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REVIEW ARTICLE

Effects of SARS CoV-2 mRNA Vaccines on Newly Onset and Relapsing Graves' Disease

Gabriella Gita Febriana*

Department of Biomedicine, Institut Bio Scientia Internasional Indonesia, Jakarta, Indonesia

**Corresponding author: gabriella.febriana@i3l.ac.id*

ABSTRACT

The development of SARS-CoV-2 mRNA vaccines has been claimed to be a breakthrough in the medical research field. Although these vaccines have been proven to reduce SARS-CoV-2 transmission, the administration of these vaccines was also found to interfere with thyroid functions in some individuals, which include the onset of Graves' disease in immunocompromised people and relapsing condition in Graves' disease patients. This article reviews cases of Graves' disease following the administration of first and second doses of SARS CoV-2 mRNA vaccines between the years 2021 and 2022. Furthermore, the possible mechanisms of Graves' disease development following mRNA vaccine administration are also discussed in this review article.

KEYWORDS

SARS CoV-2, mRNA vaccines, Graves' disease

HIGHLIGHTS

- SARS CoV-2 mRNA vaccines have been proven to reduce SARS CoV-2 virus transmission.
- However, the administration of SARS CoV-2 mRNA vaccines has been reported to result in thyroid-related autoimmune diseases, such as Graves' disease and Hashimoto's disease.
- In this review, the effects of SARS CoV-2 mRNA vaccine administration on Graves' disease onset and relapse along with the possible mechanisms are discussed.

INTRODUCTION

The catastrophic impact of the COVID-19 pandemic caused by the highly infectious virus SARS-CoV-2 has led to the rapid development of vaccines, created for the purpose of protecting individuals from experiencing serious sickness and death from this infectious disease. Among these vaccines are messenger RNA (mRNA) vaccines, which deliver mRNA that encodes the spike (S) protein of SARS-CoV-2, enabling the immune system to produce antibodies toward this viral protein (di Filippo et al., 2022) mRNA vaccines were considered as the best vaccine against SARS CoV-2 because they are safe and relatively easy to make in comparison to other vaccines. According to Stati et al. (2023), all of the currently available SARS-CoV-2 vaccines are safe. Furthermore, preclinical and clinical studies on SARS CoV-2 and other viruses have shown that mRNA vaccines can effectively induce humoral as well as cellular immune responses, in addition to being manufactured in a relatively short time. (Alberer et al., 2017; Corbett et al., 2020; Jackson et al., 2020; Pardi et al., 2017)

Despite these advantages, there have been various reports on the side effects following SARS CoV-2 mRNA vaccines administration (Bostan et al., 2022; Chee et al., n.d., 2022a; di Filippo et al., 2022; Jafarzadeh et al., 2022; Lui et al., 2021; Morita et al., 2023; Patrizio et al., 2021; Pierman et al., 2021; Peris et al., 2022; Singh & Howland, 2022; Vera-Lastra et al., 2021; Weintraub et al., 2021; Zettinig & Krebs, 2022). One of these side effects is thyroid dysfunctions, including subacute thyroiditis, autoimmune thyroiditis, and Graves' disease (GD). In GD, the administration of mRNA vaccines results in the onset of GD and relapsing GD in individuals under remission. This review article focuses on the effects of SARS CoV-2 mRNA vaccines on GD development and the current possible mechanisms that lead to GD development.

GRAVES' DISEASE (GD): EPIDEMIOLOGY, RISK FACTORS, AND PATHOPHYSIOLOGY

Graves' disease (GD), also known by the term "autoimmune hyperthyroidism", is defined by the onset of a diffuse hyper-functional goiter appearing as the swelling on the neck, as well as the bulging of the eyes occurring from a hyperactive thyroid gland. This disease is characterized by the overproduction of thyroid hormones by the thyroid gland due to the expression of autoantibodies against thyroid stimulating hormone receptors (TSHRs) (Khan et al., 2021). It was named after Robert Graves, an Irish physician who first described the disease in 1835 (Paluchamy, 2021). Since it is a systemic disease, other symptoms that are associated to it vary depending on which organ system is affected, including ophthalmopathy and dermopathy (Khan et al., 2021). Other prevalent symptoms experienced by patients include heart palpitations, muscle weakness, sleep disorders, tachycardia and arrhythmias, extreme weight loss, and digestive disorders (Wémeau et al., 2018). Furthermore, there is evidence to prove that GD is a genetic disease, as familial and twin studies have recapitulated the genetic bases of GD, with several immunomodulatory genes being implicated (Brix et al., 2001; Wémeau et al., 2018). The autoimmune reaction in GD is the outcome of interactions between genetic and environmental risk factors (Khan et al., 2021).

Epidemiology

GD is the most common cause of hyperthyroidism, affecting more females than males ages 30 to 50 years with a ratio between 5:1 to 10:1. The annual incidence rate is 16 cases per 100,000 in women, and 3 cases per 100,000 in men. Genetic predisposition accounts for around 79% of these cases, while environmental factors account for the rest (Antonelli et al., 2020). Furthermore, Graves' disease has been approximated to affect 2-3% of individuals globally (Paluchamy, 2021). A study conducted in Sheffield, UK, found that the crude incidence rate of GD was 24.8 per 100,000 individuals per year (Hussain et al., 2017). A population-based study in Denmark reveals a standardized incidence rate for hyperthyroidism of 81.6 per 100,000 people per year, with GD being the most common subtype occurring in young people (Carlé et al., 2011). There is no detailed data about GD epidemiology in Indonesia. However, according to the data from Indonesia Basic Health Research, the incidence rate of hyperthyroidism in Indonesia is 6.9%.

Risk factors

There are several genes thought to be involved in GD pathogenesis, including genes that encode for the thyroid stimulating hormone receptor (TSHR): CD40, CD25, cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), HLA, thyroglobulin, and protein tyrosine phosphatase-22 (PTPN 22) (Davies et al., 2012). In particular, there have been many HLA genes implicated in the development of GD. In a genome-wide study (GWAS) conducted on the Japanese population, protein polymorphisms of class I and II *HLA* genes that included *HLA-DRB1, HLA-DPB1, HLA-A, HLA-B* were discovered to increase the risk of developing GD (Okada et al., 2015). A recent study reported a significant association of GD risk with the presence of these alleles:

*HLA-B*08:01*,*-B*39:06*, *-B*37:01*,*-C*07:01*, *-C*14:02*, *-C*03:02*, *-C*17:01*,*-DRB1*03:01*, *-DRB1*11:01*, *-DRB1*13:03*, *-DRB1*01:03*, *-DRB1*14:01*, *-DQB1*03:01*, *DQB1*02:01* (Stasiak et al., 2023). Studies have also found that the HLA alleles *DQA1*05* and *DQB1*02* were associated with GD (Barlow et al., 1996; Gough, 2000; Yanagawa et al., 1993). Additionally, other genes that are associated include *FOXP3, IKZF3*, *FCRL3*, *ARID5B*, and *NRXN3* (Vejrazkova et al., 2018).

Endogenous factors of GD include estrogen, X chromosome inactivation, and fetal micro-chimerism (Wémeau et al., 2018). Estrogen has been known to play a role in the development of B cells and can lead to autoimmune dysfunction, while the skewing of X chromosome inactivation has been found to increase the risk of autoimmune hyperthyroidism (Yin et al., 2007). Fetal micro-chimerism is the presence of fetal cells in maternal tissue blood, which persists following the end of pregnancy. It is suggested that fetal micro-chimerism is associated with autoimmune thyroid disease development (Galofré, 2012).

As for environmental risks factors, an excess intake of iodine, low selenium levels, low vitamin D levels, smoking, high alcohol intake, stress, ionizing radiation, bacterial and viral infections, and certain medications that affect the immune system such as IFN-α treatment and Ipilimumab, are known to affect the development of GD (Wémeau et al., 2018).

Pathophysiology

Although the exact reason for autoimmunity to the thyroid is not known, the pathophysiology of GD mainly starts with an autoimmune attack towards the TSHR. Thyroid stimulating hormone receptor antibodies (TRAbs), circulating autoantibodies that mimic TSH, continuously bind and activate the TSHR. This action stimulates the thyroid gland to overproduce thyroid hormones and causes thyroid gland hyperplasia and hypertrophy (Franco, 2013).

To recapitulate the mechanism of thyroid hormone production described by Higgins (Higgins, n.d.), the hypothalamus secretes thyroid releasing hormone (TRH), which stimulates the anterior pituitary to release thyroid stimulating hormone (TSH). When in circulation, TSH will target the thyroid gland, which possesses TSH receptors. TSH binds to the receptors, stimulating the production and release of thyroid hormones, also known as triiodothyronine (T3) and thyroxine (T4). These hormones are released into systemic circulation, carried by thyroid binding proteins.

The TSH receptor is the main autoantigen In Graves' disease, which is responsible for hyperthyroidism. However, other thyroid antigens such as the thyroglobulin, thyroid peroxidase, and sodium-iodide symporter, also play a minor role (Khan et al., 2021). The continuous stimulation of TSH receptors by the autoantibodies leads to an increase in thyroglobulin synthesis and sodium-iodide symporter expression, increasing uptake of iodine, subsequently leading to increased iodination of thyroglobulin. In particular, the enzyme thyroid peroxidase converts inorganic iodide to iodine, which will bind to thyroglobulin, causing diiodotyrosine (DIT) and monoiodotyrosine (MIT) to couple, thus producing T3 and T4 (Paluchamy, 2021).

PRESENT CASES OF GD OCCURENCES AFTER VACCINATION WITH SARS CoV-2 mRNA VACCINES

Cases of newly diagnosed GD

Case reports of GD onset after administration of the mRNA COVID 19 vaccines are summarized in Table 1. Most patients that developed GD after vaccination received the PfizerBioNTech® (BNT162b2) vaccine, with most having no pre-existing diagnoses of GD before vaccination. It should be noted that some patients without a previous history of GD may or may not have family history. Interestingly, the time of onset for the manifestation of hyperthyroidism symptoms for patients varied between a few days to a couple of months after vaccination, regardless of the number. This indicates that the number of doses does not seem

to correlate with the appearance of symptoms. Common symptoms experienced by patients were excessive weight loss in a short amount of time, excessive sweating, arrhythmia, tachycardia, asthenia, fever, and heart palpitations. Furthermore, most reported cases were female patients, which is to be expected as the prevalence of GD is higher in females than in males (Kahaly et al., 2011).

As expected, the thyroid function tests revealed decreased levels of circulating TSH, and increased levels of free T3, free T4, and TRAb. Most patients received ultrasonography results of a diffuse enlarged thyroid gland with heterogeneous echotexture and increased vascularity in the parenchyma (Table 1). However, TRAb is further subdivided into stimulating (TSAb), blocking (TBAb), and neutralizing antibodies, and the tests reviewed from the cases did not signify which type of TRAb was measured. Determination of TSAb levels is a sure-fire method to diagnose GD, as TSAb leads to the stimulation of thyroid follicular cells and release of T3 and T4. Additionally, downstream effects caused by TSAb include the activation of cyclic adenosine monophosphate (cAMP) and binding of TSAb to TSHR (Paluchamy, 2021). Thus, diagnosis of GD may be more accurate if the levels of TSAb had been established in the tests.

Cases of relapsed GD

In addition to newly diagnosed occurrences of GD, there have also been reported cases of patients who were in remission for the disease, only relapsing after the administration of the COVID-19 mRNA vaccine (Table 2). Common symptoms experienced include weight loss, heart palpitations, and sweating. However, some patients were asymptomatic and were only found to have relapsed after a routine checkup for thyroid function. As with patients who were newly diagnosed with GD, most relapsing patients were women, and their thyroid function tests reveal an increase in serum free T3, T4, and TRAb, along with an increase in TSH.

Furthermore, the appearance of GD symptoms does not correlate to the number of doses administered as the manifestation of symptoms varied between occurring after receiving the first and second dose, with one patients experiencing symptoms 5 days after the first dose, and another being diagnosed 63 days after the second dose.

PROPOSED MECHANISMS OF GD MANIFESTATION AFTER SARS CoV-2 mRNA VACCINE ADMINISTRATION

There are a few mechanisms that may explain a probable causal relationship between the administration of the SARS CoV-2 mRNA vaccine and the manifestation of GD. One hypothesis is the molecular mimicry of SARS CoV-2 S protein with thyroid antigens that leads to cross-reactivity. This mechanism results in an immune response against the thyroid gland. A study by Vojdani et al. (2021) reveals that the spike protein, membrane protein, and nucleoprotein of SARS-CoV-2 cross-reacted with thyroid peroxidase (TPO). A BLAST sequence search that was done found that the same proteins and other SARS-CoV-2 proteins bared similarity and shared homology with TPO. It may be possible that this cross-reactivity is what causes autoimmune hyperthyroidism.

Another proposed mechanism is that the ACE-2 receptors on thyroid follicular cells of the thyroid gland can be directly activated by SARS-CoV-2 proteins. This mechanism is elaborated in a study by Rotondi et al. (2021), wherein ACE-2 was found to be expressed in thyroid follicular cells, potentiating the binding of SARS-CoV-2 to the thyroid gland, thus leading to hyperthyroidism. There is also the hypothesis that the polyethylene glycol (PEG) lipid conjugate, used to stabilize the nanoparticles of the virus, can act as adjuvants that can induce autoimmune reactions in predisposed individuals. This hypothesis is also known as an autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome), in which it is possible that the adjuvants are able to change the host's immune system by polyclonal activation of B cells to induce autoimmunity (Perricone et al., 2013; Vera-Lastra et al., 2021). Lastly, it is also theorized that the

development of GD may be the result of spike proteins of the mRNA vaccine sharing similarity with thyroid antigens, which are presented on antigen-presenting cells, thus activating T and B cells to induce autoimmunity against follicular epithelial cells of the thyroid gland (Chee et al., 2022b; Khan et al., 2021).

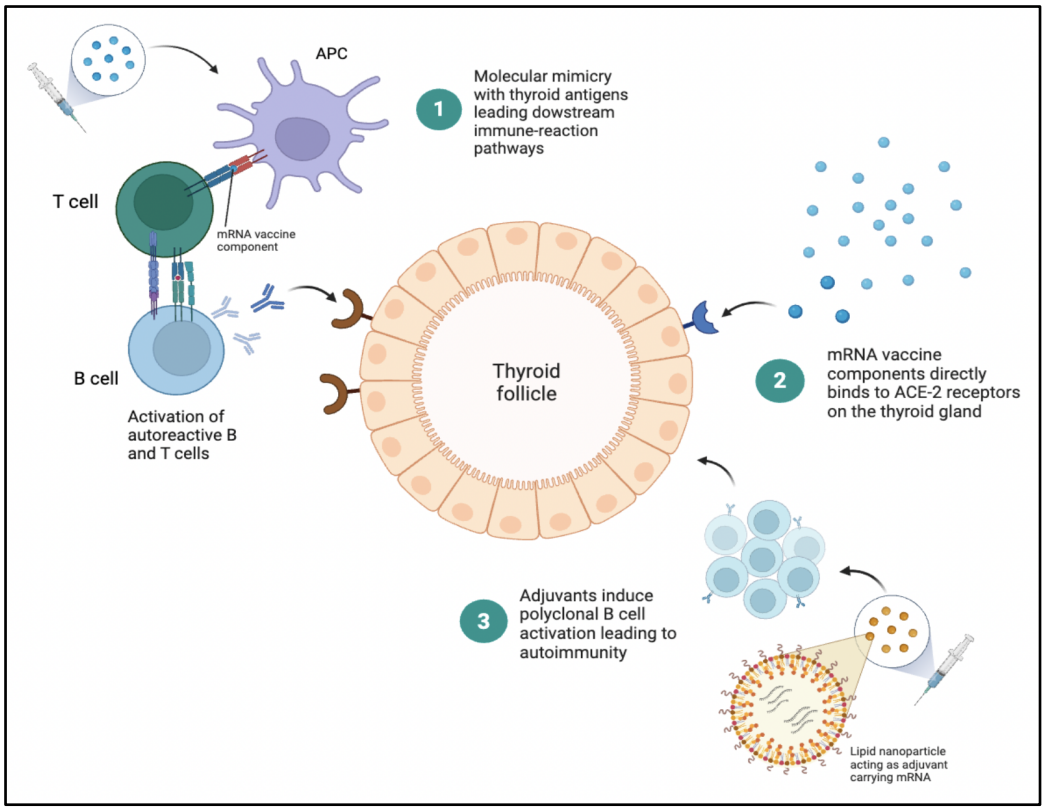

Figure 1. Proposed mechanisms of GD manifestation after SARS CoV-2 mRNA vaccines administration.

FUTURE STUDIES

As seen by one of the proposed mechanisms, the development of GD caused by SARS CoV-2 mRNA vaccine involves the direct binding of vaccine components with the ACE-2 receptors. Future research could focus on how the mechanism of direct activation of the ACE-2 receptors on thyroid follicular cells by SARS-CoV-2 proteins can lead to an increase of circulating TSAb/TRAb in GD patients. Future studies could also improve diagnostic tests by being specific to the parameters. There could also be additional research into finding the actual molecular mechanism of what has already been proposed, such as discovering the exact adjuvant that leads to polyclonal B cell activation, and the exact mechanism of molecular mimicry that leads to an increase in the thyroid hormones released by the thyroid follicular cells.

CONCLUSION

Even though the administration of SARS Cov-2 vaccines has been proven to effectively suppress the virus transmission, these vaccines might also cause newly onset GD in naïve people and relapse in GD patients who are already under remission. Research on novel vaccine adjuvants should be performed in the future to improve the safety of the vaccines. Moreover, studies on other SARS CoV-2 components that are not cross-reacted with human antigens should be done with the purpose of developing SARS CoV-2 mRNA vaccines that are safe for everyone. Additionally, SARS CoV-2 vaccines can also be redesigned by removing the epitope that cross-react with human antigens and keeping those that are virus-specific.

Table 1. A summary of newly diagnosed GD cases after administration of COVID-19 mRNA vaccine.

Age/sex	Personal history/ family history	mRNA vaccine	Time of onset symptoms after vaccination	Symptoms	TSH at diagnosis [reference range]	fT3 at diagnosis [reference range]	fT4 at diagnosis [reference range]	TRAb [reference range]	Thyroid Ultrasonography	Reference
52/M	No/N.A.	Pfizer-BioNTech	28 days after 2nd dose	Weight loss, night fever, asthenia	<0.004 mIU/L [0.4–4.00]	15 ng/L [2.7–5.7]	5.56 ng/dL [0.7–1.7])	6.48 IU/L [0–1.49]	Enlarged thyroid gland w/ heterogeneous echotexture, increased vascularization	(Patrizio et al., 2021)
38/F	No/No	Pfizer-BioNTech	5 days after 1st dose	Tachycardia, fever, abdominal pain	<0.008 µIU/mL [0.45-4.5]	10.3 nmol/L [0.9-2.8]	108 pmol/L [10.6-22.8]	32 IU/L [< 1.75]	Diffuse enlarged thyroid gland w/ heteroge-neous echogenicity, increased vascularity	(Weintraub et al., 2021)
42/M	No/N.A.	Moderna booster	2 days after booster	Weight loss, headache, dyspnea, hyperhidrosis, insomnia, muscle weakness, and nausea	<0.015 µIU/mL [0.45-4.5]	N.A.	5.96 ng/dL [0.78-2.19]	16.1 IU/L [< 1.75]	Prominent heterogeneous and hyperemic gland	(Singh & Howland, 2022)
47/F	No/N.A.	Pfizer-	5 days after 1st	Ongoing	<0.01 mIU/L	11.0 ng/L [2-4.4]	3.32 ng/dL	22.74 IU/L	Diffuse millimetric	(Bostan et

Age/sex	Personal history/ family history	mRNA vaccine	Time of onset symptoms after vaccination	Symptoms	TSH at diagnosis [reference range]	fT3 at diagnosis [reference range]	fT4 at diagnosis [reference range]	TRAb [reference range]	Thyroid Ultrasonography	Reference
		BioNTech	dose	excessive sweating and palpitations for 3 months	[0.27-4.2]		[0.93–1.7]	[<1.5]	hypoechoic areas, increased vascularity in parenchyma	al., 2022)
46/M	No/N.A.	Pfizer-BioNTech	3 weeks after 2nd dose	Weight loss, excessive sweating, emotional lability, and heart palpitation	<0.01 mIU/L [0.27–4.2]	25.30 ng/L [2–4.4]	> 7.77 ng/ dL [0.93–1.7]	9.10 IU/L [<1.5]	Diffuse millimetric hypoechoic areas, increased vascularity in parenchyma, 34 mm isoechoic thyroid nodule	(Bostan et al., 2022)
37/F	N.A/No	N.A.	7 days after 1st dose	N.A.	<0.01 mIU/L [N.A.]	N.A.	60 pmol/L [8-16]	3.8 IU/L [<1]	N.A.	(Chee et al., 2022b)
37/F	N.A./No	N.A.	21 days after 2nd dose	N.A.	<0.01 mIU/L [N.A.]	N.A.	72 pmol/L [8-16]	11.2 IU/L [<1]	N.A.	(Chee et al., 2022b)
33/F	N.A./No	N.A.	9 days after 2nd dose	N.A.	<0.01 mIU/L [N.A.]	N.A.	29 pmol/L [8-16]	4.6 IU/L [<1]	N.A.	(Chee et al., 2022b)
43/F	N.A./No	N.A.	13 days after 2nd dose	N.A.	<0.01 mIU/L [N.A.]	> 40 pmol/L [3.5-6.0]	70 pmol/L [8-16	6.2 4.6 IU/L [<1]	N.A.	(Chee et al., 2022b)

Age/sex	Personal history/ family history	mRNA vaccine	Time of onset symptoms after vaccination	Symptoms	TSH at diagnosis [reference range]	fT3 at diagnosis [reference range]	fT4 at diagnosis [reference range]	TRAb [reference range]	Thyroid Ultrasonography	Reference
46/M	No/N.A.	Pfizer-BioNTech	Routine blood test 15 days after 1st dose indicated hyperthyroidism	N.A.	N.A.	1.63 pg/ml [0.70–1.70]	5.18 pg/ml [2.15–4.12]	2.9 IU/L	Slightly enlarged thyroid, large anechogenic areas with increased vascularization in hypoechogenic parenchyma	(Zettinig & Krebs, 2022)
38/F	No/N.A.	Pfizer-BioNTech	12 days after 1st dose	Anxiety, insomnia, sweating	< 0.008 µIU/mL [0.350–4.950]	7.46 pg/mL [0.70–1.48 ng/dL]	2.01 ng/dL [0.70–1.48]	N.A.	Diffuse decrease in echogenicity with some echogenic septum, increased vascularity	(Pujol et al., 2022)
71/F	No/No	Pfizer-BioNTech	60 days after 2nd dose	Atrial fibrillation, weight loss, asthenia	< 0.005 mUI/L [0.38–5.33]	N.A.	2.3 ng/dL [0.54–1.24]	3.6 U/L [<1.75]	Enlarged thyroid, increased vascularization	(Pla Peris et al., 2022)
42/F	No/No	Pfizer-BioNTech	10 to 14 days after 1st dose	Palpitations, weight loss, asthenia	< 0.005 mUI/L [0.38–5.33]	N.A.	2.9 ng/dL [0.54–1.24]	4.39 U/L [<1.75]	Enlarged thyroid, increased vascularization	(Pla Peris et al., 2022)
54/F	No/No	Moderna	10 to 14 days the 1st dose	Palpitations, weight loss,	< 0.005 mUI/L [0.38–5.33]	N.A.	4.7 ng/dL [0.54–1.24]	5.1 U/L [<1.75]	Enlarged thyroid, increased	(Pla Peris et al.,

Age/sex	Personal history/ family history	mRNA vaccine	Time of onset symptoms after vaccination	Symptoms	TSH at diagnosis [reference range]	fT3 at diagnosis [reference range]	fT4 at diagnosis [reference range]	TRAb [reference range]	Thyroid Ultrasonography	Reference
				asthenia					vascularization	2022)
46/F	No/No	Pfizer-BioNTech	50 days after 2nd dose	Palpitations, weight loss, asthenia	< 0.005 mUI/L [0.38–5.33]	N.A.	3.2 ng/dL [0.54–1.24]	3.2 U/L [<1.75]	Enlarged thyroid, increased vascularization	(Pla Peris et al., 2022)
40/F	N.A./N.A.	Pfizer-BioNTech	2 days after vaccination*	Palpitations, insomnia, fatigue, nausea	<0.001 µgUi/mL [0.27–4.4]	10.5 pg/mL [2.04–4.4]	3.57 ng/dL [0.93–1.71]	16.56 Ui/L [0–1.75]	Enlarged thyroid, increased vascularization	(Vera-Lastra et al., 2021)
28/F	No/N.A.	Pfizer-BioNTech	3 days after vaccination*	Palpitations, insomnia, distal tremor, anxiety	<0.001 µgUi/mL [0.27–4.4]	9.2 pg/mL [2.04–4.4]	1.84 ng/dL [0.93–1.71]	5.85 Ui/L [0–1.75]	N.A.	(Vera-Lastra et al., 2021)

N.A.: Not available; M: Male; F: Female; TSH: Thyroid stimulating hormone; fT3: free Triiodothyronine; fT4: Thyroxine; TRAb: TSH Receptor Autoantibody (also known as TSHRab).

* Information on whether first or second dose is not available.

Table 2. A summary of relapsed GD cases after administration of COVID-19 mRNA vaccine.

Age/Sex	Family history	mRNA vaccine	Time of relapsing symptoms after vaccination	Time of recurrence since remission	Symptoms	TSH at diagnosis of relapse [reference range]	fT3 at diagnosis of relapse [reference range]	fT4 at diagnosis of relapse [reference range]	TRAb at diagnosis of relapse [reference range]	Thyroid Ultrasonography	Reference
71/F	N.A.	Pfizer-BioNTech	~ 30 days after ^{2n}d dose	17 years	Palpitations, sweating	<0.004 mIU/L [0.4–4.00]	11.10 pg/ml [2.15–4.12]	3.56 ng/dL [0.70–1.70]	4.2 IU/l [< 1.5]	Several confluent anechogenic areas, increased vascularization	(Zettinig & Krebs, 2022)
34/F	N.A.	Pfizer-BioNTech	10 days after ^{1s}t dose, symptoms worsened after ^{2n}d dose	7 years	Weight loss, swollen eyelids associated with distal tremor, sweating, thermophobia, dyspnea	<0.01 mU/L [0.4–2.75 mU/L]	22.09 pmol/L [3–6.5 pmol/L]	2.54 ng/dL [0.75–1.6 ng/dl]	> 40 IU/l [<0.55 IU/l]	N.A.	(Pierman et al., 2021)
49/M	N.A.	Pfizer-BioNTech	1 months after ^{2n}d dose	2 years	Palpitations, hand tremors, sweating	<0.01 mIU/L [0.27–4.2]	13.50 ng/L [2–4.4]	3.86 ng/dL [0.93–1.7]	3.01 [IU/L <1.5]	Increased parenchymal vascularity	(Bostan et al., 2022)
31/F	N.A.	Pfizer-BioNTech	3 weeks after ^{1s}t dose	1 years and 1 month	Asthenia, sweating, hot flashes	<0.01 mIU/L [0.27–4.2]	21.70 ng/L [2–4.4]	>7.77 ng/dL [0.93–1.7]	19.30 IU/L [<1.5]	Increased parenchymal vascularity	(Bostan et al., 2022)
59/M	Yes	N.A.	21 days after ^{1s}t dose	N.A.	N.A.	< 0.01 IU/L [N.A.]	N.A.	49 pmol/L [8-16]	12.8 IU/L [<1]	N.A.	(Chee et al., 2022b)

Age/Sex	Family history	mRNA vaccine	Time of relapsing symptoms after vaccination	Time of recurrence since remission	Symptoms	TSH at diagnosis of relapse [reference range]	fT3 at diagnosis of relapse [reference range]	fT4 at diagnosis of relapse [reference range]	TRAb at diagnosis of relapse [reference range]	Thyroid Ultrasonography	Reference
74/F	Yes	N.A.	11 days after ^{2n}d dose (routine TFT was don)}	N.A.	Asymptomatic	0.02 IU/L [N.A.]	N.A.	14 pmol/L [8-16]	6.2 U/L [<1]	N.A.	(Chee et al., 2022b)
25/F	Yes	N.A.	31 days after ^{2n}d dose (routine TFT was done)	N.A.	Asymptomatic	0.01 IU/L [N.A.]	6.3 pmol/L [3.5-6.0]	15 pmol/L [8-16]	2.9 U/L [<1]	N.A.	(Chee et al., 2022b)
41/F	No	N.A.	28 days after ^{2n}d dose	N.A.	N.A.	< 0.01 IU/L [N.A.]	N.A.	50 pmol/L [8-16]	3.9 U/L [<1]	N.A.	(Chee et al., 2022b)
24/F	No	N.A.	63 days after ^{2n}d dose (routine TFT was done)	N.A.	Asymptomatic	0.01 [N.A.]	N.A.	20 pmol/L [8-16]	2.4 U/L [<1]	N.A.	(Chee et al., 2022b)
22/F	No	N.A.	5 days after ^{1s}t dose	N.A.	N.A.	0.01 [N.A.]	> 40 pmol/L [3.5-6.0]	70 pmol/L [8-16]	5.8 U/L [<1]	N.A.	(Chee et al., 2022b)

N.A.: Not available; M: Male; F: Female; TSH: Thyroid stimulating hormone; fT3: free Triiodothyronine; fT4: Thyroxine; TRAb: TSH Receptor Autoantibody (also known as TSHRab)

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