]; Southwest Medical University, 2015.
[19] HEISEL C J, RIDDERING A L, ANDREWS C A, et al. Serum Vitamin D Deficiency Is an Independent Risk Factor for Thyroid Eye Disease [J]. Ophthalmic Plast Reconstr Surg, 2020, 36(1): 17-20.
[20] ZHANG H, LIANG L, XIE Z. Low Vitamin D Status is Associated with Increased Thyrotropin-Receptor Antibody Titer in Graves Disease [J]. Endocr Pract, 2015, 21(3): 258-63.
[21] PLANCK T, SHAHIDA B, MALM J, et al. Vitamin D in Graves Disease: Levels, Correlation with Laboratory and Clinical Parameters, and Genetics [J]. Eur Thyroid J, 2018, 7(1): 27-33.
[22] SMITH T J, HEGEDüS L. Graves' Disease [J]. N Engl J Med, 2016, 375(16): 1552-65.
[23] ALONSO H R, KURODA F C, PASSARINI JUNIOR J R, et al. Acupuncture and moxibustion stimulate fibroblast proliferation and neoangiogenesis during tissue repair of experimental excisional injuries in adult female Wistar rats [J]. Acupunct Med, 2020, 38(2): 93-100.
[24] FANG R, JIANG Q, GUAN Y, et al. Golgi apparatus-synthesized sulfated glycosaminoglycans mediate polymerization and activation of the cGAMP sensor STING [J]. Immunity, 2021, 54(5): 962-75.e8.
[25] ATAABADI G, DABBAGHMANESH M H, OWJI N, et al. Clinical Features of Graves' Ophthalmopathy and Impact of Enalapril on the Course of Mild Graves' Ophthalmopathy: A Pilot Study [J]. Endocr Metab Immune Disord Drug Targets, 2020, 20(1): 139-48.
[26] WOODS R S R, PILSON Q, KHARYTANIUK N, et al. Outcomes of endoscopic orbital decompression for graves' ophthalmopathy [J]. Ir J Med Sci, 2020, 189(1): 177-83.
[27] DAROSZEWSKI J, PAWLAK E, KARABON L, et al. Soluble CTLA-4 receptor an immunological marker of Graves' disease and severity of ophthalmopathy is associated with CTLA-4 Jo31 and CT60 gene polymorphisms [J]. Eur J Endocrinol, 2009, 161(5): 787-93.
[28] KHALILZADEH O, ANVARI M, ESTEGHAMATI A, et al. Genetic susceptibility to Graves' ophthalmopathy: The role of polymorphisms in anti-inflammatory cytokine genes [J]. Ophthalmic Genet, 2010, 31(4): 215-20.
[29] KIM D. The Role of Vitamin D in Thyroid Diseases [J]. Int J Mol Sci, 2017, 18(9).
[30] ATOUM M, ALZOUGHOOL F. Vitamin D and Breast Cancer: Latest Evidence and Future Steps [J]. Breast Cancer (Auckl), 2017, 11: 1178223417749816.
[31] MCCULLOUGH M L, ZOLTICK E S, WEINSTEIN S J, et al. Circulating Vitamin D and Colorectal Cancer Risk: An International Pooling Project of 17 Cohorts [J]. J Natl Cancer Inst, 2019, 111(2): 158-69.
[32] LI Y F, DONG L, WEI W B. [Research progress in relationship between vitamin D and myopia and its mechanisms] [J]. Zhonghua Yan Ke Za Zhi, 2021, 57(6): 470-6.

ISSN 2706-6819 Vol.4, Issue 4: 28-33, DOI: 10.25236/IJFM.2022.040406

[33] LOPES M, LAIGINHAS R, MADEIRA C, et al. Association between Serum Vitamin D and Diabetic Retinopathy in Portuguese Patients with Type 1 Diabetes [J]. Acta Med Port, 2020, 33(7-8): 459-65.
[34] SAXENA S. Vitamin D supplementation in diabetic retinopathy in the era of COVID-19 [J]. Indian J Ophthalmol, 2021, 69(3): 483-4.
[35] BISHOP E, ISMAILOVA A, DIMELOE S K, et al. Vitamin D and immune regulation: antibacterial, antiviral, anti-inflammatory [J]. JBMR Plus, 2020, 5(1).
[36] BOTELHO I M B, MOURA NETO A, SILVA C A, et al. Vitamin D in Hashimoto's thyroiditis and its relationship with thyroid function and inflammatory status [J]. Endocr J, 2018, 65(10): 1029-37.
[37] HARRISON S R, LI D, JEFFERY L E, et al. Vitamin D, Autoimmune Disease and Rheumatoid Arthritis [J]. Calcif Tissue Int, 2020, 106(1): 58-75.