



# Painless thyroiditis induced by the cessation of a dipeptidyl peptidase-4 inhibitor

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**Abstract:** We describe the first reported case of painless thyroiditis induced by an abrupt cessation of a dipeptidyl peptidase-4 (DPP-4) inhibitor. A 38-year-old man who had type 2 diabetes mellitus, hypertension, hyperuricemia, and pruritus, was treated with metformin, glimepiride, dapagliflozin, sitagliptin, azelnidipine, trichlormethiazide, febusostat, and fexofenadine. One year previously, his thyroid-stimulating hormone (TSH) was 1.59 (reference range, 0.34–4.94 U/mL). As his HbA1c value reached to 13%, sitagliptin was switched to dulaglutide. One month later, the HbA1c was 12.3%, TSH was <0.05, FT4 was 3.16 (0.7–1.48 ng/dL), FT3 was 7.79 (1.71–3.71 pg/mL), anti-TSH receptor antibody was 0.7 (0–1.99 IU/L), and thyroglobulin was 159.5 (0–32.6 ng/mL). Additionally, his anti-thyroglobulin and anti-thyroid microsomal antibodies were negative. Thyroid ultrasonography revealed a heterogeneous, hypoechogenic, normal-sized thyroid gland with decreased doppler flow. He was diagnosed with painless thyroiditis and was kept under observation without any change in current medication. One month later, the HbA1c was 12.4%, TSH was 9.06, FT4 was 0.81, FT3 was 2.26, and thyroglobulin was 86.7. Additionally, 2 months later, the HbA1c was 9.8%, TSH was 4.2, FT4 was 1, FT3 was 2.55, and thyroglobulin was 21.92. He continued taking dulaglutide once a week. His thyrotoxicosis disappeared within 3 months without specific drug therapy. Anti-TSH receptor antibody was negative throughout his clinical course. We speculate that the cessation of a DPP-4 inhibitor maybe one of the triggers of painless thyroiditis. However, glucagon-like peptide-1 is not likely a cause for painless thyroiditis because he continues taking dulaglutide once a week to date. Our findings indicate that it is important to examine thyroid function after termination of a DPP-4 inhibitor.

**Keywords:** Painless thyroiditis; dipeptidyl peptidase-4 inhibitors (DPP4 inhibitors); type 2 diabetes mellitus

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## Introduction

Painless thyroiditis is defined as a category of lymphocytic thyroiditis characterized by painless goiter, low thyroidal uptake of radioactive iodine, and transient thyrotoxicosis (1). It is frequently induced in the postpartum period in patients who have chronic thyroiditis (1). The decline in immunologic tolerance in the postpartum period may be related to the occurrence of painless thyroiditis by the alteration of the immune processes in patients with chronic thyroiditis.

Dipeptidyl peptidase-4 (DPP-4) is a member of a

family of ubiquitous atypical serine proteases with many physiological functions beyond incretin degradation, including effects on the endocrine and immune systems. The role of DPP-4 on the immune system relates to its extra-enzymatic activities. A population-based cohort study suggested that DPP-4 inhibitor combination therapy appear to have a decreased risk of incident autoimmune diseases including rheumatoid arthritis compared to non-DPP4 inhibitor combination therapy (2). Therefore, after DPP-4 inhibitor is terminated, immune system may be affected. Concomitant with these lines of references, we experienced

**Table 1** Clinical course of patient

Inspection item	Data							
	2016/4/13	2017/3/6	2017/4/3	2017/5/15	2017/6/12	2017/7/10	2017/8/14	2017/9/25
Body weight (kg)	85	97.4	88	92.4	90.6	92.1	92.3	92.7
TSH (0.34–4.94 $\mu$ U/mL)	1.59		<0.05	9.06	6.35	4.2	4.68	4.81
TSH receptor antibody (0–1.99 IU/L)	0.7	<0.3	0.6	0.4				
Thyroglobulin (0–32.6 ng/mL)			159.5	86.7	63.98	21.92		
Free T4 (0.7–1.48 ng/dL)			3.16	0.81	1.04	1.0	1.12	1.05
Free T3 (1.71–3.71 pg/mL)			7.79	2.26	3.04	2.55		
Anti-thyroglobulin antibody (<100)			<100	<100	<100			
Anti-thyroid microsome antibody (<100)				<100				
Plasma glucose (mg/dL)	129	276	171	159	220	147	223	134
HbA1c (%)	9.1	13	12.3	12.4	10.8	9.8	9.9	9.9
Thyroid ultrasonography			*					

Clinical course of our patient is presented as a table. Patient took sitagliptin (50 mg/day) until March 06, 2017 and dulaglutide was started instead of sitagliptin. One month later (April 03) he visited our hospital and transient thyrotoxicosis was appeared. \*, thyroid ultrasonography was performed.

the clinical case of a patient with type 2 diabetes mellitus; the patient had no prior history of thyroid dysfunction but developed painless thyroiditis following termination of a DPP-4 inhibitor.

### Case presentation

A 38-year-old Japanese man with no history of thyroid dysfunction as well as his family presented with type 2 diabetes mellitus and hypertension. He was treated with metformin (1,500 mg/day), glimepiride (2.5 mg/day), dapagliflozin (5 mg/day), sitagliptin (100 mg/day), azelnidipine (16 mg/day), trichlormethiazide (1 mg/day), febuxostat (10 mg/day), and fexofenadine (120 mg/day). One year previously, his thyroid-stimulating hormone (TSH) level was 1.59 (reference range, 0.34–4.94 U/mL) (*Table 1*). As his HbA1c value reached to 13%, sitagliptin was switched to dulaglutide to expect better body weight control (*Table 1*). His body weight reached to 97.4 kg in spite of that he was 85 kg 1 year before (*Table 1*). One month later, when he visited our hospital, he was found to have lost 9.4 kg of body weight (*Table 1*). He did not experience fever, palpitation, excess sweating, or anterior neck pain.

At this point, the HbA1c value was 12.3%, TSH level was <0.05, FT4 level was 3.16 (0.7–1.48 ng/dL), FT3 level was 7.79 (1.71–3.71 pg/mL), anti-TSH receptor antibody level was 0.7 (0–1.99 IU/L), and thyroglobulin level was 159.5 (0–32.6 ng/mL) (*Table 1*). Additionally, his anti-thyroglobulin and anti-thyroid microsomal antibodies were negative. Thyroid ultrasonography revealed a heterogeneous, hypoechogenic, normal-sized thyroid gland with decreased doppler flow. However, he disagreed to perform an inspection of scintigraphy. Base on collected clinical information, the patient was diagnosed with painless thyroiditis and was kept under observation without any change in current medication because he was free from symptoms for hyperthyroidism except for weight loss. One month later, when he visited our hospital for checkup, the HbA1c value was 12.4%, TSH level was 9.06, FT4 level was 0.81, FT3 level was 2.26, and thyroglobulin level was 86.7 (*Table 1*). Additionally, 2 months later, the HbA1c value was 9.8%, TSH level was 4.2, FT4 level was 1.0, FT3 level was 2.55, and thyroglobulin level was 21.92 (*Table 1*). He was found to have gained 4.1 kg, and he continued taking dulaglutide once a week (*Table 1*). Our patient showed thyrotoxicosis without anterior neck pain, and his

thyrotoxicosis disappeared within 3 months without specific drug therapy. Anti-TSH receptor antibody was negative throughout his clinical course. Our patient was unlikely to have Hashimoto's disease as both anti-thyroglobulin and anti-thyroid microsomal antibodies were negative.

## Discussion

When DPP-4 inhibitors are prescribed, clinicians are required to be aware of adverse effect such as interstitial pneumonia (3), pemphigoid (4), besides hypoglycemia. To our knowledge, our patient is the first reported case which painless thyroiditis was induced after the cessation of a DPP-4 inhibitor. Although this is a single case report, our experienced case suggests that the thyroid function in patients in whom the use of DPP-4 inhibitor was stopped should be monitored. Also, additional investigation into reports of painless thyroiditis induced by the cessation of DPP-4 inhibitor therapy will be necessary to identify which patients with diabetes mellitus are at risk for this disease. Finally, Glucagon-like peptide-1 is not likely a cause for painless thyroiditis because he continues taking dulaglutide once a week to date.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/aot.2018.10.06>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures were in accordance with the ethical standards of the responsible committee for human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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