Lower Serum Dipeptidyl peptidase-IV Level is Associated With 3 Types of Autoimmune Thyroid Diseases

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Research Article

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Abstract

Background:
Autoimmune thyroid diseases (AITD) are the most common organ specific autoimmune disorders. The reduction of serum dipeptidyl peptidase-IV (sDPPIV) levels have been reported in patients with autoimmune diseases. Few studies have analyzed the association between sDPPIV levels and AITD, especially in Graves’ disease (GD), Graves’ ophthalmopathy (GO) patients. So the aim of this study was to evaluate the association between sDPP-IV levels and 3 types of AITD, that is Graves’ disease (GD), Graves’ ophthalmopathy (GO), Hashimoto’s thyroiditis (HT).

Methods

65 newly diagnosed GD, 22 GO, 27 HT patients and 30 healthy individuals were recruited for this study. Clinical characteristics and thyroid function data were collected for all participants. sDPP-IV was measured by enzyme-linked immunosorbent assay.

Results

Compared with the controls, GD patients and GO patients had significantly lower sDPP-IV levels (662.2 ± 38.81 and 438.4 ± 31.78 vs. 786.3 ± 46.95, P = 0.01 or P < 0.001). It was also found that in GO individuals, sDPP-IV was lower than in GD subjects (P = 0.002). The lower the sDPP-IV level is, the higher the risk for developing GD or GD will be. In addition, sDPP-IV levels have negative association with the antithyroid peroxidase antibody (TGab) (r = -0.20, p = 0.02) and antithyroglobulin antibody (TPOab) (r = -0.19, p = 0.03). But there was no significant relationship between thyroid hormone and sDPP-IV levels. GO patients were groups by proptosis with and without muscle thicken, the sDPP-IV levels in proptosis with muscle thicken were lower than proptosis without muscle thicken (P < 0.05). Logistic regression analysis showed that sDPP4 were negatively correlated with GO and GD.

Conclusions

Take together, the present study showed for the first time that sDPP-IV concentrations are aberrant in GD and GO patients and that the reduced sDPP-IV expression may be involved in the progression of GO and GD diseases.

Introduction

Autoimmune thyroid disease (AITD) are the most common organ specific autoimmune disorder[1, 2]. 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. Graves’ ophthalmopathy
(GO) belong to the special subtype of GD which accounts for 30–50\%[3, 4]. GO has the clinical characteristics of high incidence, lesions involving multiple tissues of the eye, and symptoms and signs are relatively complex. The pathogenesis of GO and GD disease share the same pathogenesis basis. Abnormal immune regulation plays an important role. However, the pathogenesis mechanism is not fully understood. Dipeptidyl peptidase-IV (DPP-IV) is a type II transmembrane glycoprotein that having serine protease activity, and which selectively cleaves an N terminal dipeptide from peptides with a proline or alanine residue in the penultimate position. DPP-IV is expressed on the surface of epithelial cells in various tissues (liver, kidney, intestine, etc.), and also in endothelial cells, fibroblasts, and lymphocytes[5]. When expressed on the surface of lymphocytes, it is called CD26 and is involved in the maintenance of lymphocyte composition and function, activation and co-stimulation of T lymphocytes, also involved in activation of B lymphocytes and cytotoxicity of NK cells [6, 7]. Therefore, relevant studies have explored the multiple roles of DPP-IV in metabolism, immunity, endocrine and tumor biology, including diabetes, HT[8], rheumatoid arthritis[9], multiple sclerosis[10], inflammatory bowel disease and thyroid cancer[11]. Up to now, the leaves of DPP-IV in GD and GO have remained unknown. Therefore, the purpose of the current study was to evaluate DPP-IV levels in patients with GD, GO and HT and to investigate the role of DPP4 in the pathogenesis of AITD.

**Material And Methods**

**Patients.**

A total of patients, who visited the endocrinology department of the Beijing Luhe Hospital of Capital Medical University from May 2017 to Dec 2018, were included in the study. These patients included GD, GO, HT and healthy controls. All the patients accorded with the diagnosis criteria of GD disease in the 2007 Chinese thyroid disease diagnosis guidelines, follows: (1) Clinical hypermetabolic symptoms of hyperthyroidism; (2) Diffuse swelling of thyroid; (3) Serum levels of thyroid hormone are elevated and thyroid stimulating hormone are decreased; (4) exophthalmos and other infiltrating ocular signs; (5) Pretibial myxoedema; (6) TSH receptor antibodies are positive; Among them, (1), (2) and (3) are necessary conditions for diagnosis, and (4), (5) and (6) are auxiliary conditions. Exclusion criteria: (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 > 140/90mmhg after antihypertensive treatment); (5) recurrent GD; (6) women with pregnancy or lactation period; (7) complicated with malignant tumors; (8) Patients with mental illness are receiving radiation, chemotherapy, antidepressant or immunosuppressive therapy; (9) abnormal liver function, with transaminase level 2 times higher than the upper normal limit; (10) Hyperthyroidism crisis or combined with myasthenia gravis. According to Werner standard, Graves’ ophthalmopathy are classified as none (0–1) or presence (2–6)[12]. The healthy controls were negative for thyroid antibodies, and they had no relevant medical history and no family history of thyroid diseases. None of the subjects had any infectious diseases or other autoimmune diseases, including human immunodeficiency virus (HIV), hepatitis B virus (HBV), T1DM, MS, rheumatoid arthritis (RA) and systemic
lupus erythematosus (SLE). The patients of Hashimoto's thyroiditis (HT) inclusion criteria were as follows: increased TPOAb and/or TGAb, diffuse lesion in thyroid via ultrasound, normal thyroid function. The study was approved by The Luhe Hospital Ethics Committee and all participants provided signed written consent.

Sample Collection

Five-milliliter whole-blood samples were collected in EDTA vacutainers on empty stomach at early morning from patients and healthy controls. After centrifugation, blood sample stored at −80°C until use.

Laboratory Testing

The levels of TPOAb, TgAb, TRAb, free tetraiodothyronine(FT4), freetriiodothyronine (FT3) and thyroid-stimulating hormone(TSH) were detected by electrochemiluminescence immunoassay(ECLIA) using an Abbott Architect I2000 (Abbott Diagnostics, Abbott Park, IL, USA). The thyroid gland was examined by ultrasound (Thyroid ultrasound instrument)Biochemical detection included analysis of total cholesterol (TC), high-density lipoprotein (HDL), triglycerides (TG), low-density lipoprotein (LDL), C-reactive protein (CRP) and uric acid.

sDPP-IV Expression

sDPP-IV levels were measured using a human DPP-IV ELISA kit (RD, Systems, USA). The experiments were quantified in complied with the manufacture's instruction. The intra-assay and the interassay coefficient of variation was 5.8% and 8.6% respectively.

Statistical Analysis

All data were analyzed using the SPSS Statistics 20.0 software package (IBM, New York, NY, USA). Quantitative data were presented as the mean ± standard deviations (for normally distributed data) or as medians and quartiles (for non-normally distributed data), as appropriate. Between-group differences in quantitative parameters were assessed by Student's t-test in cases in which the data were normally distributed; otherwise, these differences were assessed with the Mann-Whitney U test. Correlations were analyzed using Spearman's rank test. A P-value less than 0.05 was considered statistically significant.

Results

The Expression of sDPPIV in Serum among Different Groups.

To evaluate whether the changes in the sDPPIV reflect disease activity among different autoimmune thyroid diseases. We collected the clinical data from GD, GO, HT and healthy control. As shown in Table 1, there were no significant difference in gender, age among different groups. There were increased thyroid hormones and decreased TSH levels in GD and GO patients, whereas there were decreased thyroid hormones and increased TSH levels in HT patients. Then we examined the sDPP4 level among autoimmune thyroid diseases. Results shown that patients with GO patients had significantly lower levels
of sDPP4 than GD patients (P = 0.002) and healthy controls (p < 0.001), but no significant differences were identified between HT group and the control (p = 0.24) (Fig. 1).

Table 1
Demographic data and clinical feathers of all the subjects

|                | Control | GD      | GO      | HT      | P       |
|----------------|---------|---------|---------|---------|---------|
| N              | 30      | 65      | 22      | 27      |         |
| Gender(female%)| 21      | 52      | 18      | 22      |         |
| Age(years)     | 54 ± 1.3| 55 ± 2.9| 54 ± 1.6| 53 ± 2.1|         |
| TT3(ng/mL)     | 1.19 ± 0.03| 4.81 ± 0.53| 2.83 ± 0.44| 1.14 ± 0.03| < 0.00 |
| TT4(ug/dL)     | 8.29 ± 0.26| 18.27 ± 0.81| 12.97 ± 1.52| 8.12 ± 0.3  | < 0.00 |
| FT3(pg/mL)     | 3.05 ± 0.05| 17.56 ± 1.22| 10.13 ± 1.82| 2.89 ± 0.06| < 0.00 |
| FT4(ng/mL)     | 1.28 ± 0.03| 5.37 ± 0.32| 3.17 ± 0.54| 1.22 ± 0.03| < 0.00 |
| TSH(uIU/mL)    | 1.86 ± 0.15| 0.18 ± 0.17| 4.32 ± 3.57| 4.18 ± 0.64| < 0.00 |
| TgAb(U/mL)     | 8.89 ± 0.67| 211.4 ± 33.2| 160.19 ± 61.5| 350.6 ± 38.8| < 0.00 |
| TPOAb(U/mL)    | 11.31 ± 0.98| 472.8 ± 109.8| 785.7 ± 394.22| 1131.4 ± 243.6| < 0.00 |
| 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-C(mmol/L)  | 2.88 ± 0.86| 1.72 ± 0.39| 2.30 ± 0.48| 2.86 ± 0.58| < 0.00 |
| TC(mmol/L)     | 4.83 ± 1.12| 3.27 ± 0.62| 4.34 ± 0.82| 4.84 ± 0.72| < 0.00 |
| 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| < 0.00 |

HT, Hashimoto's thyroiditis; FT3, free triiodothyronine; FT4, free tetraiodothyronine; TSH, thyroid-stimulating hormone; TgAb, antithyrogloblin antibody; TPOAb, thyroperoxidase antibody.

* P < 0.05 compared with all the group

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 any correlations between sDPPIV and other variables (Table 2).
Table 2
Spearman correlation analysis between sDPP4 levels and clinical characteristics in all the participants

|                      | Correlation coefficient | P value |
|----------------------|-------------------------|---------|
| TT3(ng/mL)           | 0.029                   | 0.729   |
| TT4(ug/dL)           | 0.040                   | 0.641   |
| FT3(pg/mL)           | 0.077                   | 0.370   |
| FT4(ng/mL)           | 0.108                   | 0.208   |
| TSH(uIU/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-C(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 T4; TT3 total T3; FT3 free T3; FT4 free T4; TSH thyroid-stimulating hormone; TPOAb anti-thyroid peroxidase antibody; TgAb anti-thyroglobulin antibody; TG triglyceride, TC total cholesterol; HDL high-density lipoprotein; LDL low-density lipoprotein; CRP C-reactive protein; *P < 0.05

Relationship between sDPPIV and severity of GO

In order to explore the relationship between sDPPIV and the severity of GO, sDPPIV patients in different subgroups were compared between the control and GO group. GO patients were groups by proptosis with and without muscle thickened, the sDPP4 levels in proptosis with muscle thickened were lower than proptosis without muscle thickened (P < 0.05) (Fig. 3).

Correlations among sDPPIV and GO, GD.

To determine the association between sDPPIV and GO, logistic regression analyses were performed in GD and GO groups. Logistic regression analysis showed sDPPIV were negatively correlated with GD and in both the unadjusted (OR = 0.999, 95% CI = 0.7-1.00, p = 0.063) and adjusted models (OR = 0.998, 95% CI = 0.996-1.00, p = 0.013, and OR = 0.998, 95% CI = 0.995-1.00, p = 0.042)(Table 3). Logistic regression analysis for GO also showed sDPPIV were negatively correlated with GD and in both the unadjusted (OR = 0.999, 95% CI = 0.997-1.00, p = 0.00) and adjusted models (OR = 0.988, 95% CI = 0.981–0.995, p = 0.001 and OR = 0.988, 95% CI = 0.978–0.998, p = 0.018) (Table 4).
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 other 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.

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) | < 0.00 |
| 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 other 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.

Receiver Operating Characteristic (ROC) curves indicated a good performance of sDPPIV to discriminate between GO, GD patients and controls. The results indicated an optimal cut-off value of sDPPIV 506.1 (ng/mL), which corresponded to a sensitivity of 90.3% and a specificity of 77.3% for differentiating between the GO and the control groups (area under curve[CI] = 0.903[0.823–0.982]). And an optimal cut-off value of sDPP4 582.65 (ng/mL), which corresponded to a sensitivity of 77.4% and a specificity of 55.4% for differentiating between the GD and the control groups (area under curve[CI] = 0.659[0.55–0.766])(Fig. 3).

Discussion

In the current study, we demonstrated that GD and GO patients had significantly lower sDPPIV compared with the controls and importantly the sDPPIV levels in GO were lower than in GD. These findings provide an insight into clinical implication of sDPPIV in GD or GO patients and is defined as early predictive biomarker in thyroid autoimmune disease.

Constantly growing literature data concerning DPPIV can be found not only involved in enzymatic activity that can cleaved and inactivated many regulatory peptides such as glucagon-like peptide-1(GLP-1), brain natriuretic peptide(BNP), glucose homeostasis, cancer progression[13], but also immunological functions[14]. There are mounting evidences that demonstrate the role of DPPIV as a protein playing an
important role in the development, maturation, activation and differentiation of T-cells and regulating immune system\[15, 16\]. So far DPPIV was widely studied in other immune disease like type 1 diabetes and multiple sclerosis \[17, 18\]. A large body of evidence showed that DPPIV is also identified as a predictive biomarker in the other autoimmunity diseases.

To our knowledge, this is the first study to report changes of sDPPIV levels in different autoimmune thyroid diseases. What the underlying mechanism of the association between DPPIV and AITD? Immunoregulation should a more reasonable explanation for this phenomenon. Firstly, previous studies have confirmed that CD26 knock out mice can increase severity of the disease and enhanced type 1 cytokine production, suggesting that CD26 acts as a negative regulatory molecule in autoimmunity\[19\]. Secondly, extensive literature shows a Th1 immune-preponderance and Th1-chemokines (CXCL 9, CXCL10, CXCL11) and their (C-X-C) R3 receptor play a crucial role in the immunopathogenesis of GD and GO\[20, 21\]. Previous study had shown increased CXCL 10 levels were observed in GD and GO\[22, 23\]. since DPPIV as a result of its N-terminal X-Pro cleaving activity regulates chemotactic responses to the inflammatory chemokines CCL3–5, 11 and 22, CXCL2, 9–12 \[24\], which to some extent explain lower sDPPIV were associated in patients of GD and GO. Importantly, we demonstrated that sDPPIV is lower in GO patients than in GD subjects, indicating a progressive increase of inflammatory state from GD to GO. In subgroups analysis of GO, sDPPIV levels negative correlate with the progress of GO. Our study also did not show reduction of DPPIV levels in HT patients, which is consistent with Yalei Liu and colleagues \[25\].

There are several limitations in our current study. First, as we all known, DPPIV was expressed both as a soluble form in body fluids such as serum, but also as a cell surface glycoproteins of various cell type including immune cells, so in future should be also evaluated membrane-bound CD26 levels on immune cells. Second, the sample size was relatively small and consisted entirely of Chinese people, which may have hampered the generalization of our findings. Although there are some limitations, it seems likely that DPPIV may have a pathophysiological role in patients with GD and GO. Further detailed studies are still needed to better elucidate the underlying molecular mechanisms.

**Conclusions**

In conclusion, Our study showed for the first time that sPPIV levels are significantly decreased in GO and GD patients and reduced sDPP-IV expression may be involved in the progression of GO and GD diseases.

**Declarations**

**Data Availability**

The data that support the findings of this study are available on request from the corresponding author Dong Zhao.

**Authors’ Contributions**
Authors’ contributions Yuanyuan Zhang analyzed the clinical data, Jing Song provided the clinical samples and information, Yuanyuan Zhang and Ying Fu wrote the manuscript; performed cell culture and related experiments; Yuxian Yang collected the clinical data and sample; Dong Zhao designed and supervised the project, interpreted the data and corrected the manuscript.

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Ethics approval and consent to participate

Approval was obtained from the ethics committee from Luhe hospital of Capital Medical University (approval no.2018-LHKY-040-02). All procedures performed in the study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from the patient before undergoing all clinical procedures.

Consent for publication

Not applicable.

Competing interests

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

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Figures
Figure 1

Serum concentrations of DPP4 with different autoimmune thyroid disease.
Figure 2

sDPP4 levels between proptosis with and without muscle thicken in GO patients
Figure 3

ROC curve analyses were performed for the prediction of (A) GD and (B) GO according to the sDPP4 level.