

Assessment of serum dipeptidyl peptidase-IV levels in autoimmune thyroid disease

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Abstract

Objective: Decreased serum dipeptidyl peptidase-IV (sDPPIV) levels have been reported in patients with autoimmune diseases. However, few studies have analyzed the association between sDPPIV levels and autoimmune thyroid disease (AITD). This study aimed to evaluate the association between sDPPIV levels and three types of AITD: Graves' disease (GD), Graves' ophthalmopathy (GO), and Hashimoto's thyroiditis (HT).

Methods: Patients newly diagnosed with GD (n = 65), GO (n = 22), and HT (n = 27) and healthy individuals (n = 30) were recruited. Clinical characteristics and thyroid function data were collected. sDPPIV was measured using enzyme-linked immunosorbent assays.

Results: Compared with controls (786.3 ± 46.95), patients with GD and GO had significantly lower sDPPIV levels (662.2 ± 38.81 and 438.4 ± 31.78). Additionally, sDPPIV levels were negatively associated with antithyroid peroxidase antibody ($r = -0.20$) and antithyroglobulin antibody ($r = -0.19$), but there was no significant relationship between thyroid hormone and sDPPIV levels. GO cases were divided by proptosis with and without muscle thickening; sDPPIV levels were lower in the muscle thickening group than those in the without muscle thickening group. Logistic regression analysis showed that sDPPIV was negatively correlated with GO and GD.

Conclusions: sDPPIV concentrations were abnormal in patients with GD and GO, and reduced sDPPIV expression may be involved in the progression of GO and GD.

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Keywords

Serum dipeptidyl peptidase-IV, autoimmune thyroid disease, Graves' disease, Graves' ophthalmopathy, pathogenesis, thyroid antibody

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Introduction

Autoimmune thyroid diseases (AITDs) are the most common organ-specific autoimmune diseases.^{1,2} Graves' disease (GD) and Hashimoto's thyroiditis (HT) are the main clinical presentations of AITD and are characterized by lymphocytic infiltration of the thyroid parenchyma. Graves' ophthalmopathy (GO) is a special subtype of GD, accounting for 30% to 50% of cases.^{3,4} Clinically, GO presents as lesions involving multiple eye tissues, and its symptoms and signs are relatively complex. However, the underlying mechanism is not fully understood. Dipeptidyl peptidase-IV (DPPIV) is a type II transmembrane glycoprotein with serine protease activity that selectively cleaves N-terminal dipeptides from peptides with a proline or alanine residue in the penultimate position. DPPIV is expressed on the surface of epithelial cells in various tissues (liver, kidney, and intestine), endothelial cells, fibroblasts, and lymphocytes.⁵ It is involved in the maintenance of lymphocyte composition and function, activation and co-stimulation of T lymphocytes, activation of B lymphocytes, and cytotoxicity of natural killer cells.^{6,7}

Relevant studies have explored the multiple roles of DPPIV in several diseases, including diabetes, HT,⁸ rheumatoid arthritis,⁹ multiple sclerosis,¹⁰ inflammatory bowel disease, and thyroid cancer.¹¹ However, the role of serum DPPIV (sDPPIV) in GD and GO remains unknown. Therefore, the purpose of the current study was to evaluate sDPPIV levels in patients with GD, GO, and HT

and investigate the role of sDPPIV in the pathogenesis of AITD.

Material and methods

Patients

All patients who visited the Endocrinology Department of the Beijing Luhe Hospital of Capital Medical University from May 2017 to December 2018 were included in the study. They included patients with GD, GO, and HT and healthy controls. Patients with HT with normal thyroid function without any drug therapy were included. Patients with GD did not receive anti-thyroid drug therapy. Those with GO received drug therapy. All patients were diagnosed in accordance with the diagnosis criteria of GD disease in the 2007 Chinese Thyroid Disease Diagnosis Guidelines as follows: (1) clinical hypermetabolic symptoms of hyperthyroidism; (2) diffuse swelling of the thyroid; (3) elevated serum levels of thyroid hormone and decreased thyroid-stimulating hormone (TSH); (4) exophthalmos and other infiltrating ocular signs; (5) pretibial myxoedema; and (6) positive TSH receptor antibodies (TRAb). Among them, (1), (2), and (3) are necessary conditions for diagnosis, and (4), (5), and (6) are auxiliary conditions. The exclusion criteria were as follows: (1) nodular goiter with hyperthyroidism or hyperthyroidism for any reasons other than GD; (2) thyroid enlargement of grade III or above; (3) hyperthyroid heart disease or atrial fibrillation; (4) uncontrolled hypertension (or blood pressure >140/90 mmHg after

antihypertensive treatment); (5) recurrent GD; (6) women who were pregnant or lactating; (7) presence of with malignant tumors; (8) patients with mental illness receiving radiation, chemotherapy, antidepressant, or immunosuppressive therapy; (9) abnormal liver function, with a transaminase level two times higher than the upper normal limit; and (10) hyperthyroidism crisis or combined with myasthenia gravis. In accordance with the Werner standard, GO was classified as none (0–1) or present (2–6).¹² Healthy controls were negative for thyroid antibodies and had no relevant medical history or family history of thyroid diseases. None of the subjects had any infectious diseases or other autoimmune diseases, including human immunodeficiency virus, hepatitis B virus, type 1 diabetes mellitus, multiple sclerosis, rheumatoid arthritis, or systemic lupus erythematosus. The HT inclusion criteria were as follows: increased thyroid peroxidase antibody (TPOAb) and/or thyroglobulin antibody (TGAb); diffuse lesion in the thyroid detected by ultrasound; and normal thyroid function. The study was approved by The Luhe Hospital Ethics Committee (approval number 2018-LHKY-040-03), and all participants provided written informed consent.

Sample collection

Five-milliliter whole-blood samples were collected in ethylenediaminetetraacetic acid vacutainers on an empty stomach in the early morning from patients and healthy controls. After centrifugation ($1000 \times g$ at 4°C for 10 minutes), blood samples were stored at -80°C until use.

Laboratory testing

TPOAb, TGAb, TRAb, free tetraiodothyronine, free triiodothyronine, and TSH levels were detected by electrochemiluminescence immunoassays using an Abbott

Architect I2000 (Abbott Diagnostics, Abbott Park, IL, USA). The thyroid gland was examined using ultrasound (thyroid ultrasound instrument).

sDPPIV expression

sDPPIV levels were measured using a human DPPIV ELISA kit (R&D Systems, Minneapolis, MN, USA). The results were quantified in compliance with the manufacturer's instruction. The intra-assay and inter-assay coefficients of variation were 5.8% and 8.6%, respectively.

Statistical analysis

All data were analyzed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). Quantitative data were presented as the mean \pm standard deviation (for normally distributed data) or as the median and quartiles (for non-normally distributed data), as appropriate. Between-group differences in quantitative parameters were assessed using the Student's t-test for normally distributed data; otherwise, these differences were assessed using the Mann–Whitney U test. Correlations were analyzed using Spearman's rank test. Receiver operating characteristic (ROC) curves were used to investigate sDPPIV's performance in distinguishing between patients with GO or GD and controls. Logistic regression analysis models were used to evaluate the relationships between DPPIV and GO or GD. A P-value less than 0.05 was considered statistically significant.

Results

sDPPIV expression among different groups

To evaluate the changes in sDPPIV reflecting disease activity among different AITDs,

we collected the clinical data from patients with GD (n=65), GO (n=22), and HT (n=27) and from healthy controls (n=30). As shown in Table 1, there were no significant differences in age among different groups, but there were statistical differences in sex, with a significantly lower proportion of female patients in the control group (0.70) compared with that in the GD (0.80), GO (0.82), and HT (0.81) groups ($P < 0.05$). Increased thyroid hormones and decreased TSH levels were observed in patients with GD and GO, whereas decreased thyroid hormones and increased TSH levels were noted in patients with HT. Then, we examined the sDPPIV level among AITDs. The results showed that patients with GO had significantly lower levels of sDPPIV than patients with GD ($P = 0.002$) and healthy controls ($P < 0.001$), but no significant differences were identified between the HT group and control group (Figure 1).

Correlations among sDPPIV and clinical characteristics

To investigate the relationship between sDPPIV and other variables for all participants, we performed a Spearman correlation analysis. sDPPIV was negatively correlated with TPOAb ($r = -0.19$, $P = 0.03$) and TGAb ($r = -0.20$, $P = 0.02$), but there were no correlations between sDPPIV and other variables (Table 2).

Relationship between sDPPIV and GO severity

To explore the relationship between sDPPIV and GO severity, patients in different subgroups were compared between the control and GO groups. Patients with GO were divided into groups on the basis of having proptosis with muscle thickening (n = 5) or proptosis without muscle thickening (n = 17); sDPPIV levels in the proptosis

Table 1. Demographic data and clinical features of all subjects.

	Control	GD	GO	HT	P-value
N	30	65	22	27	
Sex (women)	21	52	18	22	<0.05
Age (years)	54 ± 1.3	55 ± 2.9	54 ± 1.6	53 ± 2.1	>0.05
TT3 (ng/mL)	1.19 ± 0.03	4.81 ± 0.53	2.83 ± 0.44	1.14 ± 0.03	<0.001
TT4 (µg/dL)	8.29 ± 0.26	18.27 ± 0.81	12.97 ± 1.52	8.12 ± 0.3	<0.001
FT3 (pg/mL)	3.05 ± 0.05	17.56 ± 1.22	10.13 ± 1.82	2.89 ± 0.06	<0.001
FT4 (ng/mL)	1.28 ± 0.03	5.37 ± 0.32	3.17 ± 0.54	1.22 ± 0.03	<0.001
TSH (µIU/mL)	1.86 ± 0.15	0.18 ± 0.17	4.32 ± 3.57	4.18 ± 0.64	<0.001
TGAb (U/mL)	8.89 ± 0.67	211.4 ± 33.2	160.19 ± 61.5	350.6 ± 38.8	<0.001
TPOAb (U/mL)	11.31 ± 0.98	472.8 ± 109.8	785.7 ± 394.22	1131.4 ± 243.6	<0.001
TRAb (IU/L)		17.31 ± 1.72	12.44 ± 2.71		0.137
HDL (mmol/L)	1.33 ± 0.06	1.13 ± 0.03	1.20 ± 0.04	1.26 ± 0.05	0.008
LDL (mmol/L)	2.88 ± 0.86	1.72 ± 0.39	2.30 ± 0.48	2.86 ± 0.58	<0.001
TC (mmol/L)	4.83 ± 1.12	3.27 ± 0.62	4.34 ± 0.82	4.84 ± 0.72	<0.001
TG (mmol/L)	1.66 ± 0.24	1.18 ± 0.05	1.21 ± 0.13	1.78 ± 0.26	0.017
CRP (mg/L)	3.26 ± 1.23	2.50 ± 1.05	1.36 ± 0.46	1.29 ± 0.24	0.62
sDPPIV (mg/L)	786.3 ± 46.95	662.2 ± 38.81	438.4 ± 31.78	684.9 ± 33.62	<0.001

GD, Graves's disease; GO, Graves' ophthalmopathy; HT, Hashimoto's thyroiditis; TT4, total triiodothyronine; TT3, total tetraiodothyronine; FT3, free triiodothyronine; FT4, free tetraiodothyronine; TSH, thyroid-stimulating hormone; TGAb, antithyroglobulin antibody; TPOAb, thyroperoxidase antibody; TRAb, TSH receptor antibody; TG, triglyceride, TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein; sDPPIV, soluble dipeptidyl peptidase-IV.

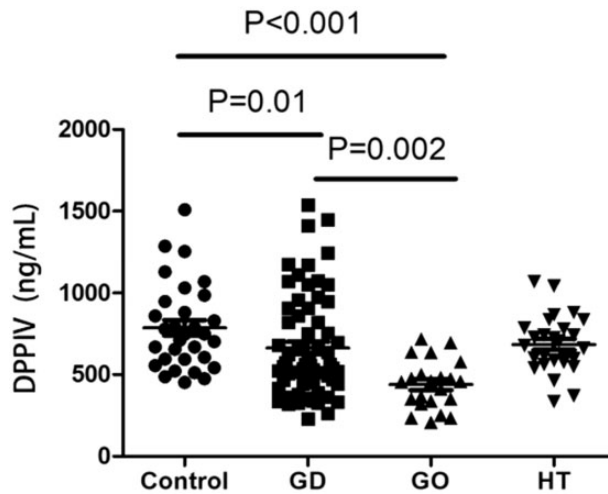


Figure 1. sDPPIV levels in patients with different autoimmune thyroid diseases. sDPPIV levels were measured in patients with GD ($n = 65$), GO ($n = 22$), and HT ($n = 27$) and healthy controls ($n = 30$) using an enzyme-linked immunosorbent assay. The data are shown as the mean \pm standard deviation. sDPPIV, soluble dipeptidyl peptidase-IV; GD, Graves's disease; GO, Graves' ophthalmopathy (GO); HT, Hashimoto's thyroiditis.

Table 2. Spearman correlation analysis between sDPP4 levels and clinical characteristics in all participants.

	Correlation coefficient	P-value
TT3 (ng/mL)	0.029	0.729
TT4 (μ g/dL)	0.040	0.641
FT3 (pg/mL)	0.077	0.370
FT4 (ng/mL)	0.108	0.208
TSH (μ IU/mL)	0.079	0.357
TGAb (U/mL)	-0.204	0.023*
TPOAb (U/mL)	-0.193	0.032*
TRAb (IU/L)	-0.095	0.353
HDL (mmol/L)	-0.032	0.699
LDL (mmol/L)	0.055	0.506
TC (mmol/L)	0.006	0.093
TG (mmol/L)	-0.042	0.612
CRP (mg/L)	0.018	0.826

TT4, total triiodothyronine; TT3, total tetraiodothyronine; FT3, free tetraiodothyronine; FT4, free triiodothyronine; TSH, thyroid-stimulating hormone; TPOAb, anti-thyropoxidase antibody; TGAb, antithyroglobulin antibody; TRAb, TSH receptor antibody; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein; sDPPIV, soluble dipeptidyl peptidase-IV.

* $P < 0.05$.

with muscle thickening group were lower than those in the proptosis without muscle thickening group ($P = 0.007$) (Figure 2).

Correlations of sDPPIV with GO and GD

To determine the association between sDPPIV and GO, logistic regression analyses were performed in GD and GO groups. Logistic regression analysis showed that sDPPIV was negatively correlated with GD in the unadjusted (odds ratio [OR] = 0.999, 95% confidence interval [CI] = 0.997–1.00, $P = 0.063$) and adjusted models (Model 1: OR = 0.998, 95% CI = 0.996–1.00, $P = 0.013$ and Model 2: OR = 0.998, 95% CI = 0.995–1.00, $P = 0.042$) (Table 3).

Logistic regression analysis for GO also showed that sDPPIV was negatively correlated with GD in the unadjusted (OR = 0.999, 95% CI = 0.997–1.00, $P < 0.001$) and adjusted models (Model 1: OR = 0.988, 95% CI = 0.981–0.995, $P = 0.001$ and Model 2: OR = 0.988, 95% CI = 0.978–0.998, $P = 0.018$) (Table 4).

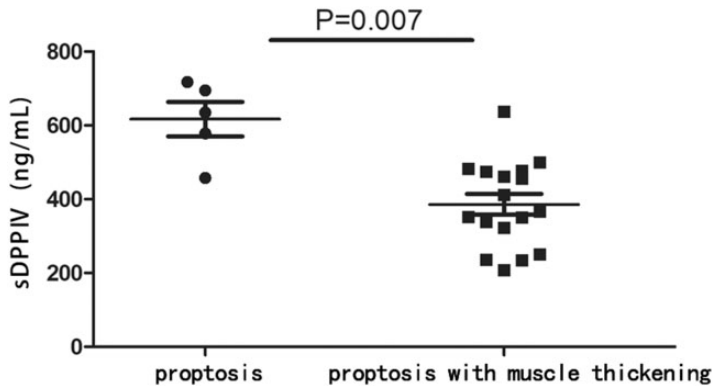


Figure 2. sDPPIV levels between proptosis with and without muscle thickening groups in patients with GO. The data are shown as the mean \pm standard deviation. sDPPIV, soluble dipeptidyl peptidase-IV; GO, Graves' ophthalmopathy (GO).

Table 3. Logistic regression to investigate the related risk factors for GD.

	OR (95% CI)	P-value
Model 1	-0.001 0.999 (0.997, 1.00)	0.063
Model 2	-0.002 0.998 (0.996, 1.00)	0.013
Model 3	-0.002 0.998 (0.995, 1.00)	0.042

Logistic regression models were used to evaluate relationships between sDPP4 and GD. Model 1 was not adjusted for variables; Model 2 was adjusted for age and sex; Model 3 was adjusted for age, sex, CRP, HDL, LDL, TG, and TC.

OR, odds ratio; 95% CI, 95% confidence interval; CRP, C-reactive protein; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GD, Graves's disease; sDPPIV, soluble dipeptidyl peptidase-IV.

ROC curves indicated a good performance of sDPPIV to distinguish between patients with GO or GD and controls. The results indicated that the optimal cut-off value of sDPPIV was 506.1 (ng/mL), which corresponded to a sensitivity of 90.3% and a specificity of 77.3% for differentiating between the GO and control groups (area under the curve [CI]=0.903 [0.823–0.982]). The optimal cut-off value of sDPPIV was 582.65 (ng/mL), which corresponded to a sensitivity of 77.4% and a specificity of 55.4% for differentiating

Table 4. Logistic regression to investigate the related risk factors for GO.

	OR (95% CI)	P-value
Model 1	-0.001 0.999 (0.997, 1.00)	<0.001
Model 2	-0.012 0.988 (0.981, 0.995)	0.001
Model 3	-0.012 0.988 (0.978, 0.998)	0.018

Logistic regression models were used to evaluate relationships between sDPP4 and GO. Model 1 was not adjusted for variables; Model 2 was adjusted for age and sex; Model 3 was adjusted for age, sex, CRP, HDL, LDL, TG, and TC.

OR, odds ratio; 95% CI, 95% confidence interval; CRP, C-reactive protein; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GO, Graves' ophthalmopathy; sDPPIV, soluble dipeptidyl peptidase-IV.

between the GD and control groups (area under the curve [CI]=0.659 [0.55–0.766]) (Figure 3).

Discussion

In the current study, we demonstrated that patients with GD and GO had significantly lower sDPPIV levels than controls, and the sDPPIV levels in GO cases were lower than those in GD cases. In a subgroup analysis of GO, sDPPIV levels were negatively correlated with the disease progression.

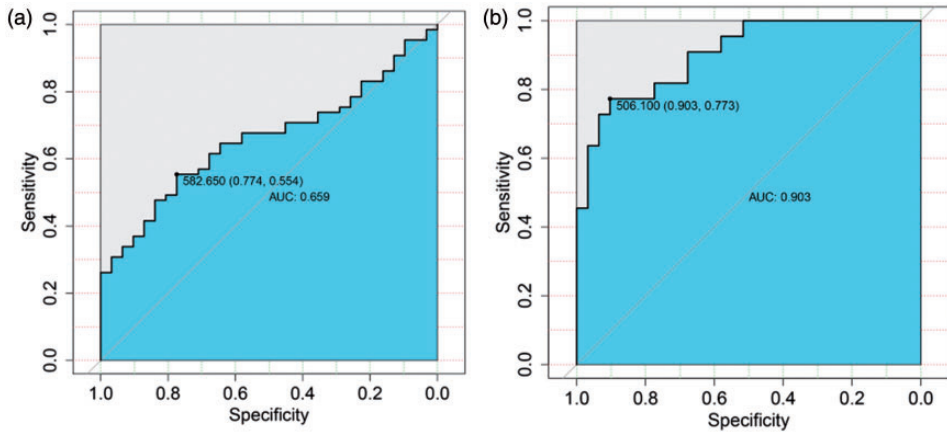


Figure 3. ROC curve analyses for the prediction of (a) GD and (b) GO on the basis of the sDPPIV levels. ROC, receiver operating characteristic; GD, Graves' disease; GO, Graves' ophthalmopathy; sDPPIV, soluble dipeptidyl peptidase-IV; AUC, area under the curve.

These findings provide insight into the clinical implication of sDPPIV in patients with GD or GO and suggest that sDPPIV may be an early predictive biomarker in AITD.

An increasing amount of information on DPPIV suggests that it is involved in cleaving and inactivating regulatory peptides (such as glucagon-like peptide-1 and brain natriuretic peptide), glucose homeostasis, and cancer progression,¹³ and it has immunological functions.¹⁴ Additionally, DPPIV plays an important role in the T-cell development, maturation, activation, and differentiation and immune system regulation.¹⁵ Therefore, DPPIV is regarded as a co-stimulator in the antigen-stimulated activation of T lymphocytes.¹⁶ To date, DPPIV has been widely studied in immune diseases, such as type 1 diabetes and multiple sclerosis.^{17,18} Extensive evidence indicates that DPPIV is associated with a potential role in the immunopathology of autoimmunity diseases.¹⁹

To the best of our knowledge, this is the first study to report changes in sDPPIV levels in different AITDs. One potential mechanism underlying the association between DPPIV and AITD is

immunoregulation. First, previous studies have confirmed that DPPIV knockout mice exhibit increased disease severity and enhanced type 1 cytokine production, suggesting that DPPIV acts as a negative regulatory molecule in autoimmunity.²⁰ Second, extensive literature shows a Th1 immune preponderance, and Th1-chemokines (CXCL9, CXCL10, CXCL11) and their receptors play a crucial role in the immunopathogenesis of GD and GO.^{21,22} Increased CXCL10 levels were observed in GD and GO.^{23,24} The N-terminal X-Pro cleaving activity of DPPIV regulates chemotactic responses to inflammatory chemokines,²⁵ which partly explains the lower sDPPIV levels in patients with GD and GO. We demonstrated that circulating DPPIV is lower in patients with GO than in subjects with GD, indicating a progressive increase in the inflammatory state from GD to GO. In a subgroup analysis, sDPPIV levels were negatively correlated with the GO progression. Our study did not show a reduction in DPPIV levels in patients with HT, which is consistent with the research by Liu and colleagues.²⁶ For HT, the difference may be attributed to

the inconsistent thyroid function and serum TPOAb and/or TGAb titers in the HT population, indicating different degrees of immunity.

There are several limitations to the current study. First, DPPIV is expressed both as a soluble form in body fluids, such as serum, and as a cell surface glycoprotein of various cell types, including immune cells. Therefore, membrane-bound DPPIV levels on immune cells should also be evaluated in future studies. Second, the sample size was relatively small and consisted entirely of Chinese people, which may limit the generalizability of our findings. Although there are some limitations, DPPIV may have a pathophysiological role in patients with GD and GO. Further detailed studies are needed to better elucidate the underlying molecular mechanisms.

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) affects many organs and systems, including the thyroid gland. Related studies have shown that SARS-CoV-2 is associated with a variety of thyroid diseases, such as subacute thyroiditis, GD, HT, and thyrotoxicosis. However, how SARS-CoV-2 affects thyroid function through DPP4 is currently unclear. Therefore, we aim to study this in the future.^{27,28}

In conclusion, sDPPIV levels are significantly decreased in patients with GO and GD and independently associated with thyroid antibodies. Our study provides clinical evidence that sDPPIV is possibly involved in the pathogenesis of GD and GO.

Author contributions

Yuanyuan Zhang analyzed the clinical data and provided the clinical samples and information, **Yuanyuan Zhang** and **Ying Fu** wrote the manuscript and performed related experiments, **Yuxian Yang** collected the clinical data and samples, and **Dong Zhao** and **Jing Ke** designed and supervised the project, interpreted the data, and corrected the manuscript.

Declaration of conflicting interest

The authors declare that they have no competing interests regarding the publication of this paper.

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