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Original Article

Association between Vitamin D and autoimmune thyroid diseases in the Uyghur and Han population in Xinjiang, China

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Abstract: Objective: To analyze the relationships between Vitamin D (Vd) level and autoimmune thyroid diseases (AITDs) in Uyghur and Han Nationalities. Methods: A total of 2253 local residents participating in this study were selected as the subjects, and their serum 25-hydroxyvitamin D, thyroid function, thyroid-related antibodies were detected by using the chemiluminescence immunoassay and analyzed. Results: The positive rates of anti-thyroid peroxidase antibody (TPOAb) and anti-thyroglobulin antibody (TGAb) in women were higher than those in men (χ^2 = 43.81, P<0.001), and higher in Uyghur than in Han (χ^2 = 7.691, P = 0.006). The incidence of Vitamin D deficiency (VdD) in women was higher than in men, as well as higher in Uyghur than in Han (P<0.001); the incidences of Vitamin D insufficiency and sufficiency in Han were higher than in Uyghur (P<0.001). Regardless of nationality, along with the increasing of Vd level, the prevalence of AITDs reduced, but the difference was not statistically significant. After adjusted such factors as age, smoking, BMI, abdominal circumference, thyroid dysfunction course, thyroid nodule combination, and urinary iodine, Logistic regression analysis revealed that the serum Vd level in female Han aging 40 to 60 years old was negatively correlated with AITDs (B = -0.052, P = 0.009). Conclusions: The prevalence of AITDs and VdD in Uyghur were both higher than in Han. As for the female Han aging 40 to 60 years old and residing in Urumqi communities, Vd can be used as a risk indicator to evaluate AITDs.

Keywords: Vitamin D, autoimmune thyroid diseases, Uyghur, Han

Introduction

Vitamin D is a fat-soluble vitamin, and as a neuroendocrine - immunoregulatory hormone, the relationship of Vd level with AITDs have obtained more and more attention [1, 2]. Numerous studies have confirmed that when human body exists VdD, the risk factors of autoimmune diseases, malignant cancer, or other diseases are significantly increased [1-4], as well as these relationships have gender differences. Professor Teng conducted one epidemiological survey of thyroid diseases in ten Chinese cities and found that the positive rate of TPOAb in the total population was 11.6%, and that of TGAb was 12.6% [5]. However, the relationships of Vd level with AITDs between Uyghur and Han have been less analyzed currently in China. This study investigated the relationships of Vd level with AITDs between Uyghur and Han and analyzed the internal reasons.

Study subjects and methods

Study subjects

From May to July 2013, a total of 2253 residents from two communities in Urumqi were sampled using the cross-sectional method. This study was approved by the ethics committee of the People's Hospital of Xinjiang Uyghur Autonomous Region.

Inclusion and exclusion criteria

Inclusion criteria: Uyghur and Han having resided locally for more than three years. Exclusion criteria: ① more than 90 years old; ② pregnant women; ③ combined with liver and kidney dysfunction; ④ combined with other autoimmune diseases besides AITDs, and needed to take corticosteroids or other immunosuppressive agents; ⑤ with previous history of thyroid sur-

Table 1. General Information of the total populations [$\bar{x}$ ± s or median (upper and lower quartiles)]

	Uyghur	Han	(t or χ^2)	P
Ratio of populations (%)	698 (43.74)	957 (56.26)	--	--
Age (years)	44.54±12.66	47.63±13.97	1.944	0.065
Male (%)	200 (39.68)	304 (60.32)	4.789	0.029
Female (%)	544 (45.45)	653 (54.55)		
History of thyroid diseases (%)	41 (5.87)	85 (8.88)	3.997	<0.001
BMI (kg/m^2)	26.39±4.51	25.24±3.76	9.018	0.003
Abdominal circumference (cm)	89.68±11.95	83.95±10.77	10.271	<0.001
Urinary iodine (μg/L)[a]	129.2 (80.2~373.4)	137.9 (90.0~386.9)	-2.797	0.005
TSH (uIUml)[a]	2.26 (1.45~3.64)	2.49 (1.68~3.83)	-3.820	<0.001
FT3 (pg/ml)	2.81±0.48 (2.88)	3.17±0.51 (2.90)	1.885	0.102
FT4 (ng/dl)	1.44±0.38 (1.36)	1.18±0.33 (1.29)	1.029	0.088
25(OH)D (ng/ml)	13.09±6.98	19.16±8.10	19.039	0.000
TPOAb[b]	1.54±0.40	1.52±0.37	-2.003	0.045
TGAb[b]	1.69±0.45	1.65±0.47	-2.212	0.027

Note: BMI: body mass index; TSH: serum thyroid-stimulating hormone; FT3: serum free triiodothyronine; FT4: serum free thyroxine; TPOAb: anti-thyroid peroxidase antibody; TGAb: anti-thyroglobulin antibody; a: median (interquartile range), with the statistic amount as the z value; b: logarithm of the data.

gery; ⑥ taking Vd supplements recently or currently; ⑦ with malignant thyroid nodules. After screening, a total of 1655 residents were finally included in this study, including 698 Uyghur (200 males and 498 females) and 957 Han (304 males and 653 females) subjects.

Serological assays

Fasting blood was obtained from all the subjects for thyroid function, 25(OH)D, and urinary iodine. The serological indexes of all the included subjects were tested in the laboratory center of our hospital, and the test results were all qualified by the control standards certified by the laboratory of Ministry of Health. The detection of thyroid function and 25(OH)D was carried out by using the chemiluminescence immunoassay (Cobas e601 automatic electro-chemiluminescence immunoassay analyzer, Roche, Germany). 10 ml of urine of each subject was collected, placed in a clean polyethylene plastic bag, sealed, and stored at 4°C for the detection of urinary iodine using the mild acid-digesting As-CE catalysis spectrophotometry by iodine automatic detector (Winters OTT-1-P1, China).

Ultrasound examination of thyroid was performed by using Philips HDI5000 (USA) ultrasound equipment, and the examiner had the related imaging experience for more than five years.

Diagnostic criteria

Vd levels were determined referring to the criteria by US Endocrine Society in 2011 [6]: Vd<20 ng/ml as a deficiency, 20~29.99 ng/ml as insufficiency, and >30 ng/ml as sufficiency. According to the diagnostic criteria of "China thyroid disease diagnosis and treatment guidelines" (2008 edition): serum TPOAb- and/or TGAb-positive (+) can be diagnosed as AITDs. This study referred to the guidelines, and set TPOAb>35 IU/ml and TGAb>116 IU/ml as positive.

Statistical analysis

SPSS 16.0 statistical software was used for the statistical analysis. Data normally distributed were expressed as mean ± standard deviation, and those non-normally distributed were expressed using upper and lower quartiles. The constituent ratio was expressed using the number of populations (%). The comparisons of measurement data were performed the t-test, while the comparisons of count data were carried out using χ^2 test, and the multivariate analysis was performed using the Logistic regression, with $P<0.05$ considered as statistically significant.

Table 2. Comparison of antibody positive rates among different groups

Grouping on gender	Total population	Male	Female	χ^2	*P*
Number of population	1655	504	1151	-	-
Antibody-positive (%)[a]	539 (32.63)	106 (21.01)	433 (37.52)	43.81	0.000
Number of population	Total population	Uyghur	Han	χ^2	*P*
Antibody-positive (%)[a]	1655	698	957	-	-
Number of population	539 (32.63)	253 (36.30)	285 (29.81)	8.069	0.005

Note: a: Antibody-positive includes TPOAb and/or TGAb-positive, and the ratio in brackets was the constituent ratio.

Table 3. Comparison of Vd nutritional status in different genders and nationalities

Grouping	25(OH)D level (ng/ml)								
	Deficiency (<20)			Insufficiency (20~29.99)			Sufficiency (>30)		
	(%)	χ^2	*P*	(%)	χ^2	*P*	(%)	χ^2	*P*
Male	63.29	33.89	0.000	30.95	53.83	0.000	5.75	1.848	0.174
Female	77.03			15.37			7.6		
Uyghur	87.5	141.8	0.000	9.27	94.92	0.000	3.23	29.57	0.000
Han	61.65			28.32			10.03		
Male									
Uyghur	76.5	24.89	0.000	20.5	16.95	0.000	3	4.637	0.000
Han	54.6			37.83			7.57		
Female									
Uyghur	91.54	118.8	0.000	5.15	89.86	0.000	3.31	26.17	0.000
Han	64.93			23.89			11.18		
Uyghur									
Male	76.5	30.26	0.000	20.5	40.97	0.000	3	0.045	0.833
Female	91.54			5.15			3.31		
Han									
Male	54.6	9.355	0.002	37.83	19.86	0.000	7.57	3.001	0.083
Female	64.93			23.89			11.18		

Results

General information

There were significant differences in the sex ratio, history of thyroid diseases, BMI, abdominal circumference, urinary iodine, TSH, TPOAb, TGAb, and 25(OH)D (P<0.05) between Uyghur and Han, but there was no significant difference in the age, FT3, and FT4 (**Table 1**).

Prevalence of AITDs

The positive rate of thyroid autoantibodies in total populations was 32.6% (539 persons); the rate in women was significantly higher than that in men (χ^2 = 43.81, P<0.001), and it was significantly higher in Uyghur than in Han (χ^2 = 8.069, P = 0.005) (**Table 2**).

Prevalence of VdD

The incidence of VdD in the total population was 72.96% (1207 persons), and those with Vd insufficiency and sufficiency were 19.99% (331) and 7.05% (117 persons), respectively. The incidence of VdD in women was higher than that in men (P<0.001), as well as higher in Uyghur than in Han (P<0.001) (**Table 3**).

Relationships between Vd and AITDs in Uyghur and Han

With the increasing of Vd levels, the incidences of AITDs in Uyghur and Han both exhibited the decreasing trend, but the difference was not statistically significant (**Table 4**).

Regression analysis of AITDs with Vd levels in Han and Uyghur with different genders

After adjusted the indexes such as age, smoking, BMI, history of thyroid dysfunction, TSH and iodine nutritional status, the relationships of AITDs with Vd levels between Uyghur and Han were compared, and its relationships with age was found. So, the study subjects were grouped with 10-year-old as an interval; the total populations were divided into six age groups, and due to fewer persons in the 18 to 20-year-old group, the groups were set as the following: 18- to 30-year-old, 31- to 40-year-old, 41- to 50-year-old, 51- to 60-year-old, 61- to 70-year-old, and >70-year-old. The comparisons showed no significant correlation between

Table 4. Comparison of AITDs prevalence between Uyghur and Han based on different Vd levels

	AITDs prevalence (%)			Z	
	VdD	VdI	VdS	χ^2	*P*
Total population	32.2	31.2	30.1	0.251	0.882
Han	30.3	27.5	27.2	0.880	0.644
Uyghur	36.1	34.8	32.7	0.117	0.943

Table 5. Regression analysis of Vd and AITDs in 40~60-year-old Han females

	Beta	OR (95% CI)	*P*
Model 1[a]	0.020	1.020 (1.001-1.067)	0.394
Model 2[b]	0.045	0.878 (0.534-0.943)	0.324
Model 3[c]	-0.057	0.911 (0.882-0.975)	0.007

Note: [a]Corrected such indexes as BMI, smoking, and abdominal circumference; [b]Model 1 was combined with the conditions of thyroid nodules (present or absent) and thyroid dysfunction history; [c]Model 2 was combined with the conditions of iodine nutritional status and menopause.

any two age groups. Recent studies have found that AITDs are correlated with Vd in women before and after menopause, so the relationships in the populations at the age of 40 to 60 years old were further compared, and the results revealed that the Vd level in men (regardless of nationality) had no statistically significant relationship with AITDs, and only Han women showed statistically significant relationships between them (P = 0.007) (**Table 5**).

Discussion

VdD has become a global public health problem [7], and Adam [8] found that about 90% of blacks and nearly three-quarters of whites in the US exist VdD. Similarly, it's also found by the health survey among Chinese general populations that the prevalence of VdD is very high [5]. The study found that the incidence of VdD in the total populations in Urumqi communities was 72.96%, together with VdI as 19.99% and VdS as only 7.05%; meanwhile, VdD was significantly higher in women than in men, as well as in Uyghur than in Han. The main supplement of Vd is via light synthesis by the skin, so the reasons of VdD between genders may result from: outdoor activities of women were fewer than men, and most women must go through pregnancy, breast-feeding, or other processes, so the demand for Vd is naturally much higher than men, and these reasons may result in more common incidence of VdD in women. The reasons of VdD between different nationalities may include: (1) compared with Han, Uyghur residents have differences in diet and lifestyle; (2) though the total sunshine in Xinjiang region ranks higher in China, the characteristics of Uyghur dress, especially that of women, significantly reduces the skin area exposed to sunlight, which further leads to the reduction of the opportunities for Vd synthesis by sunlight.

Certain research has shown that the serum 25(OH)D level depends on the age, gender, etc [9]. With the increasing age, the serum 25(OH)D level shows a gradual downward trend, and with the continuous decreasing of Vd level, the risk of AITDs shows a gradual increasing trend. The study found that the relationships between Vd and AITDs had no significant difference, but with the reduction of Vd level, the prevalence of AITDs was increased. Currently, with the improvement of people's health awareness, outdoor activities and opportunities of exposing to sunlight increase significantly, so that the decreasing trend of 25(OH)D level with age increasing in elderly populations does not become much obvious.

Relationships between Vd and AITDs

AITDs is not only related to Vd but also closely related to many other factors. A large number of studies have confirmed that the prevalence of AITDs is high in women [10], among which the estrogen level plays a major decisive role. In addition, AITDs is also closely related to genetic factors, environmental factors, stress, or infection. For example, the correlations between AITDs and the expressions of certain genes [11] revealed that the correlation gene of Graves' disease with thyroid-related eye diseases is HLA-DR3, but the correlation gene in the Japanese, who are also the same yellow race in Asia, is HLA-BW35. Han belongs to the yellow race in Asia, and due to historical reasons of its formation and development, the genotypes of Uyghur are between yellow and white races. Therefore, different genetic structures may exist between Uyghur and Han, and this may ultimately lead to different prevalence of certain diseases between these two nationalities, which may explain why many results obtained in this study were opposite to other studies.

The prevalence of AITDs is also closely associated with the iodine nutritional status. Previous studies have confirmed that iodine reinforce can lead to the generation of thyroid autoantibodies in the population with iodine deficiency. Urumqi was considered to be an area with iodine deficiency in the past [12]. With the implementation of the national policy of compulsory iodized salt, this region has become one iodine-appropriate area, and the positive rate of thyroid related antibodies has been significantly increased, which has a close relationship with the promotion of iodized salt. As an essential trace element in human body, iodine is essential for the synthesis of thyroid hormone. Animal tests and epidemiological investigation conducted by Inge BP [13] indicated that in addition to the relations to AITDs, the intake of iodine which is more than physiological doses will increase the incidence of hyperthyroidism, hypothyroidism, and thyroiditis, but this study found no correlation between Vd and thyroid antibody titers under any Vd levels, and the possible reasons may be that the factors such as iodine nutritional status, environment and heredity were confounded, so this correlation was not obvious.

Studies about the relationships of Vd with AITDs suggest that the Vd gene polymorphism is closely related to the onset of AITDs, but the difference in the distribution of Vd receptor SNPs between AITDs patients and healthy populations is statistically significant, which is one predisposing factor of AITDs [14]. There still are many studies which did not find correlation between these two, even some studies got opposite conclusions. One study [15] suggested that the polymorphisms of Vd receptor genes Apa I, Bsm I, and Fok I may be related to the susceptibility of Graves disease in Asians, but the Vd receptor gene polymorphisms were not related to the prevalence of Graves disease in Caucasians, consistent with the results obtained in this study that the serum Vd level in 40- to 60-year-old Han females was negatively correlated with AITDs, but had no association in other age groups. Uyghur and Han have different genes, and hereditary is also one key factor of autoimmune diseases, so there also exists differences between the prevalence of certain diseases and related risk factors in these two nationalities, and it perhaps can used to explain the conclusions of this study.

Furthermore, this study revealed that AITDs had a high incidence in female populations, and the probable reason is that during the development process of AITDs, estrogen (E2) is also involved in, and causes its relevance between men and women. Whitacre [7] found that compared to men, the number of $CD4^+$ lymphocytes and the absolute Th1 cytokine production rate in women are higher, prompting that female is more closely related to AITDs. Estrogen can promote the synthesis of VDR and accumulation of calcitriol in immune cells, which may explain why the serum 25(OH)D level in women is related to the TPOAb positive rate while no correlation is found in men.

This study also has limitations and shortcomings: the selected groups are the residents of two communities in Urumqi, which lacks certain deficiencies when being used to describe the population features in Urumqi region; assays of serum 25(OH)D performed in different months may differ, and this study only collected the qualified patients in May and July 2013.

In conclusion, our study suggests that the prevalence of AITDs and VdD in Uyghur were both higher than in Han. Similarly, the prevalence of AITDs and VdD were higher in female than in male. The prevalence of AITDs was increases with the reduction of Vd level. As for the female Han aging 40 to 60 years old and residing in Urumqi communities, Vd can be used as a risk indicator to evaluate AITDs. We recognized that our current study had limitations of small sample size and certain time period. Therefore, further studies with a larger sample size from the same ethnic group and at different times are necessary to determine the prevalence of AITDs and VdD, the relation of the Vd and AITDs, and a follow-up study about the relationship between the prevalence of Vd and AITDs.

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Disclosure of conflict of interest

None.

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