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SHORT REPORT

Dipeptidyl peptidase-4 inhibitor might exacerbate Graves' disease: A multicenter observational case–control study

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Keywords
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ABSTRACT

Dipeptidyl peptidase-4 (DPP-4), namely CD26, is expressed on the surface of immune cells, suggesting that inhibition of DPP-4 might affect the immune system. The current multicenter observational case–control study was carried out to investigate the effects of DPP-4 inhibitor (DPP-4i) administration on Graves' disease (GD) activity. This study comprised patients with GD and type 2 diabetes, who were administered an oral hypoglycemic agent including DPP-4i. Exacerbation of GD was defined as an increase of antithyroid drug dose by 6 months after oral hypoglycemic agent administration. A total of 80 patients were enrolled and divided into an exacerbation group or a non-exacerbation group. The frequency of DPP-4i administration was significantly higher in the exacerbation group (88%) than that in the non-exacerbation group (31%). In multivariate logistic regression analysis, there was a significant association between DPP-4i administration and GD exacerbation (odds ratio 7.39). The current study suggests that DPP-4i administration is associated with GD exacerbation.

INTRODUCTION

Dipeptidyl peptidase-4 inhibitor (DPP-4i) is an oral hypoglycemic agent (OHA) that stimulates pancreatic insulin secretion by elevating glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide concentration. DPP-4i has been widely used because of its safety profile including a low risk of hypoglycemia[1]. DPP-4, namely CD26, is expressed on the surface of immune cells including T cells, presumably suggesting that DPP-4 inhibition might affect the immune system[2]. DPP-4i-induced polyarthritis and bullous pemphigoid have been reported[3,4], and in a cohort study, DPP-4i administration increased the risk of inflammatory bowel disease[5]. Another study reported the high prevalence of Hashimoto's disease in patients on DPP-4i[6].

Graves' disease is an autoimmune condition defined by overproduction of thyroid hormone due to upregulated thyroid stimulation by thyroid-stimulating hormone receptor antibodies (TRAb). T cells have been implicated in the initiation and amplification of this process[7]. Although it has been hypothesized that DPP-4i administration might affect Graves' disease activity, as far as we could determine, no studies have investigated this potential association. In the current study, the influence of DPP-4i administration on Graves' disease activity was investigated.

MATERIALS AND METHODS

Patients

The current investigation was a retrospective multicenter case–control study. Patients with Graves' disease and type 2 diabetes mellitus who were newly or additionally administered an OHA including DPP-4i from December in 2009 to April in 2018 at Hokkaido University Hospital, Sapporo City General Hospital, Sapporo Diabetes, and Thyroid Clinic and Sapporo Medical Center, NTT East Corporation, were included in the present study. We screened patients using insurance-based disease names on medical records, and we excluded non-Graves' thyrotoxicosis or type 1 diabetes one by one. We diagnosed and ruled out type 1 diabetes according to the diagnostic criteria of

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Japan Diabetes Society[8]. Patients with other systemic diseases affecting thyroid function and those who underwent thyroidectomy or radioiodine treatment within 6 months before or after OHA administration were also excluded. The opt-out consent procedure was used. The study was reviewed and approved by the institutional review board of Hokkaido University Hospital and Medical Innovation Center (approved on 31 October 2019, Clinical Research No. 018-0201).

Methods

Data pertaining to thyroid function and antithyroid drug doses from 3 months before OHA administration to 6 months after OHA administration were acquired retrospectively by reviewing the patients' record. The patients were divided into a Graves' disease exacerbation group and a non-exacerbation group. Exacerbation of Graves' disease was defined as an increase of antithyroid drug dose at 1 month, 3 months or 6 months after OHA administration. Baseline characteristics in the exacerbation group and the non-exacerbation group were compared, and multivariate logistic regression analysis was carried out using factors extracted through these comparisons. Free T3, free T4 and thyroid-stimulating hormone were determined using an enzyme immunoassay (Tosoh Corporation, Tokyo, Japan) in Hokkaido University Hospital, a chemiluminescent enzyme immunoassay (Fujirebio Inc., Tokyo, Japan) in Sapporo City General Hospital, an electrochemiluminescence immunoassay (Roche Diagnostics, Tokyo, Japan) in Sapporo Diabetes and Thyroid Clinic, and a chemiluminescent immunoassay (Abbott Japan LLC, Tokyo, Japan) in Sapporo Medical Center, NTT East Corporation.

Statistical analysis

Data were analyzed using JMP Pro software (JMP version 14.0.0, SAS Institute Inc., Cary, NC, USA). Continuous variables are expressed as either the mean ± standard deviation or median and interquartile range. Continuous variables were analyzed using the unpaired *t*-test or the Mann–Whitney *U*-test, as appropriate. Comparisons of frequencies in the two groups were assessed by Fisher's exact test. $P < 0.05$ was deemed to show statistical significance.

RESULTS

A flow chart of the study is shown in Figure 1. A total of 645 patients with Graves' disease and type 2 diabetes were screened for enrollment, and 80 patients were ultimately included in the analysis after application of the inclusion and exclusion criteria. Among the included participants, 16 patients were in the Graves' disease exacerbation group and 64 patients were in the non-exacerbation group. In types of DPP-4i, sitagliptin was the most common (41%) followed by vildagliptin (15%), alogliptin (12%) and omarigliptin (12%; Figure 2a). In the other OHA, biguanide was the most commonly used (33%), followed by sulfonyl urea (24%) and α-glucosidase inhibitor (13%; Figure 2b).

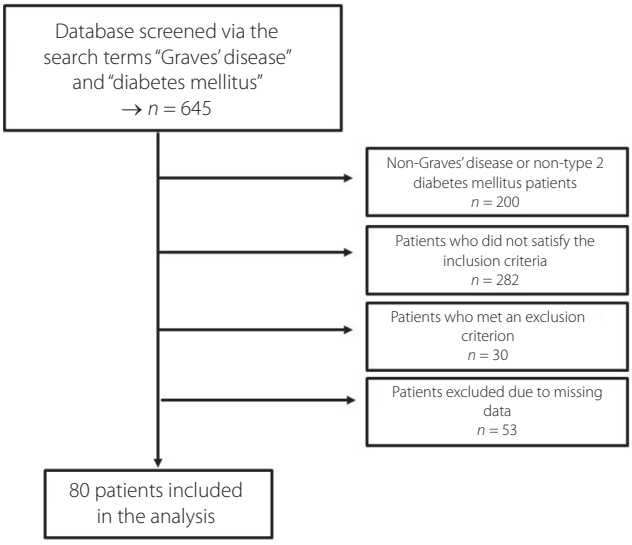

Figure 1 | Flow chart of patients with type 2 diabetes and Graves' disease.

In comparisons of baseline characteristics, mean age was significantly higher in the exacerbation group compared with that in the non-exacerbation group ($P = 0.01$). The frequency of DPP-4i administration was significantly higher in the exacerbation group (88%) than that in the non-exacerbation latter group (31%; $P < 0.01$; Table 1). There was no difference in the types of DPP-4 inhibitors between exacerbation group and non-exacerbation group. TRAb could not be evaluated due to too much data missing.

In multivariate logistic regression analysis using factors extracted by comparing baseline characteristics there was a significant association between DPP-4i administration and Graves' disease exacerbation (odds ratio 7.39, 95% confidence interval 1.30–42.1, $P = 0.02$; Table 2).

DISCUSSION

To the best of our knowledge the current study is the first to investigate the influence of DPP-4i administration on Graves' disease activity. Several reports have discussed the relationship between DPP-4i and other autoimmune diseases. There are some case reports describing DPP-4i-induced polyarthritis and bullous pemphigoid[3, 4]. In a cohort study, DPP-4i administration was associated with an increased risk of inflammatory bowel disease[5]. Another study reported the high prevalence of Hashimoto's disease in patients on DPP-4i[6]. In another cohort study, however, initiating DPP-4i administration was associated with reduced risks of autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, psoriasis, psoriatic arthritis, multiple sclerosis and inflammatory bowel disease[9]. In addition, pharmacological inhibition of DPP-4 significantly reduced Crohn's disease activity utilizing *in vivo* or *in vitro* models[10,11]. Taken together, the results of these aforementioned

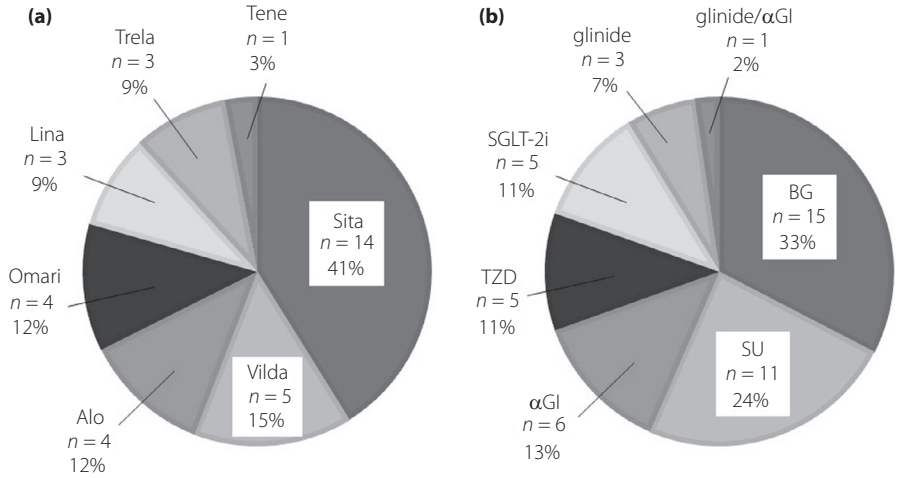

Figure 2 | Types of (a) dipeptidyl peptidase-4 inhibitor (DPP-4i) and (b) details of the other oral hypoglycemic agents (OHAs). Data are expressed as numbers followed by percentages in parentheses. α-GI, α-glucosidase inhibitor; Alo, alogliptin; BG, biguanide; Lina, linagliptin; Omari, omarigliptin; Sita, sitagliptin; SGLT-2i; sodium–glucose co-transporter-2 inhibitor; SU, sulfonyl urea; Trela, trelagliptin; Tene, teneligliptin; TZD, thiazolidine, Vilda, vildagliptin.

Table 1 | Baseline characteristics of patients in the exacerbation group and the non-exacerbation group

	Exacerbation group (n = 16)	Non-exacerbation group (n = 64)	P-value
Age (years)	64.8 ± 10.0	56.9 ± 11.1	0.01
Sex, female : male (%)	13 (81%): 3 (19%)	47 (73%): 17 (27%)	0.74
Body mass index (kg/m^2)	23.9 ± 2.9	25.6 ± 5.2	0.21
Duration of diabetes mellitus (years)	2.5 [0.8–9.3] (n = 14)	6.0 [1.0–11] (n = 50)	0.35
Duration of Grave's disease (years)	3.0 [0.5–13] (n = 13)	10 [3.8–21] (n = 50)	0.06
Random plasma glucose (mg/dL)	144 [118–202]	156 [130–216]	0.49
Hemoglobin (%)	7.2 [6.9–7.8]	7.9 [7.1–8.7]	0.13
Amount of thiamazole† (mg)	5.0 [0.0–8.8]	5.0 [1.9–11]	0.22
TSH (μIU/mL)	0.78 [0.11–1.60]	1.08 [0.46–3.26]	0.41
Free T3 (pg/mL)	2.60 [2.17–3.70]	2.80 [2.46–3.19]	0.92
Free T4 (ng/dL)	1.23 [0.93–1.47]	1.27 [0.99–1.49]	0.56
Drinker (%)	3 (23%) (n = 13)	11 (26%) (n = 43)	1.00
Smoker (%)	9 (69%) (n = 13)	21 (49%) (n = 43)	0.22
Family history of diabetes mellitus (%)	8 (73%) (n = 11)	24 (67%) (n = 33)	1.00
Overlap of Hashimoto's disease (%)	9 (75%) (n = 12)	29 (59%) (n = 49)	0.59
DPP-4i administration (%)	14 (88%)	20 (31%)	<0.01
Type of DPP-4i (%)			0.44
Sitagliptin	8	6	
Vildagliptin	1	4	
Alogliptin	1	3	
Omarigliptin	2	2	
Linagliptin	0	3	
Trelagliptin	1	2	
Teneligliptin	1	0	

Data are expressed as mean ± standard deviation, median followed by interquartile range in parentheses, or number followed by percentage in parentheses. DPP-4i, dipeptidyl peptidase-4 inhibitor; TSH, thyroid-stimulating hormone. †Propylthiouracil 50 mg was converted to thiamazole 5 mg.

studies suggest that the effects of DPP-4i on autoimmune diseases might be double-edged.

The present study suggests that DPP-4i administration is associated with Graves' disease exacerbation. Graves' disease is an autoimmune condition defined by overproduction of thyroid hormone due to upregulated thyroid stimulation by TRAb, and T cells have been implicated in the initiation and amplification of this process[7]. Some recent reports suggest the involvement

Table 2 | Multivariate logistic regression analysis with Graves' disease exacerbation as the objective variable

	Odds ratio (95% CI)	*P*-value
Age (years)	1.10 (1.02–1.18)	<0.01
Sex (female)	1.00 (0.19–5.34)	0.99
Duration of Grave's disease (years)	0.93 (0.86–1.02)	0.12
DPP-4i administration	7.39 (1.30–42.1)	0.02

CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor.

of regulatory T cells (Tregs) in the pathogenesis of Graves' disease. In a mouse model of Graves' disease, a low Treg number was reported[12]. Tregs were also significantly lower in peripheral blood and were inversely correlated with TRAb in patients with Graves' disease[13, 14]. Conversely, some positive associations between DPP-4 and Tregs have been reported[15, 16]. An experimental animal study showed that Tregs were lower in CD26/DPP-4-deficient rats than those in wild-type rats[15]. Aso *et al.*[16] reported that DPP-4i treatment for 12 weeks reduced the number of Tregs in patients with type 2 diabetes. Therefore, we speculate that a decrease in Tregs due to DPP-4i administration might cause Graves' disease exacerbation.

The present study had some limitations. It was a retrospective study, the sample size was not very large and there might be a degree of population bias in the study. Because the present study was a retrospective study, the information of DPP-4 inhibitors prescription was not blinded to the clinicians who prescribed anti-thyroid drugs, potentially causing bias. A prospective study with a large sample size is warranted, to confirm the results of the current study.

In conclusion, the present study has proven the potential association of DPP-4i administration with Graves' disease exacerbation. When contemplating the administration of DPP-4i to patients with Graves' disease, clinicians should consider the possibility of subsequent Graves' disease exacerbation.

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DISCLOSURE

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