THERAPEUTIC ADVANCES in
Endocrinology and Metabolism

Case Report

Quitting smoking as a probable trigger for new-onset hypothyroidism after successful medical treatment of Graves' disease: case report

Ther Adv Endocrinol Metab

2024, Vol. 15: 1–6

DOI: 10.1177/20420188241256470

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***Abstract*:** Graves' disease (GD) is the most common cause of hyperthyroidism while Hashimoto or autoimmune thyroiditis is the most common cause of hypothyroidism. Spontaneous hypothyroidism may develop after successful medical treatment of GD in up to 20% of cases. This report presents a gentleman who is a known smoker and was diagnosed with GD at the age of 64 years. He was counseled about smoking cessation and started with medical treatment using carbimazole (CBZ). He was adequately controlled using medical treatment, yet he continued to smoke. After 2 years of medical treatment, CBZ was stopped due to developing hypothyroidism on the minimum dose of treatment. Celebrating the discontinuation of treatment, the patient decided to quit smoking. One month later, he was euthyroid; however, 4 months later, he developed overt hypothyroidism. He received levothyroxine replacement therapy and titrated to achieve euthyroidism and remained on levothyroxine for more than 5 years. The possibility that quitting smoking may have triggered the development of hypothyroidism was raised due to the coincidence of developing hypothyroidism only 4 months after quitting smoking. Current smoking is associated with a higher risk of developing both GD and Graves' orbitopathy. Quitting smoking is associated with a higher risk of developing new-onset thyroid autoimmunity. Quitting smoking is also associated with a sevenfold higher risk of autoimmune hypothyroidism especially in the first year of smoking cessation. Involved mechanisms may include a sudden increase in oxidative stress, a sudden increase in iodide delivery to thyroid follicles, or promoting T-helper 1-mediated autoimmune thyroiditis after quitting smoking. The present case suggests that quitting smoking may be a triggering factor for the development of hypothyroidism following successful medical treatment of GD, a phenomenon that may affect one-fifth of GD patients without previously reported triggers.

Plain language summary

Quitting smoking may trigger hypothyroidism in previously treated Graves' disease patients

Graves' disease is the commonest cause of hyperthyroidism. Medical treatment is the mainstay treatment, and about 5-20% of patients may develop hypothyroidism after successful medical treatment. The triggers to this conversion are not known. The present case, a 64 years old gentleman who is a smoker, after being diagnosed with graves' disease, receives medical treatment for 2 years. On the occasion of stopping medical treatment for graves' disease, he decides to quit smoking. One month later he is euthyroid off

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medications, but 4 months later, he develops severe hypothyroidism, for which he receives replacement therapy for the following five years. The possibility that quitting smoking may have triggered this conversion was raised. Smoking is associated with a 2-folds higher risk of having graves' disease. Quitting smoking on the other hand increases the risk of acquiring thyroid autoantibodies, and new onset autoimmune hypothyroidism. Quitting smoking is also associated with symptoms of weight gain, constipation, and depression, all of which may also occur in hypothyroidism. That is why, ordering thyroid function tests is recommended in recent quitters if they develop such symptoms. Thus, quitting smoking in the present case may have triggered this severe hypothyroidism. Underlying mechanisms may involve increased oxidative stress or autoimmune reactions favoring the occurrence of autoimmune thyroiditis.

Keywords: autoimmune thyroiditis, Graves' disease, hypothyroidism, quitting smoking, trigger

Received: 13 January 2024; revised manuscript accepted: 18 April 2024.

Background

Graves' disease (GD) represents around 80% of all cases of hyperthyroidism. GD is caused by the stimulatory effect of thyroid-stimulating hormone (TSH) receptor antibodies (TRAbs) acting on TSH receptors and promoting the synthesis and release of thyroid hormones. TRAbs are the test of choice currently recommended to establish the diagnosis of GD. Antithyroid drugs are currently the recommended first-line treatment for GD, especially in elderly patients with mild disease, and can be used indefinitely in such patient profiles.[1]

Hashimoto or chronic autoimmune thyroiditis is the most common cause of hypothyroidism. It is caused by autoimmune destruction of thyroid follicles. Etiology is confirmed by the determination of thyroid peroxidase (TPO) autoantibodies. Currently recommended treatment is replacement with levothyroxine due to efficacy, safety, long-term experience, and low cost.[2]

Spontaneous hypothyroidism following successful medical treatment of GD has been reported in 5–20% of cases. Proposed mechanisms include either blocking TRAbs or destructive thyroiditis.[3]

Active smoking was shown to be associated with altered thyroid function in the form of decreased TSH and increased free T3 and free T4. It was also associated with a higher risk of goiter, GD, and Graves' orbitopathy (GO), as well as a poor response to GO treatment.[4] Quitting smoking, on the contrary, was associated with a higher risk of new-onset thyroid autoimmunity and autoimmune hypothyroidism.[5,6]

Here we present a case of GD who shortly after achieving euthyroidism, and simultaneously quitting smoking, developed overt hypothyroidism, and explore the potential that quitting smoking may have triggered this unexpected turn of events.

Case presentation

A retired male patient – 64 years of age and a heavy smoker – presented in May 2015 with a complaint of weight loss despite good appetite. He was ordered thyroid function tests revealing mild overt hyperthyroidism: TSH = 0.01 μIU/L (Normal 0.27–4.2 μIU/L), free T4 = 3.7 ng/dL (Normal 0.93–1.7 ng/dL), and free T3 = 10.9 (Normal 2.0–4.4 pg/mL). He had no goiter and no evidence of thyroid eye disease. Serological investigations were consistent with a diagnosis of GD: TRAbs = 16.3 IU/L (Normal <1.75 IU/L), TPO antibodies = 268 (Normal <34 IU/mL), and thyroglobulin (Tg) antibodies = 1731 (Normal <115 IU/mL). The patient was counseled about the nature of GD, about the benefits of quitting smoking, and he was offered medical treatment in the form of carbimazole (CBZ) 20 mg/day, given that methimazole is not available in Egypt. The dose of CBZ was then titrated against his laboratory results, to achieve low normal free T4 and free T3, and he maintained euthyroid on a dose of 5 mg/day for a

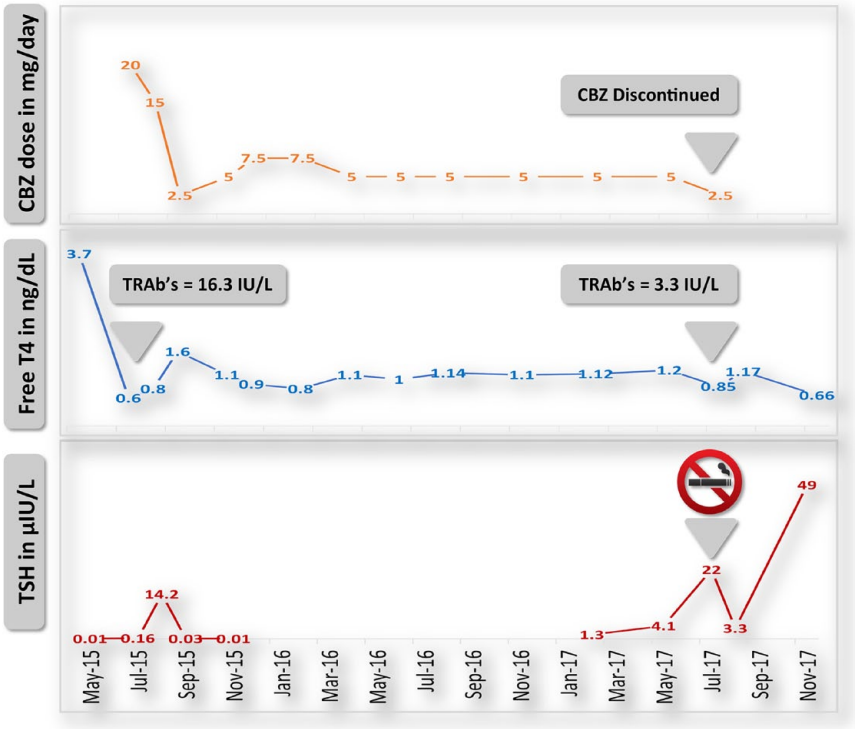

Figure 1. Thyroid function tests and antithyroid drug treatment from the diagnosis to the onset of hypothyroidism.
CBZ, carbimazole; T4, thyroxine; TRAbs, TSH receptor antibodies; TSH, thyroid-stimulating hormone.

period of 15 months (February 2016–May 2017). In July 2017, CBZ was discontinued after having a TSH result of 22 µIU/L while being on a dose of 2.5 mg/day for 2 months. Celebrating the discontinuation of treatment after more than 2 years of treatment, the patient decided to quit smoking and comply with the repeated advice of quitting smoking that was offered to the patient in almost every follow-up visit. The first follow-up off CBZ in August 2017, the patient was euthyroid with TSH = 3.3 µIU/L, free T4 = 1.17 ng/dL, and TRAbs was 3.3 IU/L. In November 2017, 4 months after stopping CBZ, the patient presented with 4 kg weight gain (67–71 kg) and severe biochemical hypothyroidism, TSH = 73.5 µIU/L and free T4 = 0.35 ng/dL, which was repeatedly confirmed, TSH = 48.9 µIU/L and free T4 = 0.66 ng/dL (Figure 1). Considering the patient age (66 years) and body weight (71 kg), the patient was started on replacement therapy in the form of levothyroxine 75 µg/day (calculated as 1.1 µg/kg/day), and the dose was later titrated to achieve a target TSH of 0.3–3 µIU/L, which was finally achieved using 100 µg/day, and this target was maintained for 45 months (July 2019–April 2023). TRAbs were measured in November 2021, and it was negative at <0.8 IU/L. The coincidence of quitting smoking in July 2017 and the spontaneous development of overt hypothyroidism in November 2017, only 4 months later, urged us to search for a possible link between quitting smoking and new onset hypothyroidism in patients with treated GD.

Discussion and conclusion

The current case report presents a case of GD who developed overt hypothyroidism only 4 months after stopping antithyroid drugs and quitting smoking. The spontaneous development of hypothyroidism following successful medical treatment of GD may occur in 5–20% of cases.[3] A recent retrospective study from Egypt reported that 10 patients out of 351 GD patients treated with antithyroid drugs developed hypothyroidism, representing 2.85% of the reviewed patients.[7] An almost identical incidence was reported from a Thai cohort of 2.7%, a slightly higher incidence

of 6% was reported from Japan, 9.3% was reported from Brazil, and 13% was reported from Europe.[8–11]

In the search for identifiable risk factors for the development of spontaneous hypothyroidism following treatment of GD, only one study found that a higher TPO antibodies titer upon withdrawal of antithyroid drugs compared to baseline was significantly more frequent among patients who developed hypothyroidism *versus* those who maintained euthyroidism. Unfortunately, TPO antibodies were not reevaluated after the withdrawal of CBZ in the present case. In the same study, no difference was observed between those prescribed methimazole or propylthiouracil regarding the occurrence of hypothyroidism.[9]

The time to development of hypothyroidism after cessation of medical treatment was reported to range from 4 to 144 months. Proposed mechanisms for this phenomenon are either a change from stimulating to blocking the activity of the TRAbs, accounting for one-third of the cases, or the occurrence of destructive thyroiditis on top of GD leading to hypothyroidism, accounting for two-thirds of the cases.[9,12]

TRAbs can be classified as stimulating, or blocking. About one-fifth of patients with GD have both stimulating and blocking TRAbs in their circulation, and the balance in favor of stimulating TRAbs leads to presentation as hyperthyroidism. The use of methimazole in GD patients leads to a decrease in circulating stimulating TRAbs, this may turn the balance in favor of blocking TRAbs leading to hypothyroidism. Our patient used CBZ, a precursor for methimazole, for more than 2 years which may have affected this balance in our patient; however, lacking TRAbs bioassays prevented us from confirming such a possibility.[13]

In the present case, the most likely mechanism to explain the development of hypothyroidism is destructive autoimmune thyroiditis on top of Grave's disease, in favor of this notion, the patient was positive for both TPO and Tg antibodies at the time of initial presentation, and although the patient was still positive for TRAbs at the time of CBZ discontinuation, he later became negative at November 2021, and yet hypothyroidism persisted afterward for 2 years. Also, this is the same proposed mechanism for hypothyroidism occurring shortly after quitting smoking.

Weight gain, constipation, and poor concentration are well-known symptoms to occur after quitting smoking, but at the same time, well-known symptoms of hypothyroidism.[14] The present case presented clinically with a 4-kg weight gain, about 6% of his baseline body weight, at the time of diagnosis of overt hypothyroidism. For this reason, it is recommended that recent quitters who experience such manifestations should be screened for the possible development of autoimmune hypothyroidism.

A number of observational studies reported a lower prevalence of thyroid autoantibodies in smokers compared to nonsmokers.[4] In a prospective study of 521 euthyroid women without thyroid autoantibodies, who were relatives of patients with autoimmune thyroid disease – followed up for 5 years – it was found that quitting smoking increases the risk of *de novo* TPO/Tg antibodies positivity. Current smoking was found to protect against TPO/Tg antibodies positivity by 41%, and TPO antibodies positivity by 46%.[5]

In a Danish study by Carle *et al.*, new-onset autoimmune hypothyroidism incidence increased sharply but temporarily within 2 years of quitting smoking. Compared to non-smokers, recent quitters, within 1 and 2 years of quitting smoking, had 7 and 6 times higher risk of developing autoimmune hypothyroidism, respectively. This risk decreased after 2 years of quitting smoking. They calculated that 85% of all hypothyroidism developing within 2 years of quitting smoking can be explained by stopping smoking.[6]

The present case developed overt hypothyroidism 4 months after quitting smoking, within the period with the highest risk of the development of autoimmune hypothyroidism as reported by Carle *et al.*[6]

Ninety-six percent of their patients were positive for TPO antibodies at the time of diagnosis,[6] and TPO antibodies can be positive in up to 75% of Egyptian GD patients; however, only less than 3% of the patients developed hypothyroidism.[7] Thyroperoxidase antibodies are a definite marker of genetic susceptibility for autoimmune hypothyroidism, but smoking cessation may be the event

that mediated the clinical onset of hypothyroidism in Carle *et al.* patients and the currently reported patient.

Proposed mechanisms for this sharp, but temporary increase in the incidence of autoimmune hypothyroidism may be related to a combination of a sudden increase in oxidative stress and a sudden increase in iodide delivery to thyroid follicles after quitting smoking. Smoking leads to partial hypoxia to thyroid tissue; thus, quitting smoking may lead to an abrupt increase in oxygen delivery to thyroid tissue, thus generating reactive oxygen species and oxidative damage to thyroid tissue. Smoking also decreases iodide delivery to thyroid follicles by half, which would be compensated by chronic upregulation of sodium–iodide symporter, such adaptation if persistent after quitting smoking, would lead to increased iodide delivery to thyroid follicles which may provoke thyroid autoimmunity.[15]

A third suggested mechanism may be related to the ability of smoking to inhibit T-helper 1 responses, thus favoring T-helper 2 responses.[16] Knowing that GD is mainly mediated by T-helper 2 responses, while autoimmune thyroiditis is mainly mediated by T-helper 1 responses, active smoking may increase the risk of GD twofold by promoting T-helper 2 responses, while quitting smoking may increase the risk of autoimmune thyroiditis by loss of this permissive effect on T-helper 2 responses, allowing T-helper 1 responses to promote the risk of autoimmune thyroiditis by sixfolds.[17,18]

In a recently published study of the opposite phenomenon presented in the current report, that is the development of GD on top of autoimmune hypothyroidism, they found that current smoking was significantly higher in those who developed GD compared to persistent autoimmune hypothyroidism, which can be taken as an argument in favor of the notion that in the presently reported patient, quitting smoking may mediate the opposite event. They explained the effect of current smoking on the development of Graves' effect by its permissive effect on T-helper 2 responses, the opposite of the explanation listed here to explain the effect of quitting smoking on the development of hypothyroidism.[19]

In conclusion, the present case suggests that quitting smoking may be a triggering factor for the development of hypothyroidism following successful medical treatment of GD. This phenomenon may affect up to one-fifth of GD patients without previously reported triggers. Hypothyroidism in the present report is mediated by autoimmune thyroiditis. Quitting smoking may have triggered autoimmune thyroiditis through oxidative stress, increased iodide delivery to thyroid tissues, or T-helper 1-mediated responses.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent for publication of their clinical details and clinical images was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

Author contribution

Tamer Mohamed Elsherbiny: Conceptualization; Data curation; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing.

Acknowledgements

None.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The author declares that there is no conflict of interest.

Availability of data and materials

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

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Appendix

Abbreviations

CBZ	carbimazole
GD	Graves' disease
GO	Graves' orbitopathy
Tg	thyroglobulin
TPO	thyroid peroxidase
TRAbs	TSH receptor antibodies