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Lower Serum 25-Hydroxyvitamin D Level is Associated With 3 Types of Autoimmune Thyroid Diseases

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Abstract: Autoimmune thyroid diseases (AITD) are common autoimmune disorders. A few studies have analyzed the association between serum vitamin D levels and AITD, and available data remain inconclusive.

The aim of this study was to evaluate the association between serum vitamin D levels and 3 types of AITD, that is Graves' disease (GD), Hashimoto's thyroiditis (HT), and postpartum thyroiditis (PPT).

Two independent case-control studies were designed. The first is a cross-sectional case-control study in which we examined the levels of 25(OH)D in patients with newly diagnosed GD or HT and in controls; the second is a nested case-control study in which we compared 25(OH)D levels in 610 women who developed PPT during the follow-up after delivery and those who did not.

Compared with the controls, GD patients and HT patients had significantly lower 25(OH)D levels. PPT cases also had a lower serum 25(OH)D concentration than controls. Serum 25(OH)D levels were associated with neither antithyroid peroxidase antibody nor antithyroglobulin antibody in GD and HT. There was no significant relationship between thyroid-stimulating hormone and 25(OH)D levels. Every 5 nmol/L increase in serum 25(OH)D concentrations was associated with a 1.55-, 1.62-, and 1.51-fold reduction in GD, HT, and PPT risk, respectively.

We observed a lower serum vitamin D levels in AITD patients compared with controls. The lower the vitamin D level is, not vitamin D deficiency per se, the higher the risk for developing AITD will be. However, vitamin D does not have strong association with the titers of thyroid antibodies or the levels of thyroid hormones.

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Abbreviations: AITD = autoimmune thyroid disease, CI = confidence interval, FT_3 = free T_3, FT_4 = free T_4, GD = Graves' disease, HT = Hashimoto's thyroiditis, ICMA = immunochemiluminescent assay, O-PPT = overt postpartum thyroiditis, OR = odds ratio, PPT = postpartum thyroiditis, S-PPT = subclinical postpartum thyroiditis, TgAb = antithyroglobulin antibody, TPOAb = antithyroid peroxidase antibody, TRAb = thyroid-stimulating hormone receptor autoantibody.

INTRODUCTION

Autoimmune thyroid diseases (AITD) are the most common organ specific autoimmune disorder.[1–3] Graves' disease (GD) and Hashimoto's thyroiditis (HT) are the 2 main clinical presentations of AITD and are both characterized by lymphocytic infiltration of the thyroid parenchyma. The clinical hallmarks of GD and HT are thyrotoxicosis and hypothyroidism, respectively.[2] Postpartum thyroiditis (PPT) is a special subtype of AITD in euthyroid women of childbearing age that manifests as thyroid dysfunction in the first postpartum year. Typically, a thyrotoxic phase is followed by transient hypothyroidism with a return to the euthyroid state within the first postpartum year.[4]

Our previous studies have reported the prevalence of GD, HT, and PPT in Chinese populations living in iodine-sufficient areas, which was 1.3%, 1.0%, and 11.9%, respectively.[5,6] Owing to China's large population base, AITD has become a great thyroid health concern in many people. Therefore, further studying the mechanisms, risk factors and preventive measures of AITD are of great importance.

In spite of the advancements in understanding the pathophysiologic mechanisms of AITD, its primary underlying cause remains elusive.[7,8] The majority of investigators agree that AITD is a multifactorial disease in which autoimmune attack on the thyroid plays a fundamental role through infiltration of the gland by T- and B-cells and production of specific autoantibodies reactive to thyroid antigens, such as thyroid peroxidase, thyroglobulin, and thyroid-stimulating hormone (TSH) receptor.[8] As with other autoimmune diseases, the interactions among genetic susceptible factors, existential factors, and various environmental triggers contribute to the occurrence of AITD.[7–9]

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Lately, the involvement of vitamin D in AITD has been of interest. Apart from a role in skeletal metabolism, vitamin D has been recognized as both an exogenous and an endogenous player in endocrinopathies such as type 1 and type 2 diabetes mellitus, adrenal diseases, and polycystic ovary syndrome.[10–13] A few studies have analyzed the association between serum vitamin D levels and AITD, and available data remain inconclusive. In addition, previous reports have several limitations: first, seasonal variations in blood sampling were common; second, cases and controls were not well matched to exclude other factors that may influence vitamin D levels; third, in the limited number of studies on GD, the sample size was small; fourth, there is a lack of well-designed study on PPT and vitamin D. Therefore, further research addressing the link of vitamin D levels to different types of AITD is still in need.

The present study aimed to evaluate the association between serum vitamin D levels and 3 different types of AITD separately, that is GD, HT, and PPT. With this objective in mind, 2 separate case-control studies were designed. One is a cross-sectional case-control study in which we examined the levels of vitamin D, namely 25(OH)D, in patients with newly diagnosed GD or HT and in controls; the other is a nested case-control study in which we compared vitamin D levels in euthyroid women who developed PPT during the postpartum follow-up with those who did not.

SUBJECTS AND METHODS

Subjects and Sampling

Cross-Sectional Case-Control Study: Vitamin D and Newly Diagnosed GD and HT

A total of 140 consecutive cases (70 patients with newly diagnosed GD and 70 patients with newly diagnosed HT) were recruited from the endocrinology outpatient clinic of the First Affiliated Hospital of China Medical University, China, between November 2012 and March 2013. Seventy control subjects who had normal thyroid function without TSH receptor autoantibody (TRAb), antithyroid peroxidase antibody (TPOAb), and antithyroglobulin antibody (TgAb) were recruited in the same period. Controls were identified from the physical checkup center of the hospital and matched for sex, age, and smoking status with the patients of GD. The exclusion criteria included a history of other autoimmune diseases, pregnancy during the study period for female subjects, or any medication history that involved taking calcium or vitamin D supplements 3 months before blood sampling. Also excluded were individuals who used to take immunosuppressive agents, such as glucocorticoids.

GD was diagnosed by the presence of overt hyperthyroidism, diffuse goiter or normal thyroid volume on B ultrasonography, and positive TRAb. HT was diagnosed by clinically overt hypothyroidism, the presence of diffuse goiter thyroid volume on B ultrasonography, and a high titer of TPOAb and/or TgAb (>300 IU/mL).[5]

Nested Case-Control Study: Vitamin D and PPT

Fifty-seven previously euthyroid subjects diagnosed with PPT were matched for age, smoking habit, and body mass index (BMI) with 114 euthyroid non-PPT mothers as controls. These subjects were selected from our prevalence study of PPT described previously[4] in which we screened for PPT patients in a Shenyang cohort of 610 women who had normal thyroid function before delivery. PPT was defined as abnormal TSH occurring within 6 months postpartum without positive TRAb and exophthalmos.[6] Subjects who showed only TSH abnormality were classified as subclinical PPT (S-PPT), whereas those who showed abnormalities in TSH and thyroid hormones were classified as overt PPT (O-PPT).

Blood Sampling

All venous blood samples were collected from the subjects in the morning (7:00–9:00 AM) after an overnight fast of >8 hours. The blood samples from pregnant women in the nested case-control study were taken 5 days before delivery. Blood samples were centrifuged shortly after sampling, and the sera were separated, then sent to the endocrinology laboratory for testing or frozen in a serum bank at −70°C until analysis.

Thyroid Function Test and Antithyroid Antibodies

In the cross-sectional case-control study, the levels of serum TSH (reference range, 0.35–4.94 mIU/L), free T_3 (FT_3) (reference range, 2.63–5.70 pmol/L), free T_4 (FT_4) (reference range, 9.01–19.05 pmol/L), TPOAb (cutoff level, 5.61 IU/mL), and TgAb (cutoff level, 4.11 IU/mL) were determined in all subjects on the same day of sampling, using the automated immunochemiluminescent assay (ICMA) kits (Abbott, IL, USA). Also, TRAb levels (cutoff level, 1.75 IU/L) were detected in patients with hyperthyroidism, using a commercial euglobulin clot lysis assay (ECLA) assay kit (Roche, Germany).

In the nested case-control study, the levels of serum TSH (detection limit, 0.002 mIU/L; reference range, 0.3–4.8 mIU/L), TPOAb (detection limit, 10 U/mL; cutoff level, 50 U/mL), and TgAb (detection limit, 20 U/mL; cutoff level, 40 U/mL) were determined in all subjects within 3 days after sampling, using the automated ICMA kits (Diagnostic Products Corporation, Los Angeles, CA). If TSH was abnormal, FT_3 (reference range, 2.3–6.3 pmol/L), FT_4 (reference range, 10.3–24.5 pmol/L), and TRAb (cutoff level, 2 IU/L) were subsequently measured using the ICMA kits (FT_3 and FT_4, Diagnostic Products Corporation) and a commercial ELISA kit (TRAb; Medipan Diagnostica Co., Germany), respectively.

The intra- and interassay coefficient of variation for these serum parameters were <8.1%.

Evaluation of Vitamin D Status

Serum 25(OH)D levels were used to evaluate the vitamin D status. All sera from both case-control studies were measured for 25(OH)D levels by ECLA using a commercial kits (Roche). The intra-assay coefficient of variation of the commercial kit was <8.8%.

Based on the Endocrine Society guidelines, 25(OH)D status was defined as vitamin D deficient (<50nmol/L), insufficient (50–75nmol/L), and sufficient (>75nmol/L).[14]

Statistical Analysis

Data are presented as mean ± standard deviation, or median with 25th and 75th percentiles. Student *t* test and ANOVA test were used for continuous variables. Non-Gaussian parameters underwent log-transformation to normal distribution before comparison, or directly compared with Mann-Whitney *U* test and Wilcoxon signed-rank test. The χ^2 and Fisher exact test were used for categorical variables. Linear regression was used to find the independent factors for GD or HT in the cross-sectional case-control study, and for PPT in the nested

TABLE 1. Characteristics and Serum 25(OH)D Levels of Subjects (Cross-Sectional Case-Control Study)

	GD	HT	Control	*P*
N	70	70	70	–
Age, y*	40.04 ± 15.24	40.11 ± 14.60	41.99 ± 13.31	0.409 (NS)
Sex (female/male)	48/22	51/19	49/21	0.158 (NS)
FT_3, pmol/L†	38.06 (18.61–46.08)	3.53 (2.97–4.29)	5.01 (4.73–5.25)	<0.001‡
FT_4, pmol/L†	45.03 (35.11–51.83)	7.92 (5.92–9.97)	16.82 (15.89–17.54)	<0.001‡
TSH, mIU/L†	0.002 (0.001–0.003)	30.37 (18.57–87.76)	2.08 (1.33–2.75)	<0.001‡
TPOAb, IU/mL†	252.70 (111.40–506.80)	1000.00 (572.40–1000.00)	4.64 (2.33–6.75)	<0.001‡
TGAb, IU/mL†	57.69 (6.25–225.40)	653.40 (79.50–1000.00)	2.78 (2.50–4.79)	<0.001‡
TRAb, IU/L†	14.16 (5.81–27.92)			–
25(OH)D, nmol/L*	31.71 ± 13.10	31.00 ± 11.15	41.33 ± 14.48	<0.001‡
Sufficiency (n, %)	1 (1.43)	0 (0.00)	3 (4.29)	0.168§
Insufficiency (n, %)	4 (5.71)	4 (5.71)	13 (18.57)	0.014§
Deficiency (n, %)	65 (92.86)	66 (94.29)	54 (77.14)	0.002§

GD = Graves' disease, HT = Hashimoto's thyroiditis, NS = not significant.
Vitamin D sufficiency: 25(OH)D > 75 nmol/L; insufficiency: 50 nmol/L < 25(OH)D < 75 nmol/L; deficiency: 25(OH)D < 50 nmol/L.
* Mean ± standard deviation.
† Median with interquartile range.
‡ ANOVA *P* value.
§ χ^2 *P* value.

case-control study. Multivariate logistic regression analysis was further used to evaluate the impact of these independent factors. The level of significance was set at 0.05. Statistical analysis was performed using the SPSS software (version 16.0; Chicago, IL).

Ethical Aspects

Research protocols were approved by the Medical Ethics Committee of The First Affiliated Hospital of China Medical University. The protocols were carefully explained to all participants, and written consent was obtained from all subjects.

RESULTS

Cross-Sectional Case-Control Study: Vitamin D and Newly Diagnosed GD and HT

Clinical and Laboratory Characteristics of the Subjects

The clinical and laboratory characteristics of the 210 subjects (62 males and 148 females; age 14–76 years) are shown in Table 1. There were no significant age and sex differences between GD patients, HT patients, and controls. There were increased thyroid hormones and decreased TSH levels in GD patients, whereas there were decreased thyroid hormones and increased TSH levels in HT patients.

Serum 25(OH)D Levels of the Subjects

The serum 25(OH)D levels in the 3 groups are shown in Table 1. Compared with the controls, GD patients had significantly lower 25(OH)D levels (31.71 vs 41.33 nmol/L, $P < 0.001$), as did HT patients (31.00 vs 41.33 nmol/L, $P < 0.001$). However, no significant difference in serum 25(OH)D was found between the HT cases and the GD cases ($P = 0.97$) (Figure 1A).

Vitamin D deficiency was prevalent in 92.86% of GD cases, 94.29% of HT cases, and 77.14% of controls ($P = 0.002$) (Table 1 and Figure 2A).

Serum 25(OH)D Levels and the Autoantibody Levels in GD and HT

Upon correlation analysis of vitamin D levels and the autoantibodies of GD, we found that higher 25(OH)D levels

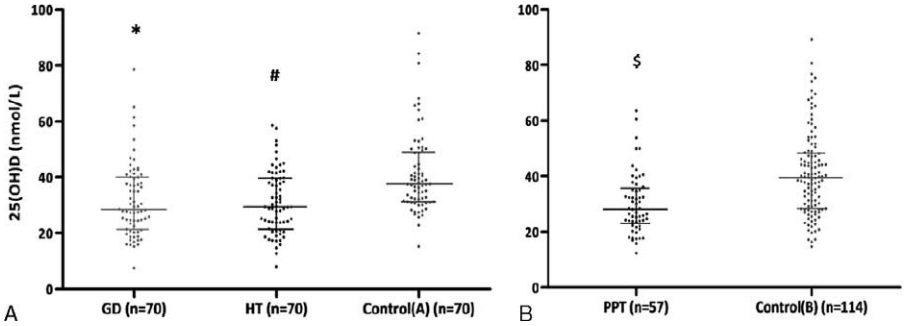

FIGURE 1. Serum levels of 25(OH)D in AITD patients and controls. (A) Cross-sectional case-control study, 25(OH)D levels in GD patients, HT patients, and controls. ∗GD group compared with control group, $P < 0.001$. #HT group compared with control group, $P < 0.001$. (B) Nested case-control study, 25(OH)D levels in PPT patients and controls. $PPT group compared with control group, $P < 0.001$. AITD = autoimmune thyroid disease, GD = Graves' disease, HT = Hashimoto's thyroiditis.

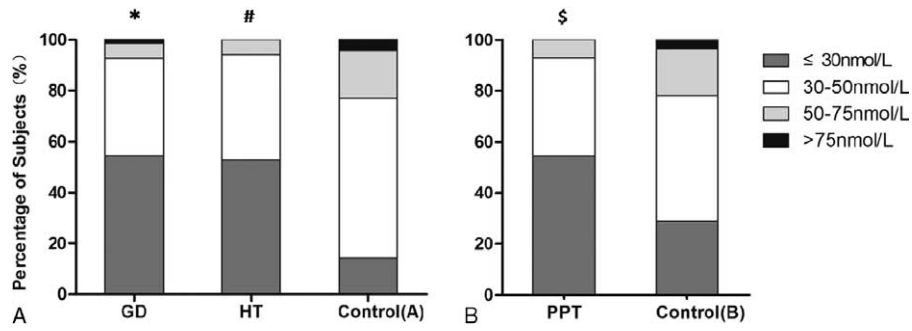

FIGURE 2. Prevalence of vitamin D deficiency in AITD patients and controls. (A) Cross-sectional case-control study, prevalence of vitamin D deficiency in GD patients, HT patients, and controls. *GD group compared with control group, $P = 0.009$. #HT group compared with control group, $P = 0.004$. (B) Nested case-control study, prevalence of vitamin D deficiency in PPT patients and controls. $PPT group compared with control group, $P < 0.05$. AITD = autoimmune thyroid disease, GD = Graves' disease, HT = Hashimoto's thyroiditis.

were weakly associated with lower TRAb ($r = -0.25$, $P = 0.036$), but were not associated with TPOAb ($P = 0.277$) and TgAb ($P = 0.709$).

As to the relationship between vitamin D levels and the autoantibodies of HT, we found that 25(OH)D levels were associated with neither TPOAb ($P = 0.134$) nor TgAb ($P = 0.422$).

Serum 25(OH)D Levels and Odds Ratios of GD and HT

Lower serum 25(OH)D level was associated with an increased risk of GD after adjustment for age, TSH, and all thyroid autoantibodies (odds ratio [OR] = 1.09, 95% confidence interval [CI] 1.03–1.15, $P = 0.001$). The same association was seen for HT (OR = 1.08, 95% CI 1.04–1.12, $P < 0.001$). According to the multivariate logistic regression analysis, every 5 nmol/L decrease in serum 25(OH)D concentration was associated with a 1.55-fold (95% CI 1.18–2.02) increase in GD risk and a 1.62-fold (95% CI 1.30–2.05) reduction in HT risk.

Nested Case-Control Study: Vitamin D and PPT

Clinical and Laboratory Characteristics of the Subjects

Among the 171 pregnant subjects who were euthyroid before delivery, 57 subjects developed PPT during the postpartum follow-up, whereas 114 subjects remained euthyroid (Table 2). There was no significant difference in age, BMI, and smoking status between subjects who developed PPT and those who did not ($P > 0.05$). Overall, 32% of the PPT patients (n = 18) were positive for TPOAb and/or TgAb, whereas 68% (n = 39) were negative for thyroid autoantibodies.

TABLE 2. Characteristics and Serum 25(OH)D Levels of Subjects (Nested Case-Control Study)

	PPT	Control	*P*
N	57	114	–
Age, y*	25.70 ± 2.60	26.00 ± 3.16	0.47‡ (NS)
BMI, kg/m²*	25.19 ± 0.88	25.17 ± 1.01	0.14‡ (NS)
Smoker (n, %)	2 (3.51)	3 (2.63)	0.74‡ (NS)
FT_3, pmol/L†	4.03 (3.34–4.82)	–	–
FT_4, pmol/L†	13.71 (10.95–15.20)	–	–
TSH, mIU/L†	2.68 (2.03–3.65)	2.36 (1.50–3.20)	0.01‡
TPOAb, IU/mL†	25.03 (20.19–94.17)	10.00 (10.00–10.30)	<0.001‡
25(OH)D, nmol/L*	30.21 ± 10.96	40.79 ± 15.29	<0.001‡
Sufficiency (n, %)	0 (0.00)	4 (3.51)	0.152§
Insufficiency (n, %)	4 (7.02)	21 (18.42)	0.047§
Deficiency (n, %)	53 (92.98)	89 (78.07)	0.014§

PPT = postpartum thyroiditis, BMI = body mass index, NS = not significant.
Vitamin D sufficiency: 25(OH)D > 75 nmol/L; insufficiency: 50 nmol/L < 25(OH)D < 75 nmol/L; deficiency: 25(OH)D < 50 nmol/L.
* Mean ± standard deviation.
† Median with interquartile range.
‡ *t* test *P* value.
§ χ^2 *P* value.

The PPT group had higher TSH (2.68 vs 2.36 mIU/L, $P = 0.01$) and TPOAb (25.03 vs 10.00 nmol/L, $P < 0.001$) levels 5 days before parturition compared with the control group.

Serum 25(OH)D Levels of the Subjects

Serum 25(OH)D levels of the PPT subjects before delivery in the 2 groups are shown in Table 2. Cases had a significantly lower serum 25(OH)D concentration than controls ($P < 0.001$) (Figure 1B).

The prevalence of vitamin D deficiency was higher in cases than in controls (92.98% vs 78.07%, $P = 0.014$) (Figure 2B).

Serum 25(OH)D Levels According to the Severity of PPT

We subgrouped PPT cases into S-PPT (n = 23) and O-PPT (n = 34) according to whether their TSH abnormality coexisted with abnormal thyroid hormones during the postpartum follow-up. Although 25(OH)D levels in S-PPT was slightly higher than that in O-PPT, the difference between the 2 subgroups was statistically insignificant (33.27 nmol/L in S-PPT vs 28.15 nmol/L in O-PPT, $P = 0.083$).

Serum 25(OH)D Levels and TSH, TPOAb, and TgAb Levels Before Delivery in PPT

In PPT cases, there was no significant relationship between TSH and 25(OH)D levels 5 days before delivery ($P = 0.71$). As for the antibodies of PPT, we found that 25(OH)D levels were not associated with TPOAb ($P = 0.19$) or TgAb ($P = 0.95$) before parturition.

Serum 25(OH)D Levels and ORs for Developing PPT

A significant difference in predelivery TPOAb titers, TSH, and 25(OH)D levels was found between PPT patients and controls. A multivariate regression analysis found that lower serum 25(OH)D level is an independent risk factor for PPT (OR = 1.09, 95% CI 1.05–1.43, $P < 0.001$). Every 5 nmol/L decrease in serum 25(OH)D concentrations was associated with a 1.51-fold (95% CI 1.25–1.82) increase in PPT risk.

DISCUSSION

It has been recognized that vitamin D deficiency is a global health problem. Reports from the Americas, Australia, Africa, and Asia covering extensive latitudes all indicated that the world's current state of vitamin D inadequacy is discouraging.[15,16] Recently, it has been shown that even in tropical climates, the population is at high risk of vitamin D deficiency, which may be attributed to a changed lifestyle.[17]

Vitamin D is of great importance because of its role in calcium homeostasis, as well as in decreasing the risk of rickets, fractures, osteoporosis, and osteomalacia. In addition to its classic skeletomuscular functions, vitamin D was recently identified as a factor involved in both innate and adaptive immunity.[18] Low vitamin D absorption and vitamin D deficiency were found to be associated with several autoimmune conditions, such as type 1 diabetes mellitus, Crohn disease, rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis.[11,19] Studies in animal models of autoimmune diseases consistently showed that the administration of $1,25(OH)_2D_3$ produces selective immunosuppressant effects able to either prevent or markedly suppress various experimental autoimmune diseases.[18]

Inspired by studies on the relationship of vitamin D and other autoimmune diseases, researchers have been focusing on the link between vitamin D and AITD in recent years. In 1990, an animal study first demonstrated that 25(OH)D administration could prevent the induction of experimental autoimmune thyroiditis.[20] Subsequent research found that vitamin D deficient BALB/c mice were more prone to persistent hyperthyroidism than their counterparts receiving adequate vitamin D after immunizations with TSH receptor.[21] In human studies, in 2009 Goswami et al[22] found that serum 25(OH)D level was not significantly different between TPOAb-positive and TPOAb-negative subjects. The correlation of vitamin D with AITD was initially confirmed by Kivity's group in 2011, in which they found that the presence of antithyroid antibodies and abnormal thyroid functions was more prevalent in vitamin D deficient subjects.[23] One year later, the first study specifically focused on GD was published.[24] Although available data remain controversial, vitamin D has shown to be a new developing issue in the pathogenesis of AITD.

We designed the present study to test the hypothesis that lower vitamin D levels may be related to the occurrence of AITD. One part of the study is a cross-sectional case-control analysis in which we examined the levels of 25(OH)D in patients with GD and HT and in controls. This is the fourth investigation of vitamin D and GD. The first 2 reports were both case-control studies conducted by Yasuda's group, they found that vitamin D may be related to newly diagnosed GD and GD remission.[24,25] The third report was conducted by Zhang et al,[26] which focused on the association between vitamin D status and TRAb titers. We obtained similar findings in that vitamin D deficiency was more prevalent in GD, and that lower 25(OH)D level was associated with higher risk of GD and with increased TRAb titer. With regard to vitamin D and HT, our study distinctively selected winter months for blood sampling, thereby eliminating the confounding factor of seasonal variation and sunlight exposure. Our results were similar to previous studies particularly that vitamin D deficiency was associated with an increased risk of HT. However, we found no association between vitamin D and the antibodies of HT, which is in contrast to previous studies where most researchers conclude that the severity of 25(OH)D deficiency correlates to higher thyroid antibody levels.[19,22,23,27,28] One reason for this discrepancy may be that HT patients in our study had exceedingly high levels of antibodies above the detection limit of the assays, therefore its correlation with vitamin D was inadequately expressed. In addition, we found that vitamin D levels were not associated with thyroid function. Both GD with thyrotoxicosis and HT with hypothyroidism showed decreased 25(OH)D levels, suggesting that vitamin D was associated with occurrence of overt AITD but not with thyroid hormone levels. This finding was different from some previous reports, which proposed vitamin D deficiency was linked to abnormal thyroid functions.[23,29–32]

Currently, there is a lack of a well-designed study investigating the relationship between vitamin D and the development of PPT. In the present study, we conducted a nested case-control study to explore the relationship between vitamin D and PPT. The large sample size of the Shenyang PPT cohort allowed us to match for a number of variables known to influence 25(OH)D levels, including age, BMI, smoking status, and sampling season. Subjects with low 25(OH)D levels detected at 5 days before delivery eventually developed PPT. However, 25(OH)D levels were associated with neither the severity of PPT nor the titers of thyroid antibodies. TPOAb is a definite risk

factor for developing PPT.[33] We showed in this study that lower 25(OH)D was a another strong and independent risk factor for developing PPT.

The lack of the association between serum 25(OH)D levels and TPOAb titers in PPT may have been because of the following reasons: first, the sample size was not sufficiently large enough to reveal a strong correlation. Second, the blood sampling time for PPT subjects was during late gestational period when immune tolerance has suppressed antibody titers. Third, as the inception criteria for the nested case-control study, the PPT patients had normal thyroid function and no record of thyroid disorders before delivery, meaning that there was no clinical development of AITD beforehand. Also, they were relatively younger. Effraimidis et al[34] prospectively evaluated the relationship between vitamin D and the development of TPOAb, and concluded that vitamin D deficiency is not associated with early stages of thyroid autoimmunity. Furthermore, the pathophysiology of AITD is complex, involving other possible factors such as IgG4-related thyroiditis.

The results of our study raised 2 questions to consider: What are the underlying mechanisms of the association between vitamin D insufficiency/deficiency and the different phenotypes of AITD? Vitamin D status does not directly affect thyroid hormone levels leading to hypo- or hyperthyroidism. Immunoregulation seems to be a more reasonable explanation for this phenomenon. For example, vitamin D takes part in the regulation of cytokines, such as interleukin (IL)-1, IL-6, IL-17, TNF-α, and leptin, which has been found to play an important role in AITD.[1–4,35–37] Further research is required in this field. Would supplementation of vitamin D be beneficial to AITD patients, given that lower serum vitamin D level is associated with higher risk of this disease? Specifically, whether supplementation of vitamin D could prevent the onset of AITD in susceptible populations, decrease thyroid autoantibody titrates, decrease the recurrence of GD after drug cessation, or decrease the thyroid hormone replacement dosage for HT? The current Endocrine Society's guideline recommends prescribing vitamin D supplementation for fracture prevention but not for preventing nonskeletal outcomes.[14] Therefore, in order to answer the questions above, a number of well-designed random control trials with large sample size and long-term follow-up are needed. The vitamin D dosage should be determined carefully as well. Before such clinical trials are completed, ''to D or not to D'' will continue to be uncertain.

In comparison to other reports (see Table, Supplemental Content, http://links.lww.com/MD/A435, which summarizes the literature on the association of vitamin D and AITD), our study has the following characteristics: the 3 different types of AITD was compared separately, which is novel compared with many other previous reports and meta-analyses that analyzed AITD collectively.[38] PPT is distinctive from other common types of AITD, that is HT and GD. It has unique features, such as postpartum manifestation and transient thyroid dysfunction. It is also the lesser analyzed AITD in previous studies. The nested case-control method used in the PPT study can more accurately reflect the population than case-control studies, more accurately reflect the population with smaller selection bias than case-control studies, cases and controls are well matched from the same well-defined cohort, and statistical analyses have higher efficiency than case-control studies,[39] and revealed that lower serum vitamin D levels correlate to the development of PPT. The sample size in this study is relatively larger than some other studies. Our study method removed the confounding factor of seasonal variation, and matched for age, sex, and other covariates. The cases and controls were well matched. Our study obtained the increase in AITD risk for every 5 nmol/L decrease in serum 25(OH)D. The major limitation of our study is its nonprospective nature, particularly in the cross-sectional case-control study. Therefore, based on current findings, we cannot determine at which stage of disease in HT or GD does vitamin D deficiency occur, and we also cannot confirm whether lower vitamin D level is the cause or the result of AITD. The nested case-control study on the relationship between vitamin D and PPT mitigated this limitation to some extent; however, weaknesses in the study design still exists compared with the standard prospective follow-up studies.

In conclusion, we observed a lower serum vitamin D levels in AITD patients compared with non-AITD controls. Vitamin D deficiency is a risk factor in the development of AITD, but not associated with the titers of TPOAb and TgAb nor the levels of thyroid hormones. Every 5 nmol/L decrease in serum 25(OH)D concentrations was associated with a 1.55-, 1.62-, and 1.51-fold reduction in GD, HT, and PPT risk, respectively. Randomized controlled trials that evaluate the effects of vitamin D in the prevention and treatment of AITD are needed.

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