In patients with type 2 diabetes the presence of Hashimoto’s thyroiditis reduces the beneficial effect of dipeptidyl peptidase–4 inhibitor on plasma glucose control

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Abstract. In this study, we compared the efficacy of a dipeptidyl peptidase–4 inhibitor (DPP4i) to improve glucose control in patients with type 2 diabetes mellitus (T2DM) with or without Hashimoto’s thyroiditis (HT). First, we compared the change in glycated hemoglobin (HbA1c) between the hypothyroid condition (before levothyroxine sodium hydrate [LT4] treatment) and euthyroid condition (after LT4 treatment when patients had achieved euthyroidism for at least six months) in patients with T2DM and HT. Next, we compared the change in HbA1c levels before and six months of DPP4i treatment in patients with T2DM with and without HT. In hypothyroid condition the change in HbA1c after six months of DPP4i treatment was 0.13% ± 0.86%. The change in HbA1c levels from when patients first achieved euthyroidism to after six months in the euthyroid condition was 0.26% ± 0.90%. DPP4i efficacy in patients with T2DM and HT was reduced compared to patients with T2DM but without HT (–0.40 ± 0.90 vs. –0.99 ± 0.5, p = 0.0032). These data suggest that hypothyroidism does not impact on DPP4i efficacy. However, the effect of DPP4i in patients with T2DM and HT was reduced compared to that in T2DM patients without HT. An estimation of thyroid function before prescribing DPP4i may be useful tool for predicting the efficacy of DPP4i, allowing the ruling out complications from HT.

Key words: Type 2 diabetes mellitus, Dipeptidyl peptidase–4 inhibitors, Hashimoto’s thyroiditis

Methods

Participants
The study protocol was reviewed and approved by hospital review boards and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

HT was diagnosed by the presence of diffuse goiter, elevated serum thyroid-stimulating hormone (TSH; reference range, 0.35–4.94 μU/mL) level, decreased serum free triiodothyronine (FT3; reference range, 1.88–3.18 pg/mL) and free thyroxine (FT4; reference range, 0.70–1.48 ng/dL), as well as the presence of antithyroglobulin antibody (reference range, <28.0 IU/mL) and/or antithyroid peroxidase (TPO) antibody (reference range, <16.0 IU/mL). The measured values are presented in Tables 1, 2, and 3.
In the first clinical study, we recruited 10 patients with T2DM and HT, and who were treated naïve for hypothyroidism.

In the second clinical study, 52 patients with T2DM and HT (designated as the Hashimoto group, Table 3) and 26 patients with T2DM patients without HT (designated as the without Hashimoto group) were recruited (Table 3). Thyroid function at the time of diagnosis is presented in Table 2.

Subjects were selected based on an initial (before levothyroxine sodium hydrate [LT4] administration) glycated hemoglobin (HbA1c) of between 7%–9%. If a patient’s HbA1c was >9% we tended to select insulin therapy rather than DPP4i. If a patient’s HbA1c was <7%, we did not need to add another medication to prevent hypoglycemia. Furthermore, diabetic complications are not expected when the HbA1c is maintained at <7% [3]. Age, body mass index, HbA1c, TSH, FT3, and FT4 were not different between the two groups.

**Table 1** Characteristics of type 2 diabetes mellitus patients with Hashimoto’s thyroiditis in the first clinical study

| Characteristics | Before treatment | After treatment |
|-----------------|-----------------|----------------|
| Gender (M/F)    | 4/6             | 4/6            |
| Age (years)     | 67 ± 10.4       | 68 ± 10.6      |
| TSH             | 32.8 ± 47.6     | 4.3 ± 4.8      |
| FT3             | 2.0 ± 0.9       | 2.8 ± 0.7      |
| FT4             | 0.9 ± 0.4       | 1.4 ± 0.3      |
| TgAb            | 192.5 ± 315.1   |                |
| TPOAb           | 39.4 ± 58.5     |                |

All values measured are shown. TSH, thyroid-stimulating hormone (μU/mL); FT3, free triiodothyronine (pg/mL); FT4, free thyroxine (ng/dL); TgAb, anti-thyroglobulin antibody (reference range, <28.0 IU/mL); TPOAb, antithyroid peroxidase antibody (reference range, <16.0 IU/mL). Data are expressed as mean ± standard deviation.

**Table 2** Thyroid function of patients in the second clinical study with type 2 diabetes mellitus at time of Hashimoto’s thyroiditis diagnosis

| Characteristics | TSH       | FT3        | FT4         | TgAb   | TPOAb     |
|-----------------|-----------|------------|-------------|--------|-----------|
|                 | 26.4 ± 35.6 | 1.93 ± 0.73 | 0.86 ± 0.36 | 120.1 ± 222.8 | 36.2 ± 48.3 |

All values measured are shown. TSH, thyroid-stimulating hormone (μU/mL); FT3, free triiodothyronine (pg/mL); FT4, free thyroxine (ng/dL); TgAb, anti-thyroglobulin antibody (reference range, <28.0 IU/mL); TPOAb, antithyroid peroxidase antibody (reference range, <16.0 IU/mL). Data are expressed as mean ± standard deviation.

**Table 3** Characteristics of type 2 diabetes mellitus patients with or without Hashimoto’s thyroiditis in the second clinical study

| Characteristics | With Hashimoto’s thyroiditis | Without Hashimoto’s thyroiditis |
|-----------------|-----------------------------|---------------------------------|
| Subjects number | 52                          | 26                              |
| Gender (M/F)    | 21/31                       | 17/9                            |
| Age (years)     | 75.00 ± 10.6                | 74.30 ± 11.6                    |
| BMI             | 23.20 ± 5.2                 | 23.60 ± 4.9                     |
| HbA1c           | 7.00 ± 0.6                  | 7.89 ± 1.5                      |
| TSH             | 2.70 ± 2.5                  | 1.85 ± 0.66                     |
| FT3             | 2.50 ± 0.5                  | 2.48 ± 0.25                     |
| FT4             | 1.36 ± 0.2                  | 1.04 ± 0.11                     |

All values measured are shown. BMI, body mass index (kg/m²); HbA1c, glycated hemoglobin A1c (%); TSH, thyroid-stimulating hormone (μU/mL); FT3, free triiodothyronine (pg/mL); FT4, free thyroxine (ng/dL). Data are expressed as mean ± standard deviation.

In the second clinical study, patients were randomized to DPP4i or placebo treatment and followed for six months. The proportion of participants prescribed DPP4i is summarized in Table 4. DPP4i alone was prescribed in 29.4% of participants, biguanide in 23.5%, sulfonyl urea in 23.5%, and insulin in 5.9%. DPP4i was prescribed as an add on therapy and as the last anti-diabetic medicine in the all subjects.

The second clinical study was designed to compared the change in HbA1c before and after six months of DPP4i treatment in patients with T2DM with or without HT. We confirmed that all subjects in the second clinical study had achieved a euthyroid condition (Table 3). The proportion of participants prescribed DPP4i is summarized in Table 4.

**Table 4** Proportion of prescribed DPP4 inhibitors in the first clinical study

| DPP4i Type  | Proportion |
|-------------|------------|
| Sitagliptin | 37.5       |
| Alogliptin  | 18.75      |
| Vildagliptin| 18.75      |
| Teneligliptin| 12.5     |
| Linagliptin | 12.5       |
| Saxagliptin | 0.0        |

Proportion of prescribed DPP4i in this first clinical study was summarized.
rized in Table 5. The percentage of participants prescribed only DPP4i was 29.6%, biguanide was prescribed in 20.8% of participants, sulfonyl urea in 17.6%, α-GI in 8.8%, glinide was prescribed in 7.2%, pioglitazone in 1.6%, a GLP-1 analogue in 0.8%, and insulin in 11.7% of subjects.

Table 5 Proportion of prescribed DPP4 inhibitors in the second clinical study

| DPP4i Inhibitor   | Proportion (%) |
|-------------------|---------------|
| Sitagliptin       | 54.3          |
| Alogliptin        | 19.2          |
| Vildagliptin      | 11.7          |
| Teneligliptin     | 10.6          |
| Linagliptin       | 2.1           |
| Saxagliptin       | 2.1           |

Proportion of prescribed DPP4i in this second clinical study was summarized.

Statistical analysis

Statistical differences between group means were determined one-factor analysis of variance with Tukey–Kramer multiple-comparisons using InStat 2.00 program. The change in HbA1c was analyzed statistically using a paired t-test in the first clinical study. A p value of <0.05 was considered statistically significant. All data are expressed as mean ± standard deviation.

Results

Comparison of the change in HbA1c in patients with T2DM and HT treated with DPP4i before and after LT4 treatment

HbA1c levels were unchanged (0.13% ± 0.86%) after six months of treatment with DPP4i without LT4 medication. This indicates that patients started and continued to take DPP4i under the hypothyroid condition throughout the observation period, and that DPP4i did not improve plasma glucose control.

Without cessation of DPP4i, the study participants began LT4 treatment. The LT4 dose was adjusted until patients were euthyroid. There was no change in HbA1c levels between the time patients became euthyroid and six months of euthyroidism (p = 0.7746; Fig. 1). This suggests that hypothyroidism due to HT does not affect the efficacy of DPP4i to improve plasma glucose control.

Comparison of the change in HbA1c after administration of DPP4i in patients with T2DM with or without HT

Next, we examined whether the presence of HT influenced the efficacy of DPP4i to improve plasma glucose control. To evaluate this, 52 patients with T2DM and HT (Hashimoto group) and 26 patients with T2DM and without HT (without Hashimoto group) were prescribed DPP4i. The DPP4i efficacy was estimated by the change in HbA1c levels (HbA1c after six months of DPP4i treatment—HbA1c before DPP4i treatment). DPP4i efficacy was reduced in patients with HT (Hashimoto group –0.40 ± 0.90 vs. without Hashimoto group –0.99 ± 0.5, p = 0.0032; Fig. 2a). There was no differences in HbA1c levels between Hashimoto group (7.68 ± 0.57) and without Hashimoto group (7.62 ± 0.50) before DPP4i treatment (p = 0.6032; Fig. 2b).

Discussion

In this paper, we demonstrated two important points about the relationship between HT and the efficacy of DPP4i to improve plasma glucose control. First, hypothyroidism as a result of HT does not impact on DPP4i efficacy. This is in constant to the prediction that TH induced hypothyroidism reduces DPP4i’s efficacy, as patients with HT have reduced shedding of DPP4 from the membrane, as well as decreased DPP4 levels and activity [1]. Our data suggests that plasma glucose control does not rely on DPP4 activity in HT induced hypothyroidism. It was recently reported that thyroxin is negatively associated with pancreatic beta-cell function in humans [4]. This could explain, at least in part, the
reason hypothyroidism does not rely on DPP4 and why in our patients DPP4i did not improve plasma glucose control.

Second, although it has been reported that serum GLP-1 is increased in patients with HT [2], the effect of DPP4i in our Hashimoto group was smaller than that in the without Hashimoto group. However, it is not clear whether in previous studies GLP-1 measurements were only of the active form [2], as assay systems are crucial as it is important to only measure the active form of GLP-1 [5]. On the other hand, proteolytic cleavage of DPP4 at the extracellular region by kallikrein-related peptide 5 (KLK5) has been reported to be an alternative source of serum DPP4 [1]. The serum concentration KLK5 and KLK5 mRNA expression are significantly decreased in patients with HT [1].

It has been reported that patients with T2DM have a higher DPP4 activity and that GLP-1 is degraded compared with patients with normal glucose tolerance [6]. In our study, all subjects had T2DM meaning that the reduction in GLP-1 seen in T2DM might be offset by the presence of HT, potentially explaining why the presence of HT decreased the efficacy of DPP4i to improve plasma glucose control, as compared to the without Hashimoto group.

This clinical study has limitations that warrant discussion. First, our sample size was small (n = 78) and the range of ethnicities, ages, sexes, weights was limited. So, the generality of the results is restricted. Therefore, these current results should be verified in a larger cohort with a wider demographic. Second, we were not able to compare DPP4 activity and active GLP-1 in patients with T2DM with and without HT. Third, diabetes is correlated significantly with dyslipidemia and atherogenic risk as well as an increase in interferon-γ production [7] and Xu at al reported that interferon-γ increases DPP4 shedding from the membrane [1]. This leads to the possibility that the results may differ in patients at a high risk for atherosclerosis.

Conclusion

As estimation of thyroid function may be useful for predicting DPP4i efficacy.

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Conflicts of Interest Disclosure

The authors have no potential conflicts of interest.

Competing Interest Disclosure

There are no significant competing financial, professional, or personal interests that have influenced the work described in this manuscript.

Fig. 2  Comparison of change in HbA1c in patients with type 2 diabetes mellitus with or without Hashimoto’s thyroiditis during DPP4i treatment

(a) Subtracted HbA1c level (after six months of DPP4i treatment - before DPP4i treatment). Type 2 diabetes mellitus with Hashimoto’s thyroiditis (closed bar, n = 52) and type 2 diabetes mellitus without Hashimoto’s thyroiditis (open bar, n = 26). Data are presented as mean ± standard deviation and there was a significant difference between the two groups (p = 0.032).

(b) HbA1c levels are similar in patients with type 2 diabetes mellitus with Hashimoto’s thyroiditis (closed bar, n = 52), and without Hashimoto’s thyroiditis (open bar, n = 26). Data are presented as mean ± standard deviation and there was not a significant difference between the two groups (p = 0.6032).
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