



## Case Report

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## Is Dipeptidyl Peptidase-4 Inhibitor a Risk Factor to Develop Permanent Hypothyroidism in Subacute Thyroiditis in Patients with Type 2 Diabetes Mellitus?

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### Abstract

**Introduction:** Permanent hypothyroidism rationale is presented in 5 - 26% of the subacute thyroiditis patients. In the last decade, three cases of Subacute Thyroiditis (SAT) were treated with Dipeptidyl Peptidase-4 Inhibitor (DPP-4i) in patients with Type 2 Diabetes Mellitus (T2DM).

**Case Presentation:** Case 1: 52-year-old woman presented with T2DM on tolbutamide and sitagliptin. She was diagnosed with SAT and managed with loxoprofen sodium hydrate while maintaining her antidiabetic agents. Three months later, the thyroid function returned to euthyroid condition.

**Case 2:** 74-year-old man T2DM patient on metformin, glimepiride, and sitagliptin. He was diagnosed with SAT and managed with loxoprofen sodium hydrate while maintaining ongoing antidiabetic management. One month later, his thyroid function deteriorated to hypothyroidism and further nine months later, the thyroid returned to euthyroid function.

**Case 3:** 69-year-old-man T2DM patient on vildagliptin. He was diagnosed with SAT and managed with prednisolone (10mg/day) with cessation of vildagliptin and introduction of insulin therapy. One month later, the thyroid function returned to euthyroid function.

**Conclusions:** We experienced SAT during the administration of DPP-4i in three T2DM patients. Although one of them experienced transient hypothyroidism, none developed permanent hypothyroidism. DPP-4i may not be a risk factor of permanent hypothyroidism in SAT patients with T2DM.

**Keywords:** DPP4 inhibitors; Subacute thyroiditis; Type 2 diabetes mellitus

**Abbreviations:** DPP-4i: Dipeptidyl Peptidase-4 Inhibitor; TSH: Thyroid Stimulating Hormone; FT3: Free Triiodothyronine; FT4: Free Thyroxine; Tg: Thyroglobulin; CRP: C-Reactive Protein; Trab: TSH Receptor Antibody; Anti-Tg-Ab: Anti-Thyroglobulin Antibody

### Introduction

Subacute Thyroiditis (SAT) (de Quervain's granulomatous or giant cell thyroiditis) is a transient inflammatory thyroid disease that often occurs after an upper respiratory tract infection caused by mumps, coxsackie, influenza, echo and adenoviruses [1,2]. Usually, patients present with complaints of neck pain and symptoms of hyperthyroidism. For mild cases Nonsteroidal Anti-

Inflammatory Drugs (NSAID) are often used as treatment option. For moderate to severe cases, glucocorticoids are mostly prescribed [3]. Permanent hypothyroidism rationale is presented in 5 - 26% of the SAT patients [4]. In the last decade, three SAT cases with T2DM were managed with DPP-4i. Therefore, we sought to determine if DPP-4i is a risk factor of permanent hypothyroidism in SAT patients with T2DM.

## Case Presentation

### Case 1

A 52-year-old T2DM on tolbutamide and sitagliptin. Nine months prior to consultation, her TSH level was at 2.06 (reference range, 0.436 - 3.78  $\mu$ IU/mL) and FT4 at 1.5 (1.0 - 1.7 ng/dL). Later, she experienced flu-like symptoms, and reported a remarkable anterior neck pain with a low-grade fever (38.4°C). Presently, TSH level was at 0.185, FT4 at 4.3, thyroglobulin at 246 (normal range < 32.7 ng/mL), and CRP was at 4.79 (normal range < 0.1mg/dL). Thyroid ultrasonography revealed a hypoechoic pattern. One month later, TSH level was at 0.185, FT3 at 5.5 (2.1 - 4.1 pg/mL), FT4 at 2.6, thyroglobulin at 307, CRP at 3.23, anti-TSH receptor antibody at 0.4 (< 1.0 IU/L), and anti-microsome antibody at 0.3 (normal range < 100 times). She was diagnosed of SAT and managed with loxoprofen sodium hydrate while maintaining ongoing antidiabetic agents. HbA1c was maintained at 7.0% throughout the clinical course. Three months later, HbA1c levels were at 6.9%, TSH at 1.72, FT3 at 2.9, FT4 at 1.2, thyroglobulin at 28.6, and CRP at 0.06. All these are displayed in Table 1A.

	Normal range	Unit	2008/11/18	2009/3/10	2010/7/8	2010/8/5	2010/9/2	2010/10/28	2010/11/25
DPP4i	Sitagliptin (50mg/day)								
TSH	0.436-3.78	$\mu$ IU/mL	0.871	2.06	0.185	0.009	0.009	0.345	1.72
FT3	2.1-4.1	pg/mL				5.5	3.6		
FT4	1.0-1.7	ng/mL	1.3	1.5	4.3	2.6	1.4	1.2	1.2
Tg	$\leq$ 32.7	ng/mL			246	307	105	37.6	28.6
CRP		mg/dL			4.79	3.23	0.06	0.03	0.06
TRAb	<1.0	IU/L				0.4			
MHA	<100	times				0.3			

**Table 1A:** clinical laboratory data for case 1 is summarized.

### Case 2

A 74-year-old man with T2DM on metformin, glimepiride, and sitagliptin. One year prior to consultation, TSH level was at 2.07 (reference range, 0.35 - 4.94  $\mu$ IU/mL). After flu-like symptoms were reported, he had an anterior neck pain, with a low-grade fever (37.8°C), heart palpitations, and a 3.5 kg decrease in body weight over a two-months period. TSH was at 0.021, FT3 at 4.12 (1.8 - 3.18 pg/mL), FT4 at 1.71 (0.7 - 1.48 ng/dL), thyroglobulin at 407, CRP at 3.72 (< 0.3 mg/dL), anti-TSH receptor antibody at 0.5 (< 2.0 IU/L), and anti-thyroglobulin antibody at 1.4 (< 4.11 IU/mL). Thyroid ultrasonography revealed a hypoechoic pattern.

He was diagnosed of SAT and managed with loxoprofen sodium hydrate while maintaining ongoing antidiabetic treatment. One month later, TSH level was at 6.172, FT4 at 0.62, FT3 at 1.44, and thyroglobulin at 36.3. Another one month later, TSH was at 65.535, FT4 at 0.57, and FT3 at 1.53. He was tested negative for the anti-TSH receptor antibody throughout his clinical course. On maintaining ongoing antidiabetic treatment, his HbA1c increased to from 7% to 9.7% due to transient hyperthyroidism. Seven months later, TSH was at 4.52, FT4 at 1.54, FT3 at 2.13, thyroglobulin at 16.6, and HbA1c at 7.2%. All these are summarized in Table 1B.

	Normal range	Unit	2017/12/10	2018/10/13	2018/11/13	2018/12/19	2019/1/30	2019/3/26	2019/5/29
DPP4i			Vildagliptin (100mg/day)						
TSH	0.35-4.94	μIU/mL	2.07	0.021	6.172	65.535	30.912	12.8	11.1
FT3	1.8-3.18	pg/mL		4.12	1.44	1.53	2.19	2.49	2.23
FT4	0.7-1.48	ng/mL	1	1.71	0.62	0.57	0.66	0.82	0.7
Tg	≤32.7	ng/mL		407	36.3			16.6	
CRP	<0.3	mg/dL		3.72	0.11				
TRAb	<2.0	IU/L		0.5					
Anti-Tg-Ab	<4.11	IU/mL		1.4					

**Table 1B:** clinical laboratory data for case 2 is summarized.

### Case 3

A 69-year-old man with T2DM was on vildagliptin. After flu-like symptoms were reported, he had an anterior neck pain with low-grade fever (38.2°C), and heart palpitations. TSH level was < 0.05, FT3 at 3.22 (1.8 - 3.18 pg/mL), FT4 at 1.65 (0.7 - 1.48 ng/dL), thyroglobulin at 189, CRP at 6.80 (< 0.1 mg/dL), anti-TSH receptor antibody at 0.8 (< 2.0 IU/L), and anti-thyroglobulin antibody was < 100 (< 100 IU/mL). Thyroid ultrasonography revealed a hypoechogenic pattern. He was diagnosed of SAT and managed with prednisolone (10mg/day) with cessation of vildagliptin and initiation of insulin therapy. This was done because of an elevated plasma glucose by hyperthyroidism and prednisolone leading to an increase in HbA1c from 7.5% to 8.2%. One month later, TSH level was at 1.93, FT4 at 0.72, FT3 at 2.29, and thyroglobulin at 18.7. Another month later, TSH level was at 1.13, FT4 at 0.93, FT3 at 2.37. He was tested negative for the anti-TSH receptor antibody. Five months later, his TSH level was at 1.30, FT4 at 0.92, FT3 at 2.31, thyroglobulin at 24.8, CRP at 0.05, and HbA1c at 6.7%. All these are displayed in Table 1C.

	Normal range	Unit	2020/1/10	2020/1/20	2020/2/17	2020/3/16	2020/4/17	2020/5/15	2020/6/19
PSL		mg/day	10	10	10	5	5	5	5
DPP4i		mg/day	Vildagliptin (0mg/day)						
TSH	0.35-4.94	μIU/mL	<0.05		2.07	1.13	1.41	1.64	1.3
FT3	1.8-3.18	pg/mL	3.22	2.9	2.29	2.37	2.99	2.59	2.31
FT4	0.7-1.48	ng/mL	1.65	1.45	0.72	0.93	0.89	0.9	0.92
Tg	≤32.7	ng/mL	189	6.78	18.7	33.2	29.4	30.7	24.8
CRP	<0.1	mg/dL	6.3	0.27	0.08	1.14	0.27	0.21	0.05
TRAb	<2.0	IU/L	<0.8						
Anti-Tg-Ab	<100	IU/mL	<100						

**Table 1C:** clinical case data for case 3 is summarized.

### Discussion

SAT is thought to be caused by a viral infection of the thyroid gland, and it often occurs after an upper respiratory tract illness [3,5,6]. Previous studies elucidate a seasonal and geographical role in the onset of disease [3,5,6]. Clinical features of SAT include the gradual appearance of pain radiating from the thyroid gland with or without fever [3,5,6]. Hoarseness of voice and heart palpitations can also be seen. Laboratory findings vary with the phase of the disease [3,5,6]. During the active phase, CRP levels may be elevated. The serum

thyroglobulin level is also characteristically high during this phase. The uptake of radioactive iodine by the thyroid is subnormal [7,8]. Usually, TPO (thyroperoxidase) and thyroglobulin autoantibodies are either undetectable or are present at low levels. During the hypothyroid phase, the serum TSH levels are elevated and serum FT3 and FT4 levels are low [7,8]. Upon recovery, values for serum FT3 and FT4 concentrations return to normal.

Permanent hypothyroidism rationale is presented in 5 - 26% of the SAT patients [4]. However, little or no evidence exist on whether DPP-4i is a risk factor of permanent hypothyroidism in SAT in patients with T2DM or not. Based on our three cases, none of them developed permanent hypothyroidism, though one of them developed transient hypothyroidism. On DPP-4i administration, case 1 could maintain euthyroid function after transient hyperthyroidism due to SAT. Case 2 also continued DPP-4i after the diagnosis and developed transient hypothyroidism. On the contrary, case 3 discontinued DPP-4i after the diagnosis and did not develop hypothyroidism. Therefore, DPP-4i is not a risk factor to develop permanent hypothyroidism due to SAT in patients with T2DM.

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## Ethics Approval and Consent to Participate

The study protocol was reviewed and approved by the review board in accordance to the principles of the Declaration of Helsinki. Written informed consent was obtained from the participants prior to publication of this manuscript and any accompanying images. A copy of written consent is available for review by the Editor-in-Chief of this journal.

## Consent for Publication

All participants understand that the information will be published anonymously, but that full anonymity cannot be guaranteed. We understand that the text and any pictures or videos published in the article will be freely available on the internet and may be seen by the general public. Pictures, videos, and text may also appear on other websites or in print, may be translated into other languages or used for commercial purposes.

## Availability of Data and Materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Competing Interests

None of the authors have any potential conflicts of interest to report.

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## Authors' Contributions

SM (Muto), SO, YN (Niijima), TI, and YU took care of case 1. HH (Hoshi), TI, YU, and SO took care of case 2.

MY, HH (Hiraga), JN, SM (Matsumoto), EY, YN (Nakajima), and YM took care of case 3. JO, KO, TS, SO, and YM interpreted data, prepared figures, and wrote and edited the manuscript.

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