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REVIEW

Thyroid dysfunction following vaccination with COVID-19 vaccines: a basic review of the preliminary evidence

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Abstract

Purpose The safety and efficacy of the several types of COVID-19 vaccines, including mRNA-based, viral vector-based, and inactivated vaccines, have been approved by WHO. The vaccines can confer protection against severe SARS-CoV-2 infection through induction of the anti-spike protein neutralizing antibodies. However, SARS-CoV-2 vaccines have been associated with very rare complications, such as thyroid disorders. This review was conducted to highlight main features of thyroid abnormalities following COVID-19 vaccination.

Methods A comprehensive search within electronic databases was performed to collect reports of thyroid disorders after vaccination with COVID-19 vaccines.

Results Among 83 reported cases including in this review, the most cases of thyroid abnormalities were observed after vaccination with mRNA-based vaccines (68.7%), followed by viral vector vaccines (15.7%) and 14.5% cases following inactivated vaccines. Subacute thyroiditis (SAT) was the most common COVID-19 vaccination-related thyroid disease, accounting for 60.2% of all cases, followed by Graves' disease (GD) with 25.3%. Moreover, some cases with focal painful thyroiditis (3.6%), silent thyroiditis (3.6%), concurrent GD and SAT (2.4%), thyroid eye disease (1.2%), overt hypothyroidism (1.2%), atypical subacute thyroiditis (1.2%), and painless thyroiditis with TPP (1.2%) were also reported. Overall, in 58.0% of SAT cases and in 61.9% of GD cases, the onset of the symptoms occurred following the first vaccine dose with a median of 10.0 days (ranged: 3–21 days) and 10.0 days (ranged: 1–60 days) after vaccination, respectively. Moreover, 40.0% of SAT patients and 38.1% of GD patients developed the symptoms after the second dose with a median of 10.5 days (ranged: 0.5–37 days) and 14.0 days (ranged: 2–35 days) after vaccination, respectively.

Conclusion Fortunately, almost all cases with COVID-19 vaccination-associated thyroid dysfunctions had a favorable outcome following therapy. The benefits of COVID-19 vaccinations in terms of terminating the pandemic and/or reducing mortality rates can exceed any risk of infrequent complications such as a transient thyroid malfunction.

Keywords Thyroid · COVID-19 · Thyroiditis · Subacute thyroiditis · Graves' disease

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Introduction

Since the emergence of COVID-19 at the end of 2019, more than 426 million infections and 5,800,000 deaths have been documented due to this disease, as of 20 February 2022 [1]. While there is currently no confirmed curative treatment for the COVID-19, various types of vaccines have been developed including innovative technology-based vaccines (mRNA-based and virus-vector-based vaccines), which can induce high protection against severe forms of COVID-19. The World Health Organization (WHO) confirmed on November 15, 2021 that some mRNA-based vaccines (Moderna and Pfizer/BioNTech), viral vector-based vaccines (AstraZeneca/Oxford and Johnson and Johnson), and inactivated vaccines (Sinopharm, Sinovac, and Covaxin) are safe and effective [2, 3]. As of 20 February 2022, a total of more than 10.4 billion vaccine doses have been administered, globally [1]. The COVID-19 vaccines can confer protection through induction of the anti-spike (S) protein neutralizing antibodies [4]. The overall safety and efficacy of currently available COVID-19 vaccines have been indicated in multiple studies [5–7]. However, the occurrence of a few cases of post-vaccination complications, such as thyroid disorders, has been observed after administration of various types of COVID-19 vaccines [5].

Thyroid hormones influence almost all nucleated cells and play a fundamental role in the regulation of vital activities, such as metabolism, growth, haematopoiesis, and reproduction [8, 9]. Thyroid gland-derived hormones regulate the function of the majority of organs and maintain the body's internal homeostasis [10]. Thyroid disorders are frequent and have detrimental influences on the general health of all patients. Thyroid illnesses are diagnosed based on evidence of structural abnormalities in the gland as well as impaired secretory function [8, 10]. Based on the above explanation, in evaluating the safety of many drugs and vaccines, there is special attention to their impacts on thyroid function. This attention to the side effects of the COVID-19 vaccines on this gland was explored and reported in a few papers mainly as case reports/series. However, a summary review is needed to generate a comprehensive view to compare and combine their findings. Therefore, we reviewed the published papers to compile their results.

Methods

We conducted a review of the literature to identify all reports regarding thyroid dysfunction after COVID-19 vaccination by searching for indexed articles until 20 February 2022 in PubMed, PubMed Central, Web of Science, and Scopus. The following keywords were used: COVID-19, SARS-CoV-2, Vaccine, Vaccination, thyroid, thyroiditis, and Graves' disease (GD). Inclusion criteria were administration of the SARS-CoV-2 vaccine, case reports, and case series describing patients with the approved thyroid dysfunction. Articles that were not written in English were excluded from this analysis. Among 80 papers, 40 articles were suitable for inclusion in the analysis, and in a total, 83 patients with thyroid dysfunction were included.

Thyroid dysfunctions after COVID-19 vaccination

Thyroid disorders have been documented following the administration of all COVID-19 vaccine types. To characterize the COVID-19 vaccination-associated thyroid disorders, we categorized them based on the administered vaccine type (Table 1). Among 83 reported cases which were included in this review, the most frequent cases of thyroid abnormalities

Table 1 Distribution of the thyroid disorders after COVID-19 vaccination according to the vaccine type

Thyroid disorders	mRNA-based vaccines	Vector-based vaccines	Inactivated vaccines	Total
Subacute thyroiditis[a]	31	6	12	50 (60.2%)
Graves' disease	16	5	–	21 (25.3%)
Focal painful thyroiditis	3	–	–	3 (3.6%)
Silent thyroiditis	3	-	–	3 (3.6%)
Concurrent GD and SAT	1	1	–	2 (2.4%)
Thyroid eye disease	1	–	–	1 (1.2%)
Painless thyroiditis with TPP	–	1	–	1 (1.2%)
Overt hypothyroidism	1	–	–	1 (1.2%)
Atypical subacute thyroiditis	1	–	–	1 (1.2%)
Total	57 (68.7%)	13 (15.7%)	12 (14.5%)	83 (100.0%)

GD Graves' disease, *SAT* Subacute thyroiditis, *TPP* thyrotoxic periodic paralysis

[a]The vaccine type was not reported for 1 patient with subacute thyroiditis

were observed after vaccination with mRNA-based vaccines [57/83 (68.7%)], followed by viral vector vaccines [13/83 (15.7%)] and 12/83 (14.5%) cases following inactivated vaccines. Moreover, SAT was the most common COVID-19 vaccination-related thyroid disease, accounting for 50/83 (60.2%) of all cases, followed by GD with 21/83 (25.3%). Moreover, some cases with focal painful thyroiditis [3/83 (3.6%)], silent thyroiditis [3/83 (3.6%)], and concurrent GD and SAT [2/83 (2.4%)] were also reported. Thyroid eye disease, overt hypothyroidism, atypical subacute thyroiditis, and painless thyroiditis with thyrotoxic periodic paralysis (TPP) were found with lower frequency [1/83 (1.2%) for each disorder] (Table 1).

Subacute thyroiditis after COVID-19 vaccination

Subacute thyroiditis (SAT), also known as granulomatous thyroiditis or de Quervain's thyroiditis, is a self-limiting inflammatory illness that is caused by viral infections or postviral inflammatory reactions [11, 12]. A recent viral infection (around 2–6 weeks prior) is thought to be a triggering agent in genetically susceptible individuals [12]. The pathogenesis of SAT has been associated with some viral infections, such as measles, mumps, coxsackie, rubella, and adenovirus, either directly or through an inflammatory reaction to the virus [12]. SARS-CoV-2 infection can also operate as a trigger factor for the development of SAT [11]. Some HLA haplotypes, such as HLA-Bw35, HLA-B67, HLA-B35, HLA-DRB1*08, HLA-DRB1*01, HLA-B*18:01, HLA-DRB1*01, and HLA-C*04:01, have been linked to SAT [13–15].

The most prevalent symptom of SAT is anterior neck pain; however, some cases of SAT without any neck pain are also documented [12, 16, 17]. The clinical course of SAT often consists of three sequential phases: thyrotoxicosis in the first months, hypothyroidism for about 3 months, and ultimately euthyroidism [17, 18].

Table 2 summarizes the main characteristics of the 50 COVID-19 vaccination-related SAT cases reported as of February 20, 2022. According to vaccine type, the distribution of SAT cases was: 31/50 (62.0%) after vaccination with mRNA-based vaccines, 12/50 (24.0%) after vaccination with inactivated vaccines, and 6/50 (12.0%) after vaccination with vector-based vaccines (Tables 1 and 2). Vaccine type and brand were not reported for one case with SAT [19] (Table 2).

According to vaccine brand, 25/50 (50.0%) of SAT cases were reported after Pfizer vaccination, 11/50 (22.0%) of cases after Sinovac (Life Sciences, Beijing) vaccination, 6/50 (12.0%) of cases after AstraZeneca vaccination, 6/50 (12.0%) of cases after Moderna vaccination, and 1/50 (2.0%) of cases after Covaxin (Bharat Biotech, India) vaccination.

The frequency of the SAT is highest in middle-aged women, and females account for 75.0–80.0% of patients [20, 21]. According to the gender of patients, 36/50 (72.0%) of SAT cases were women, while 14/50 (28.0%) were men, and the women/men ratio was about 2.57:1. The median age was 39.5 years (ranged: 26–73 years) for SAT women and was 45.5 years (ranged: 26–75 years) for SAT men. In 19/36 (52.8%) of women and in 10/14 (71.4%) of men, the onset of SAT symptoms occurred following the first vaccine dose with a median of 10.0 days (ranged: 3–21 days) and 10 days (ranged: 3–15 days) after vaccination, respectively (Table 3). In 16/36 (44.4%) of women and in 4/14 (28.6%) of men, the onset of SAT symptoms occurred following the second vaccine dose with a median of 6.5 days (ranged: 0.5–30 days) and 18.5 days (ranged: 7–37 days) after vaccination, respectively. Overall, in 29/50 (58.0%) of patients, the onset of SAT symptoms occurred following the first vaccine dose with a median of 10.0 days (ranged: 3–21 days) after vaccination, whereas 20/50 (40.0%) of patients developed the symptoms after the second dose with a median of 10.5 days (ranged: 0.5–37 days) after vaccination. The onset time of symptoms was not reported in one SAT woman. The reported SAT cases were from 11 countries, including Germany, USA, Greece, Spain, Turkey, UK, Cyprus, Iran, South Korea, Ireland, and Brazil (Table 2).

Regarding the characteristics of SAT, the inflammatory indicators such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are virtually increased [22]. The ultrasonography features of SAT include hypoechoic and heterogeneous patches with blurred borders, as well as weak vascularization [23, 24]. In examined cases, the thyroid ultrasonography or scintigraphy imaging was consistent with SAT characteristics. COVID-19 vaccination-associated SAT mainly presented with the clinical characteristics of neck pain, thyrotoxicosis-related thyroid function tests (TFTs) (low TSH along with high free T4), and confirmatory ultrasonography and scintigraphy findings. Regarding the therapeutic and outcome aspects, steroidal and non-steroidal anti-inflammatory drugs (NSAIDs) were effective for the improvement of symptoms, thyrotoxicosis resolution, and inflammatory marker normalization.

Graves' disease after COVID-19 vaccination

Graves' disease (GD) as an autoimmune disease is caused by agonist autoantibodies to the thyroid-stimulating hormone receptor (TSHR), inducing hyperthyroidism, independent of pituitary regulation [50]. The binding of thyroid-stimulating antibodies (TSAb) to thyrocyte TSHR induces cell proliferation, thyroid growth, and hyper-secretion of T4 and T3 hormones [51]. Anti-TSHR, anti-TPO, and anti-TG antibodies are found in 90.0, 80.0, and 50.0–60.0% of GD patients, respectively [52].

Table 2 Characteristics of cases presenting with subacute thyroiditis following COVID-19 vaccination

Country (case no.)	Gender–age, years	Vaccine name (Vaccine type)	Onset time of symptoms-Primary clinical symptoms	Physical, histopathological examination of thyroid	Thyroid function tests (TFTs)	Other related laboratory tests	Medication and Outcome	Ref
Germany (1)	F-26	AstraZeneca (Vector-based)	- 14 days after 1st dose- - Cervical pain	- TPE: Thyroid tenderness with pain on palpation. Neck lymphadenopathy - TUSG: Hypoechoic parts with reduced blood flow - Pathologic: Mononuclear lymphocytic cells, follicular cells, granulomatous cells, and multinucleated giant cells	- FT3 (3.72 ng/L), FT4 (9.3 ng/L), TSH (1.75 mIU/L) were normal	- Anti-TG, anti-TPO, and anti-TSH were negative - Elevated CRP (29.4 mg/l) and WBC (14,300 cell/µl) count	- Treatment with Ibuprofen and prednisolone completely improved symptoms within 2 weeks	[25]
Germany (2)	F-49	Moderna (mRNA-based)	- 14 days after 1st dose- -Headaches and difficulty in concentrating and then a right cervical sore throat	- TUSG: Distinct ill-defined hypoechoic area with decreased blood flow - Pathologic: Follicular cells, lymphocytes, macrophages, and multinucleated giant cells	- Euthyroid status, although TSH (0.5 mIU/l) level was in the low zone of normal range	- Elevated CRP (21.9 mg/L) level	- Ibuprofen, then diclofenac due to gastrointestinal intolerance - Symptoms improved after 2 weeks - The patient discontinued the treatment and at the four-week follow-up, displayed thyrotoxicosis with positive anti-TPO - Symptoms improved after treatment with prednisolone	
USA (3)[1]	F-42	Moderna (mRNA-based)	- 5–6 days after the 2nd dose - Earache radiating down to the lateral and anterior neck and bilateral lower jaw	- TUSG: The right lobe had a heterogeneous mass, while the left lobe had a hypoechoic-heterogeneous mass - Pathologic: Disseminated multinucleated giant cells, epithelioid granulomas, follicular cells, lymphocytes, and karyorrhexis	- Low TSH (<0.0005 IU/mL), low T3 (1.90 ng/dL), normal FT4 (1.51 ng/dL)	- Anti-TPO (< 0 IU/mL) was negative - High ESR (81 mm/h)	- NSAIDs - Neck pain and TFTs were improved at 2 months	[26]
Greece (4)	F-51	Pfizer (mRNA-based)	- 14 days after 1st dose- - Nausea, mild anterior neck pain, and fever up to 38.2 °C	- TSG: Low thyroid uptake	- Low TSH (0.08 mIU/mL) and high FT4 (24.84 pmol/L)	- Anti-TG (< .9 IU/mL), anti-TPO (0.6 IU/mL), and anti-TSHR were negative - Elevated CRP (135 mg/L) and ESR (103 mm/h)	-Methylprednisolone - Fever and neck pain was resolved 2 days following treatment - 2 months after the initial assessment, the patient was euthyroid and asymptomatic	[27]

Table 2 (continued)

Country (case no.)	Gender–age, years	Vaccine name (Vaccine type)	Onset time of symptoms-Primary clinical symptoms	Physical, histopathological examination of thyroid	Thyroid function tests (TFTs)	Other related laboratory tests	Medication and Outcome	Ref
Greece (5)	F-39	AstraZeneca (Vector-based)	NR	- TPE: No abnormal findings - TSG: Low uptake - TUSG: Diffused hypoechoic echotexture with reduced blood flow	- Low TSH (<0.03 mIU/mL), high FT4 (20.47 mIU/mL) and normal level of total T3 (2.22 nmol/L)	- Anti-TPO (777.4 IU/mL) and anti-TG (275.3 IU/mL) were positive, while TRAb (0.2 IU/L) was negative	- No specific treatment was done - 2 months later TFTs returned to the normal range	
Spain (6)[2]	F-38	Moderna (mRNA-based)	- 8 days after 1st dose - Anterior neck pain, palpitations, distal tremor, axillar and inguinal bilateral ganglionic reaction	- TPE: Right lobe was enlarged and painful on superficial palpation - TUSG: An enlarged right lobe with diffused hypoechogenicity - TSG: Low uptake - Pathologic: The existence of giant cells with other inflammatory cells indicated granulomatous thyroiditis	- TFTs: Low TSH (<0.008 µUIU/mL) and elevated FT4 (1.86 ng/dL) and FT3 (5.44 pg/mL)	- Anti-TG (7.40 IU/mL), anti-TPO, and anti-TSHR were negative	- Prednisone, propranolol, and ibuprofen - The symptoms were disappeared and TFTs were normalized	[28]
Greece (7)[3]*	F-35	Pfizer (mRNA-based)	- 12 days after 1st dose - Neck pain, fatigue, palpitations	- TUSG: Raised thyroid dimensions with heterogeneous morphology and hypoechogenic regions - The technetium pertechnetate ($^{99m}TcO_4$) thyroid scan displayed low uptake from the gland parenchyma with abnormal thyroid borders	- Low TSH and elevated FT4	- Anti-TG, anti-TPO, and Anti-TRAB were negative - Elevated CRP (498 mg/L) and ESR (75 mm/h)	- Treatment with prednisolone was initiated - Follow-up and outcome were not reported	[29]
Greece (8)**	F-32	Pfizer (mRNA-based)	- 4 days after 1st dose - Neck pain radiating to the jaw and ear, and mild fatigue	TUSG: Raised thyroid dimensions with heterogeneous morphology and with hypoechogenic regions - The technetium pertechnetate ($^{99m}TcO_4$) thyroid scan showed low uptake from the gland parenchyma with abnormal thyroid borders	- Low TSH and elevated FT4	- Anti-TG, anti-TPO, and Anti-TRAB were negative - Elevated CRP (10 mg/L) and ESR (40 mm/h)	- Treatment with prednisolone was initiated - Follow-up and outcome were not reported	
Turkey (9)[4]	M-67	Sinovac Life Sciences (Inactivated)	- 18 days after 2nd dose - Hypertension and frequent atrial extra beats, fever, weight loss, neck pain	- TUSG: Thyroid dimensions were increased, and the echotexture was heterogeneous, with poorly defined regions of diminished echogenicity and pseudonodules	- Low TSH (0.005 uIU/mL) and elevated FT4 (2.87 ng/dl) and FT3 (8.06 pg/mL)	- Anti-TG, anti-TPO, and anti-TRAB were negative - Elevated CRP (53.9 mg/L) and ESR (67 mm/h)	- Ibuprofen - The symptoms were improved gradually and TFTs were normalized about 2 months later	[30]

Table 2 (continued)

Country (case no.)	Gender–age, years	Vaccine name (Vaccine type)	Onset time of symptoms-Primary clinical symptoms	Physical, histopathological examination of thyroid	Thyroid function tests (TFTs)	Other related laboratory tests	Medication and Outcome	Ref
UK (10)[5]	F-55	AstraZeneca (Vector-based)	- 21 days after 1st dose- - Neck pain and, swelling, headache, sore throat, palpitations, generalized aches	- TUSG: An enlarged thyroid with heterogeneous echotexture	- Low TSH (0.09 mU/L) and elevated FT4 (25.2 pmol/L)	-Anti-TPO (<10 IU/mL) was negative - Elevated CRP (87 mg/L) and ESR (51 mm/h)	- Propranolol to control the palpitations - Ibuprofen and paracetamol for neck pain - After 6 weeks severe hypothyroidism was observed and treatment was done with levothyroxine - 6 weeks later improvement was observed. TRAb was negative, but anti-TG was positive - Levothyroxine dose was raised and the patient remained well	[31]
Turkey (11)	F-35	Sinovac Life Sciences (Inactivated)	- 4 days after 2nd dose - Anterior cervical pain, palpitations and fatigue	- TUSG: Bilateral focal hypoechoic areas with declined blood flow	- TSH (0.473 mIU/L) and FT4 (14.1 pmol/L) were within normal range while FT3 (6.15 pmol/L) was elevated	- Anti-TG (<0.9 IU/mL), anti-TPO (1.2 IU/mL), and anti-TRAB (<.5 IU/L) were negative - Elevated CRP (100.5 mg/L) and ESR (53 mm/h)	- Methylprednisolone - Neck pain and palpitation improved within a day - Patient was under followed up regarding thyroid function	[32]
Turkey (12)	F-34	Sinovac Life Sciences (Inactivated)	- 4 days after 1st dose - Anterior neck pain, fever, fatigue, and palpitations	- TUSG: Bilateral focal hypoechoic areas with declined blood flow	- Low TSH (0.01 mIU/L) and FT4 (5.2 pmol/L)	- Anti-TG (<0.9 IU/mL), anti-TPO (1.2 IU/mL), and anti-TRAB (<1.5 IU/L) were negative - Elevated CRP (6 mg/L) and normal ESR (19 mm/h)	- Methylprednisolone - The patient was under followed up	

Table 2 (continued)

Country (case no.)	Gender–age, years	Vaccine name (Vaccine type)	Onset time of symptoms-Primary clinical symptoms	Physical, histopathological examination of thyroid	Thyroid function tests (TFTs)	Other related laboratory tests	Medication and Outcome	Ref
Turkey (13)	F-37	Sinovac Life Sciences (Inactivated)	- 7 days after 2nd dose - Mild anterior neck pain	-TPE: Mild tenderness on palpation over the right lobe of the gland - TUSG: Bilateral hypoechoic areas with irregular borders and reduced blood flow	- TSH (0.9 mIU/L) and FT4 (13.85 pmol/L) were within normal range while FT3 (6.05 pmol/L) was elevated	- Anti-TG (<0.9 IU/mL), anti-TPO (4.1 IU/mL), and anti-TRAB (<1.5 IU/L) were negative - Normal CRP (2.4 mg/L), while elevated ESR (25 mm/h)	- No treatment - Neck pain was seldom treated with paracetamol - At 4th week, right lobe of the gland was palpated as quite sensitive and enlarged. Thyrotoxicosis and an elevated level of ESR were observed - At the 8th week, the patient became asymptomatic and TFTs were normalized	
USA (14)	F-42	Pfizer (mRNA-based)	- 5 days after 1st dose - Sore throat, palpitations	NR	- Low TSH (0.01 mIU/L) and elevated level of FT4 and FT3	- Elevated ESR (62 mm/h)	- Prednisone, propranolol - Rapid improvement of symptoms was observed after treatment with prednisone	[33]
UK (15)	F-mid age	Pfizer (mRNA-based)	14 days after 2nd dose--Thyroid painful swelling - Thyrotoxicosis signs such as poor sleep, night sweats, weight loss, hyper-defaecation	- TSG: Minimal isotope uptake, consistent with destructive thyroiditis	- Low TSH (<0.010 mU/L) and elevated total T3 (3.3 nmol/L), and FT4 (27 pmol/L)	- Anti-TPO (79.5 IU/mL) and anti-TRAB (<1.2 IU/L) were within the normal range - Elevated CRP (23 mg/L)	- A short course of an NSAID for pain relief - Symptoms resolved over 6 weeks -TFT normalized within 8 weeks	[34]
Cyprus (16)	F-40	Pfizer (mRNA-based)	- 12 h after the 2nd dose - Anterior neck pain, malaise, bony aches, emotional lability, hyperhidrosis, palpitations	- TUSG: A heterogeneous parenchyma, modest enlargement of the gland and diffusely hypoechoic appearances, reduced vascularity and reactive lymphadenopathy	- Low TSH (0.11 mIU/L) and elevated FT4 (33.74 pmol/L)	- Anti-TPO and anti-TRAB were within the normal range - Elevated CRP (174.3 mg/L) and ESR (67 mm/h)	- Prednisolone and propranolol - Full symptom resolution occurred within 24–48 h - One month later, inflammation was reduced and TFTs were normalized	[35]

Table 2 (continued)

Country (case no.)	Gender–age, years	Vaccine name (Vaccine type)	Onset time of symptoms-Primary clinical symptoms	Physical, histopathological examination of thyroid	Thyroid function tests (TFTs)	Other related laboratory tests	Medication and Outcome	Ref
Turkey (17)	F-38	Sinovac Life Sciences (Inactivated)	- 14 days after 2nd dose - Neck swelling pain, fatigue, lack of appetite and sweating in the evening	- TPE: Stage 2 goitre, and pain in right lobe when it was touched - TUSG: An enlargement of the right lobe, with an irregularly defined hypoechoic region beginning at the lateral capsule and spreading into the lobe	- Low TSH (0.008 uIU/mL), and elevated FT3 (12.88 pg/mL) and FT4 (4.65 ng/dL)	- Anti-TPO (9.49 IU/mL) and anti-TG (81.58 IU/mL) were within the normal range - Elevated ESR (78 mm/h), CRP (8.76 mg/L)	- Naproxen sodium and propranolol - The neck pain was lessened - The majority of symptoms were vanished by the 14th day of the follow-up - On the 30th day, levothyroxine started due to a high TSH and low FT4 levels On the 45th day, TUSG displayed thyroid recovery	[36]
Iran (18)	F-34	Bharat Biotech (Inactivated)	- 5 days after 1st dose - Mild fever, palpitation, anterior neck pain	- TPE: Thyroid was painful to the touch and mild swollen - TSG: Reduced radiotracer uptake, and elevated background activity - TUSG: Thyroid heterogeneity and reduced vascularity	- Low TSH (0.05 mIU/L) and elevated T3 (2.7 ng/mL), T4 (20.9 µg/dl)	- The level of anti-TPO and anti-TG was within the normal range - Elevated ESR (60 mm/h), CRP (8.9 mg/L)	- Prednisolone and propranolol - At 7 weeks after treatment, TFTs were normalized	[37]
USA (19)	M-48	Vaccine type was not reported	- 7 days after 2nd dose - Right neck swelling, fevers, palpitations, and weight loss	- TPE: Subtle painful fullness at the level of gland in the anterior right lower of neck - TUSG: Hypoechoic and heterogeneous echotexture with diffuse hypertrophy	- Low TSH (0.01 uIU/mL) and elevated FT4 (3.6 ng/dL)	- Elevated ESR and CRP	- NSAIDs and prednisone - Neck pain and fever resolved within 24 h after starting the medication - ESR, CRP, and FT4 levels were reduced	[19]
USA (20)	F-42	Pfizer (mRNA-based)	-5 days after 1st dose - Palpitations and sore throat	NR	- Low TSH (<0.01 uIU/mL), elevated FT3 (11.8 pg/mL) and FT4 (4.52 ng/dL)	- Anti-TG, TRAb, and TSI were negative - Elevated ESR and CRP	- Prednisone and propranolol - The symptoms were improved	[33]
USA (21)	F-57	Pfizer (mRNA-based)	- 13 days after 2nd dose - Neck pain and swelling	- TPE: TPE: Enlargement of the right gland with diffuse tenderness - TUSG: The right lobe was asymmetrically swollen, hypervascular, and heterogeneous	- Low TSH (0.008 lU/mL), elevated FT4 (1.92 ng/dL) and normal total T3 (137 ng/dL)	- Anti-TG (3.4 U/mL), anti-TPO (<0.5 U/mL) and TRAbs (<1.10 U/L) were negative	- Treatment was stated with propranolol and ibuprofen	[38]

Table 2 (continued)

Country (case no.)	Gender–age, years	Vaccine name (Vaccine type)	Onset time of symptoms-Primary clinical symptoms	Physical, histopathological examination of thyroid	Thyroid function tests (TFTs)	Other related laboratory tests	Medication and Outcome	Ref
UK (22)	M-75	AstraZeneca (Vector-based)	- 14 days after 1st dose - Tenderness and pain in the front of the neck, shortness of breath, palpitations, sleeplessness, and anxiety	NR	- Low TSH (<0.01 µIU/mL), elevated FT3 (7.8 pmol/L) and FT4 (28.2 pmol/L)	- Anti-TG, anti-TPO, and TRAbs were negative - Elevated CRP and ESR	- Ibuprofen - Symptoms improved gradually - One month later, TFTs were normalized	[39]
South Korea (23)	F-39	AstraZeneca (Vector-based)	- 4 days after 2nd dose - Neck pain	- TUSG: Ill-defined hypoechoic lesions - Thyroid scan (Tc-99 m uptake): 3.2	- Low TSH (0.113 µIU/mL), elevated FT4 (31.4 ng/dL)	- Anti-TPO (<15 IU/mL) and anti-TSHR (<1.1 IU/mL) were normal - Elevated CRP (28.60 mg/L) and ESR (63 mm/h)	NR	[40]
South Korea (24)	F-73	AstraZeneca (Vector-based)	- 11 days after 1st dose - Neck pain and fever	- TUSG: Ill-defined hypoechoic lesions	- Low TSH (0.012 µIU/mL), elevated FT4 (94.73 ng/dL)	- Anti-TPO (<15 IU/mL), anti-TG (39.71 IU/mL), and anti-TSHR (1.41 IU/mL) were normal - Elevated CRP (85 mg/L) and ESR (34.65 mm/h)	NR	[40]
Ireland (25)[6]	F-42	Pfizer (mRNA-based)	- 4 days after 2nd dose - Palpitations, fever, neck pain on the left side	- TUSG: Thyroid was diffusely heterogeneous, with some hypoechoic nodules, peripheral and interior vascularity	-TFTs: low TSH (<0.005 mIU/L), elevated FT4 (35.3 pmol/L)	- Anti-TPO (10 IU/mL) and anti-TSHR (<1.10 IU/L) were normal - Elevated CRP (91 mmol/L) and ESR (60 mm/h)	- Prednisolone, propranolol, and ibuprofen - The symptoms were improved in a few days - TFTs were normalized at 4 weeks	[41]
Brazil (26)	F-32	Sinovac Life Sciences (Inactivated)	- 12 h after the 2nd dose - Low visual acuity and pain on movement of the left eye and headache	NR	- Elevated TSH and normal FT4	- Anti-TG and anti-TPO were positive - Elevated CRP and ESR	-Methylprednisolone - The symptoms were improved -TSH was normalized	[42]

Table 2 (continued)

Country (case no.)	Gender–age, years	Vaccine name (Vaccine type)	Onset time of symptoms-Primary clinical symptoms	Physical, histopathological examination of thyroid	Thyroid function tests (TFTs)	Other related laboratory tests	Medication and Outcome	Ref
Turkey (27)	M-41	Pfizer (mRNA-based)	- 8 days after 1st dose - Neck pain, palpitation, fatigue	- TPE: Thyroid was painful, sensitive, and enlarged - TUSG: A reduction in bilateral focal parenchymal echogenicity, heterogeneous tissue with pseudonodular zones and reduced blood flow	- Low TSH (0.01 mIU/L), elevated FT3 (9.35 ng/dL) and FT4 (3.18 ng/dL)	- Anti-TG, anti-TPO, and TRAbs were negative - Elevated CRP (124 mg/L) and ESR (32 mm/h)	- Acetylsalicylic acid, propranolol - Within a few days, symptomatic alleviation was attained - There was asymptomatic overt hypothyroidism, which improved over the next several months	[43]
Turkey (28)	F-40	Pfizer (mRNA-based)	- 6 days after 2nd dose - Neck pain, palpitation and sweating	- TPE: Thyroid was painful and sensitive - TUSG: Heterogeneity in the gland parenchyma, bilateral hypoechoic areas, and declined blood flow	- Low TSH (0.18), elevated FT3 (3.77) and FT4 (1.58)	Anti-TG (160 IU/mL) was positive, while anti-TPO and TRAbs were negative	- Acetylsalicylic acid, propranolol - Symptoms were reduced on the second week	
Turkey (29)	M-40	Pfizer (mRNA-based)	- 4 days after 1st dose - Neck pain, nervousness, fatigue	- TPE: Thyroid was painful, sensitive, and enlarged - TUSG: In the left lobe, a subcapsular heterogeneous hypoechoic thyroiditis part was found	- TSH (1.1 mIU/L), FT3 (3.78 ng/dL) and FT4 (1.55 ng/dL) were normal	- Anti-TG and anti-TPO were negative - Elevated CRP (15 mg/L) and ESR (28 mm/h)	- Ibuprofen was started	
Turkey (30)	F-26	Pfizer (mRNA-based)	- 6 days after 1st dose - Neck pain	- TPE: Tenderness and warmth in left lobe - TUSG: A thyroiditis zone with an unusual boundary, which was hypoechoic, heterogeneous, and had a poor blood flow - TSG: Inhibited 99mTc pertechnetate	- Low TSH (0.01 mIU/L), elevated FT3 (4.6 ng/dL) and FT4 (2.02 ng/dL)	- Anti-TG (562 IU/mL) and anti-TPO (424 IU/mL) were positive, while TRAbs was negative - Elevated CRP (27 mg/L) and ESR (34 mm/h)	- Acetylsalicylic acid, propranolol - Symptoms were reduced on the second week -TFTs and CRP were normalized at the follow-up one month later	
Turkey (31)	F-44	Pfizer (mRNA-based)	- 9 days after 1st dose - Neck pain, headache, palpitation, sweating and tremor	- TPE: Thyroid was painful, sensitive, and enlarged - TUSG: Diffused heterogeneity and hypoechoic zones with reduced blood flow	- Low TSH (0.24 mIU/L), elevated FT3 (4.32 ng/dL) and FT4 (1.58 ng/dL)	- Anti-TPO (362 IU/mL) was positive, while anti-TG and TRAbs were negative - Elevated CRP and ESR	- Ibuprofen - Symptoms were resolved, TFTs and CRP were normalized within the next weeks	

Table 2 (continued)

Country (case no.)	Gender–age, years	Vaccine name (Vaccine type)	Onset time of symptoms-Primary clinical symptoms	Physical, histopathological examination of thyroid	Thyroid function tests (TFTs)	Other related laboratory tests	Medication and Outcome	Ref
USA (32)	M-37	Moderna (mRNA-based)	- 15 days after 1st dose - Neck pain, tachycardia, palpitations	- TUSG: A heterogeneous and swollen thyroid, lacking nodules	- Low TSH (<0.01 mIU/mL), elevated T3 (328 ng/dl) and FT4 (6.96 ng/dl)	-Anti-TG, anti-TPO, and TSI were negative - Elevated ESR (51 mm/h)	- Propranolol, Ibuprofen, and Prednisone - The symptoms were alleviated	[44]
USA (33)	M-35	Pfizer (mRNA-based)	- 10 days after 1st dose -Palpitations and neck pain	- TUSG: A heterogeneous and swollen thyroid, lacking nodules	- Low TSH (0.019 mIU/mL), elevated T3 (233 ng/dl) and FT4 (2.52 ng/dl)	-Anti-Tg, anti-TPO, and TSI were negative	- Propranolol and ibuprofen - The symptoms were alleviated	
USA (34)	F-41	Pfizer (mRNA-based)	- 20 days after 2nd dose - Palpitations and tachycardia	- TUSG: A heterogeneous and swollen thyroid, without nodules	- Low TSH (0.07 mIU/mL), elevated T3 (200 ng/dl) and FT4 (3.04 ng/dl)	-Anti-Tg, anti-TPO, and TSI were negative	- Cardizem and ibuprofen	
Spain (35)	M-67	Moderna (mRNA-based)	- 10 days after 1st dose - Neck pain radiating to ears, asthenia, mild fever, tachycardia	- TUSG: Unstructured thyroid, diffuse hypoechoic areas, decrease vascularity - Thyroid iodine scan: Decreased uptake	- Low TSH (<0.005 mUI/L), elevated FT4 (3.5 ng/dl)	- Anti-TPO (10 UI/mL) was positive, while anti-TG (0.9 UI/mL), and anti-TSHR 3.2 U/L) were positive - Elevated CRP (92 mg/dl) and ESR (70 mm/h)	- Treatment with NSAIDs improved TFTs and decreased acute phase reactants,	[45]
Spain (36)	M-47	Pfizer (mRNA-based)	- 10 days after 1st dose - Neck pain radiating to ears, asthenia, mild fever, tachycardia	- TUSG: Unstructured thyroid, diffuse hypoechoic areas, decrease vascularity - Thyroid iodine scan: Decreased uptake	- Low TSH (<0.005 mUI/L), elevated FT4 (2.6 ng/dl)	- Anti-TG (0.9 UI/mL), anti-TPO (0.5 UI/mL) and anti-TSHR (0.8 U/L) were negative - Elevated CRP (120 mg/dl) and ESR (75 mm/h)	- Treatment with NSAIDs improved TFTs and decreased acute phase reactants,	

Table 2 (continued)

Country (case no.)	Gender–age, years	Vaccine name (Vaccine type)	Onset time of symptoms-Primary clinical symptoms	Physical, histopathological examination of thyroid	Thyroid function tests (TFTs)	Other related laboratory tests	Medication and Outcome	Ref
Turkey (37)	M-61	Sinovac Life Sciences (Inactivated)	- 6 days after 1st dose - Neck swelling in the anterior area and pain radiating to the jaw, palpitations, fever	- TPE: Swelling and tenderness that limited the palpation, largely on the right side of the gland - TUSG: Devascularized patchy hypoechoic parts in both lobes, greater intensely in the right lobe, and diffuse enlargement in the gland	- Low TSH (0.02 mUI/L), elevated FT4 (53.5 pmol/L) and FT3 (14.5 pmol/L)	- Anti-TG (3.41 IU/mL), and anti-TPO (2.32 IU/mL) were negative - Elevated CRP (28.6 mg/L) and ESR (29 mm/h)	- Treatment with Ibuprofen and propranolol remarkably improved the symptoms and laboratory tests during two weeks follow-up	[46]
Turkey (38)	F-32	Pfizer (mRNA-based)	- 3 days after 1st dose - Neck pain, fever, arthralgia	- TPE: Tenderness and swelling in both thyroid lobes, more prominently in the right thyroid lobe with palpation - TUSG: Diffuse swelling of both thyroid glands and patchy hypoechoic areas	- TFTs: Low TSH (<0.01 mUI/L), elevated FT4 (27.8 pmol/L) and normal FT3 (6.61 pmol/L)	- Anti-TG (1.51 IU/mL), anti-TPO (0.51 IU/mL) and anti-TSHR (0.25 IU/L) were negative - Elevated CRP (24.09 mg/L) and ESR (62 mm/h)	- Treatment with methylprednisolone and propranolol remarkably improved the symptoms and laboratory tests at 3 week follow-up	
South Korea (39)	M-34	Moderna (mRNA-based)	- 3 days after 1st dose - Feeling a lump when swallowing, neck pain, weight loss fatigue, headache, muscle weakness	- TPE: Goiter, and pain when gland was touched - TUSG: Enlarged gland and heterogeneous echotexture	- Low TSH (0.005 μIU/mL), elevated FT4 (4.35 ng/dL) and T3 (2.82 ng/dL)	- Anti-TG (11.10 IU/mL) and anti-TPO (9 IU/mL) were positive, while anti-TSHR (0.1 IU/L) was negative - Elevated CRP (6.54 mg/L) and ESR (79 mm/h)	- The symptoms quickly improved after treatment with prednisone - On the 55th day, TFTs were normalized	[47]

Table 2 (continued)

Country (case no.)	Gender–age, years	Vaccine name (Vaccine type)	Onset time of symptoms-Primary clinical symptoms	Physical, histopathological examination of thyroid	Thyroid function tests (TFTs)	Other related laboratory tests	Medication and Outcome	Ref
Greece (40)	F-36	Pfizer (mRNA-based)	- 10 days after 1st dose - Fatigue, palpitations, and neck pain that radiated to the ear and jaw	- TPE: Tenderness and a mild tremor - TUSG: Enlarged gland with heterogeneous echogenicity and bilateral hypoechoic regions - TSG: Low isotope uptake	- TFTs: Low TSH (0.225 mUI/mL), elevated FT4 (22.01 pmol/l) and normal T3 (2.29 nmol/l)	- Anti-TG (292 IU/mL) was positive, while anti-TPO (15.72 IU/mL) and anti-TSHR (0.1 U/L) were negative - Elevated CRP (1.96 mg/dl) and ESR (59 mm/h)	- The symptoms were remitted without medication. The 2nd dose of the vaccine was administrated. 10 days later, the symptoms recurred. Treatment was done with paracetamol and ibuprofen but the symptoms were worsened. TFTs were abnormal and thyroid was enlarged and tender on palpitation. Treatment with methylprednisolone improved the pain and tenderness, and 2 weeks later TFTs were normalized	[48]
Turkey (41)	M-67	Sinovac Life Sciences (Inactivated)	- 19 days after 2nd dose - Neck pain, fever, weight loss, tachycardia	- TUSG: Echotexture was heterogeneous, with weak defined areas of diminished echogenicity and pseudonodules	- Low TSH (<0.005 µIU/mL), elevated FT4 (2.87 ng/dL) and FT3 (8.06 pg/mL)	- Anti-TG, anti-TPO and anti-TSHR were negative - Elevated CRP (53.9 mg/L) and ESR (67 mm/h)	Treatment with an NSAID and beta-blocker improved the symptoms around 2 months	[49]
Turkey (42)	F-47	Sinovac Life Sciences (Inactivated)	- 21 days after 1st dose - Neck pain, tremors, sweating, headache	- TUSG: hypoechoic areas	- TFTs: Low TSH (0.015 µIU/mL), elevated FT4 (2.93 ng/dL) and FT3 (6.84 pg/mL)	- Anti-TG, anti-TPO and anti-TSHR were negative - Elevated CRP (193 mg/L) and ESR (81 mm/h)	Treatment with an NSAID improved the symptoms around 1 month	
Turkey (43)	F-62	Pfizer (mRNA-based)	- 30 days after 2nd dose - Neck pain	- TUSG: Bilateral inflammation, hypo-vascularity, lymphadenopathy	- Low TSH (0.01 µIU/mL), elevated FT4 (2.36 ng/dL) and FT3 (5.18 pg/mL)	- Anti-TG (142 IU/mL) was positive, while anti-TPO and anti-TSHR were negative - Elevated CRP (88.9 mg/L) and ESR (89 mm/h)	Treatment with a NSAID improved the symptoms around 2 months	

Table 2 (continued)

Country (case no.)	Gender–age, years	Vaccine name (Vaccine type)	Onset time of symptoms-Primary clinical symptoms	Physical, histopathological examination of thyroid	Thyroid function tests (TFTs)	Other related laboratory tests	Medication and Outcome	Ref
Turkey (44)	M-44	Pfizer (mRNA-based)	- 15 days after 1st dose - Neck pain, fever, weight loss, sweating	- TUSG: Hypoechoic and heterogeneous parts with blurred borders	- Low TSH (<0.005 µIU/mL), elevated FT4 (3.74 ng/dL) and FT3 (9.55 pg/mL)	- Anti-TG, anti-TPO and anti-TSHR were negative - Elevated CRP (38.4 mg/L) and ESR (72 mm/h)	Treatment with an NSAID improved the symptoms around 2 months	[49]
Turkey (45)	M-26	Pfizer (mRNA-based)	- 37 days after 2nd dose - Neck pain, fever, weight loss, tremors, myalgia	- TUSG: No remarkable changes - TSG: Low 99mTc-perthecnetate uptake	- Low TSH (0.01 µIU/mL), elevated FT4 (2.59 ng/dL) and FT3 (4.62 pg/mL)	- Anti-TG (307 IU/mL) was positive, while anti-TPO and anti-TSHR were negative - Elevated CRP (78 mg/L) and ESR (82 mm/h)	Treatment with a NSAID improved the symptoms around 45 days	
Turkey (46)	F-37	Sinovac Life Sciences (Inactivated)	- 15 days after 2nd dose - Neck pain, dysphagia	- TUSG: Bilateral enlargement, demarcated hypoechoic regions, and reduced vascularity	- Low TSH (0.018 µIU/mL), normal FT4 (0.942 ng/dL), and high FT3 (6.63 pg/mL)	- Anti-TG (>4000 IU/mL), anti-TPO (>4000 IU/mL) and anti-TSHR (>0 U/L) were positive - Elevated CRP (27 mg/L) and ESR (79 mm/h)	Treatment with an NSAID improved the symptoms around 1 month	[49]
Turkey (47)	F-39	Pfizer (mRNA-based)	- 18 days after 1st dose - Weight loss, tachycardia	- TUSG: Hypoechoic and heterogeneous regions with blurred borders, and low vascularization	- Low TSH (<0.005 µIU/mL), elevated FT4 (2.04 ng/dL) and FT3 (5.11 pg/mL)	- Anti-TG (222 IU/mL) was positive, while anti-TPO and anti-TSHR were negative - Elevated CRP (34 mg/L) and ESR (89 mm/h)	Treatment with an NSAID improved the symptoms around 2.5 months	
Turkey (48)	F-40	Pfizer (mRNA-based)	- 15 days after 2nd dose - Neck pain, fever	- TUSG: Inflammation and pseudonodularity	- Low TSH (<0,005 µIU/mL), elevated FT4 (3.05 ng/dL) and FT3 (6.59 pg/mL)	- Anti-TG (542 IU/mL) was positive, while anti-TPO and anti-TSHR were negative - Elevated CRP (51.8 mg/L) and ESR (51 mm/h)	Treatment with an NSAID improved the symptoms around 2 months	

Table 2 (continued)

Country (case no.)	Gender–age, years	Vaccine name (Vaccine type)	Onset time of symptoms-Primary clinical symptoms	Physical, histopathological examination of thyroid	Thyroid function tests (TFTs)	Other related laboratory tests	Medication and Outcome	Ref
Turkey (49)	F-73	Sinovac Life Sciences (Inactivated)	- 30 days after 2nd dose - Neck pain, tachycardia	- TUSG: Diminished in thyroid size, while bilateral inflammation	- Low TSH (0.01 µIU/mL), elevated FT4 (2.32 ng/dL) and normal FT3 (4.22 pg/mL)	- Anti-TG, anti-TPO and anti-TSHR were negative - Elevated CRP (109 mg/L) and ESR (83 mm/h)	Treatment with an NSAID and a beta-blocker improved the symptoms around 1 month	[49]
Turkey (50)	F-30	Pfizer (mRNA-based)	- 30 days after 2nd dose - Neck pain	- TUSG: Diffuse hypoechoic regions, and low vascularity	- TFTs: Low TSH (0.024 µIU/mL), elevated FT4 (4.27 ng/dL) and FT3 (9.03 pg/mL)	- Anti-TG, anti-TPO and anti-TSHR were negative - Elevated CRP (125.4 mg/L) and ESR (79 mm/h)	Treatment with an NSAID improved the symptoms around 2 months	

[1]The patient has a past medical history of colon adenocarcinoma. [2]The patient had a history of asthma and Gilbert disease. [3]The patient had endometritis infection 1 month earlier, which was treated. [4]The patient was under treatment for hypertension. [5]The patient had well-controlled asthma. [6]The patients expressed thyroiditis together with bilateral optic neuritis after COVID-19 vaccination. * and **: The patients were each other's sisters. Abbreviations: ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; TSH: Thyroid-stimulating hormone; T3:Triiodothyronine; T4: Thyroxine. TSI: thyroid-stimulating immunoglobulin; Tc: technetium; TRAbs: Thyrotropin receptor antibodies; FT3: Free T3; FT4: Free T4; TFTs: Thyroid function tests; TPO, thyroid peroxidase; TG: Thyroglobulin; TSHR: Thyroid-stimulating hormone receptor; TPE: Thyroid physical examination; TUSG: Thyroid ultrasonography; TSG: Thyroid scintigraphy. ·: The laboratory measurements were done 26 days after the 2nd dose of vaccine. TSH: (0.27–4.2 uIU/mL), FT4: (0.93–1.70 ng/dL), FT3: (2.3–4.5 pg/mL), ESR: (0–20 mm/h). CRP: (0–5 mg/L), Anti-TG antibodies: (0–115 IU/mL), Anti-TPO antibodies (0–34 IU/mL), and Anti-TSHR antibodies. (0–1.5 U/L)

Table 3 Age of subjects and the onset time of thyroid disorder-related symptoms following COVID-19 vaccination according to the gender of patients

Thyroid disorders	Gender	No (%)	Age, years -mean ± SD Median (min–max)	Cases with disease onset after 1st dose	Onset time after 1st dose (days)	Cases with disease onset after 2nd dose	Onset time after 2nd dose (days)
Subacute thyroiditis	Men	14 (28.0)	49.21 ± 15.34 45.5 (26–75)	10 (71.4%[c])	9.50 ± 4.32[a] 10 (3–15)[b]	4 (28.6%[c])	20.25 ± 12.41[a] 18.5 (7–37)[b]
	Women[e]	36 (72.0)	41.63 ± 10.97 39.5 (26–73)	19 (52.8%[c])	10.73 ± 6.08 10.0 (3–21)	16 (44.4%[c])	11.25 ± 10.57 6.5 (0.5–30)
	Total	50 (100.0)	43.76 ± 12.65 40 (26–75)	29 (58.0%[d])	10.31 ± 5.49 10 (3–21)	20 (40.0%[d])	13.05 ± 11.23 10.5 (0.5–37)
Graves' disease	Men	5 (23.8)	46.40 ± 15.89 46 (30–70)	2 (40.0%[c])	14.50 ± 0.70 14.5 (14–15)	3 (60.0%[c])	19.33 ± 15.01 28.0 (2–28)
	Women	16 (76.2)	49.37 ± 15.44 44 (28–73)	11 (68.8%[c])	15.18 ± 20.08 7.0 (1–60)	5 (31.2%[c])	15.60 ± 11.45 14.0 (5–35)
	Total	21 (100)	48.66 ± 15.20 46 (28–73)	13 (61.9%[d])	15.07 ± 18.33 10 (1–60)	8 (38.1%[d])	17.0 ± 11.96 14.0 (2–35)

[a, b] The onset time expressed as mean ± SD and median (min–max), respectively

[c, d] The percent was calculated within a specified gender and according to the onset time of symptoms, respectively

[e]The onset time of symptoms has not been reported for 1 woman with subacute thyroiditis

A combination of environmental and genetic parameters can contribute to the development of GD. The association of GD susceptibility with certain HLA genes, such as HLA-A*68, HLA-B*08, HLA-DRB1*03, DQB1*02, and DQA1*0501, has been reported [53, 54]. Due to molecular mimicry between thyroid molecules and infectious agents, some bacterial infections (such as *Yersinia enterocolitica* and *Helicobacter pylori*) and viral infections (hepatitis C and congenital rubella) can induce GD by inducing cross-reactive antibodies [53]. Moreover, influenza B virus, Foamy viruses, Parvovirus B19, and Epstein–Barr virus can also contribute to GD development [51]. The association of GD with COVID-19 was also indicated which mainly affected females about 30–60 days from the day of COVID-19 beginning. COVID-19-related hyper-inflammatory responses can trigger the GD development [53].

Table 4 summarizes the main characteristics of the 21 COVID-19 vaccination-related GD cases reported on February 20, 2022. In reported GD cases, the primary clinical symptoms, TFTs, and thyroid ultrasonography or scintigraphy imaging were consistent with GD characteristics. GD is the second COVID-19 vaccination-related thyroid disease, accounting for 31.6% of all cases. According to vaccine type, the distribution of GD cases was: 16/21 (76.2%) after vaccination with mRNA-based vaccines, and 5/21 (23.8%) after vaccination with vector-based vaccines. According to vaccine brand, the distribution of GD patients was: 14/21 (66.7%) of cases after vaccination with the Pfizer vaccine, 4/21 (19.0%) of cases after vaccination with the AstraZeneca vaccine, 2/21 (9.5%) of cases after vaccination with the Moderna vaccine, and 1/21 (4.8%) of cases after vaccination with the Janssen vaccine (Table 4).

GD affects people of all ages, although it is more prevalent among women of reproductive age, with a female-to-male ratio of 5–10:1 [50, 51]. According to the gender of patients, 16/21 (76.2%) of GD cases were women, while 5/21 (23.8%) were men, and the women/men ratio was 3.2:1 (Table 3). The median age was 44 years (ranged: 28–73 years) for GD women and was 46 years (ranged: 30–70 years) for GD men. In 11/16 (68.8%) of women and in 2/5 (40.0%) of men, the onset of GD symptoms occurred following the first vaccine dose, with a median of 7 days (ranged: 1–60 days), and 14.5 days (range: 14–15 days) after vaccination, respectively. In 5/16 (31.2%) of women and in 3/5 (60.0%) of men, the onset of GD symptoms occurred following the second vaccine dose with a median of 14 days (ranged: 5–35 days), and 28 days (ranged: 2–28 days) after vaccination, respectively. Overall, in 13/21 (61.9%) of patients, the onset of GD symptoms occurred following the first vaccine dose with a median of 10 days (ranged: 1–60 days) after vaccination, whereas 8/21 (38.1%) of patients developed the symptoms after the second dose with a median of 14 days (ranged: 2–35 days) after vaccination (Table 3). Previous thyroid abnormalities were observed in two GD cases (Table 4). The reported GD cases were from ten countries, including Spain, Austria, Australia, Mexico, South Korea, China, USA, Thailand, Italy, and Belgium (Table 4).

Other thyroid disorders after COVID-19 vaccination

Table 5 summarizes the main characteristics of 12 cases who expressed focal painful thyroiditis, silent thyroiditis, concurrent GD and SAT, thyroid eye disease, overt

hypothyroidism, atypical subacute thyroiditis, and painless thyroiditis with thyrotoxic periodic paralysis after COVID-19 vaccination. Focal painful thyroiditis was reported in 3 women with a median age of 38.0 years (ranged: 35–59 years) after vaccination with the Pfizer vaccine. Painless or silent thyroiditis is caused by the destruction of thyroid follicles by inflammation, which results in the release of preformed T3 and T4, causing transitory thyrotoxicosis. Patients display thyrotoxicosis symptoms, but unlike the SAT, they have no pain or tenderness in their thyroid. In 2–12 weeks, the thyrotoxic status recovers spontaneously, and the patients either return to euthyroid condition or pass through a temporary hypothyroid stage [64]. Moreover, 3 patients (2 women and 1 man) with a median age of 32.0 years (ranged: 29–34 years) exhibited silent thyroiditis after receiving the first dose of the mRNA-based vaccines (Pfizer and Moderna). Two patients (1 woman and 1 man with 69 and 39 years old, respectively) also displayed concurrent GD and SAT after receiving the first dose of the Pfizer or Janssen vaccines.

Thyroid eye disease (TED), also known as Graves' eye disease or Graves' ophthalmopathy, is a self-limiting orbital inflammatory disorder, that can be sight disfiguring and debilitating. TED is more prevalent among women, and the women/men is about 5.5:1 [65, 66]. The majority of TED patients exhibit biochemical indicators of GD. However, TED can be developed in individuals with hypothyroidism or euthyroidism [65]. The activation of fibroblasts by anti-TSHR and anti-insulin-like growth factor-1 (IGF-1) antibodies contributes to the development of TED. Th1 cells, B cells, macrophages, and mast cells are also infiltrated [67]. Inflammation of the extraocular muscles leads to proptosis and reduced eye movements. The compression of the optic nerve results in optic neuropathy and irreversible eyesight loss [65]. A 50 year old American woman with controlled GD expressed TED at 3 days after vaccination with the 2nd dose of the Pfizer-BioNTech vaccine [68]. The characteristics of 3 other cases from Italy, Spain, and South Korea who expressed overt hypothyroidism, atypical SAT, and painless thyroiditis with thyrotoxic periodic paralysis (TPP) were also exhibited in Table 5.

Mechanisms of COVID-19 vaccination-induced thyroid dysfunctions

The results of this study indicate the occurrence of thyroid disorders following COVID-19 vaccination. The occurrence of the SAT was also reported after vaccination with influenza [72–75], human papillomavirus [76, 77], and hepatitis B [78] vaccines. In 8 cases of SAT reported after influenza vaccination, the symptoms have occurred during 2–60 days following the administration of vaccine [72–75, 79]. All cases were successfully treated and completely recovered [79]. Thyroid cells express the SARS-CoV-2 receptor named angiotensin-converting enzyme 2 (ACE2) as well as transmembrane protease, serine 2 (TMPRSS2) facilitating the virus infectivity [80]. Thus, SARS-CoV-2 can directly attack the thyroid tissue, leading to gland dysfunction during and after COVID-19. SARS-CoV-2 can be considered as a driver of SAT, GD, and Hashimoto's thyroiditis [80]. The results from a systematic review indicated that 13–64% of COVID-19 patients display thyroid dysfunction, and a positive correlation was also found between the COVID-19-related clinical severity and gland abnormalities [81]. The SARS-CoV-2-related SAT mainly occurred in COVID-19 patients with ages 18–63 years and women accounting for 73.6% of the cases [80].

However, the etiology of thyroid abnormalities remains to be proven in future investigations. Just like infections, vaccines can play a role in the development of autoimmune diseases through various mechanisms, such as molecular mimicry, epitope spreading, polyclonal activation, bystander activation, and presentation of cryptic antigenic determinants [5]. If the antigenic content of a vaccine shares structural similarities with autoantigens, then the immune response to the vaccine antigen could extend to host cells exhibiting the similar self-antigen. In genetically susceptible people, the molecular mimicry between the vaccination antigen and thyroid proteins might trigger an autoimmune response [82]. A cross-reactive immune response against the thyroid cells can result from immune responses to SARS-CoV-2-related proteins. It has been indicated that antibody against SARS-CoV-2 S protein potently reacts with TPO [83]. These antibodies may have a role in initiating the autoimmunity via molecular mimicry in susceptible individuals [84]. SARS-CoV-2 S protein, nucleoprotein, and membrane protein, all cross-react with TPO. According to BLAST matching, a number of TPO-related gene sequences exhibit similarity with gene sequences in multiple SARS-CoV-2 proteins. As a result, antibodies generated against SARS-CoV-2 may contribute to the development of autoimmune thyroiditis. As there is a high similarity between genomic sequences of SARS-CoV and SARS-CoV-2, patients with SARS may also exhibit destruction of thyroid follicular cells [82]. Cross-reactivity of SARS-CoV-2 with thyroid proteins might result in the emergence of autoimmune thyroiditis after COVID-19 vaccination. It should be noted that the existence of molecular similarity does not necessarily lead to autoimmunity. In addition to molecular mimicry, other factors, such as tissue injury, prolonged inflammatory reaction, and genetically predisposed background, may be necessary to cause autoimmune disease. For instance, a Lyme disease vaccine consists an antigenic determinant of Borrelia burgdorferi outer surface protein A, which has high similarity to human lymphocyte function-associated antigen-1, a member

Table 4 Characteristics of cases presenting with Graves' disease following COVID-19 vaccination

Country (Case NO.)	Gender–age, years	Vaccine name (vaccine type)	Onset time of symptoms-primary clinical symptoms	Physical, histopathological examination of thyroid	Thyroid function tests (TFTs)	Other related laboratory tests	Medication and outcome	Ref
Spain (1)[1]	F-38	Pfizer (mRNA-based)	- 12 days after 1st dose - Insomnia, nervousness, high sweating	-TPE: Gland enlargement, particularly in the right lobe - TSG: Hyper-functional diffuse goiter - TUSG: An increase in vascularity and a generalized reduction in echogenicity with some echogenic septum	- Low TSH (<0.008 μIU/mL) and elevated FT4 (2.01 ng/dL) and FT3 (7.46 pg/mL)	- Anti-TG (36.57 IU/mL), Anti-TPO (3303.71 IU/mL) and TSI (12.54 UI/mL) were positive	- Methimazole was started	[28]
Austria (2)	F-71	Pfizer (mRNA-based)	- 35 days after 2nd dose - Sweating, palpitations	TUSG: A significant shift with several confluent anechogenic regions and enhanced vascularization - TSG: The left lobe was small, while the right lobe was bigger, with a patchy inhomogeneous tracer distribution. A little increase in uptake was seen	- Elevated FT3 (11.10 pg/mL) and FT4 (3.56 ng/dl)	- Anti-TRAb (4.2 IU/l) were positive	- TFTs were quickly corrected using thyreostatic therapy	[55]
Austria (3)	M-46	Pfizer (mRNA-based)	- 15 days after 1st dose - Blood testing indicated hyperthyroidism	- TSG: Thyroid was slightly enlarged. Large anechogenic regions with enhanced vascularization were seen in the hypoechogenic parenchyma. Inhomogenous accumulation of Tc99m with normal uptake	- FT4 (1.63 ng/dl) was in upper borderline limit and FT3 (5.18 pg/mL) was elevated	- Anti-TRAb (2.9 IU/l) was positive	- TFTs were quickly corrected using thyreostatic therapy	
Australia (4)	F-35	AstraZeneca (Vector-based)	- 5 days after 1st dose - Palpitations, heat intolerance, hyperphagia, tremor	- TUSG: Thyroid was diffusely heterogeneous with enhanced vascularization	- Low TSH (<0.02 mIU/L), elevated T3 (>30 pmol/L) and FT4 (64 pmol/L)	- Anti-TPO (> 1300 IU/mL), anti-TG (33 IU/mL) and TSAb (24 IU/L) were positive	NR	[56]

Table 4 (continued)

Country (Case NO.)	Gender–age, years	Vaccine name (vaccine type)	Onset time of symptoms-primary clinical symptoms	Physical, histopathological examination of thyroid	Thyroid function tests (TFTs)	Other related laboratory tests	Medication and outcome	Ref
Mexico (5)[2]	F-40	Pfizer (mRNA-based)	-4 days after 1st dose - Nausea, vomiting, fatigue, insomnia, and palpitations	-TUSG: Enlargement and hyper-vascularity	- Low TSH (<0.001 mIU/L), elevated T3 (251 ng/dL) and FT4 (3.57 ng/dL)	- Anti-TG (210 Ui/mL), anti-TPO (3405 Ui/mL) and anti-TSHR (16.56 Ui/mL) were positive	- Treatment with propranolol, ivabradine, diltiazem, and thiamazole resulted in a favorable response	[57]
Mexico (6)	F-28	Pfizer (mRNA-based)	-3 days after 1st dose - Anxiety, insomnia, palpitations and distal tremor	TSG: Diffused toxic goiter	-[a]TFTs: Low TSH (<0.001 mIU/L), elevated T3 (216 ng/dL) and FT4 (1.84 ng/dL)	- Anti-TG (33 Ui/mL) was negative, while anti-TPO (833 Ui/mL) and anti-TSHR (5.85 Ui/mL) were positive	- Treatment with propranolol and thiamazole resulted in a favorable response	
South Korea (7)[3]	F-46	AstraZeneca (Vector-based)	- 1 days after 1st dose - Chest pain and dyspnea	- TUSG: Increased vascularity - Thyroid scan (Tc-99 m uptake): 38.6	- Low TSH (0.010 μIU/mL), elevated FT4 (33.92 ng/dL)	- Anti-TG (137.5 IU/mL), anti-TPO (77.72 IU/mL) and anti-TSHR (6.42 IU/L) were positive - Normal CRP (0.05 mg/L) and ESR (5 mm/h)	NR	[40]
South Korea (8)	F-73	AstraZeneca (Vector-based)	- 14 days after 2nd dose - Dyspnea and weight loss	- TUSG: Increased vascularity - Thyroid scan (Tc-99 m uptake): 54.2	- Low TSH (<0.008 μIU/mL), elevated FT4 (73.80 ng/dL)	- Anti-TPO (41.03 IU/mL) and anti-TSHR (6.30 IU/L) were positive	NR	
South Korea (9)	M-34	Janssen (Vector-based)	- 14 days after vaccination - Palpitation and weight loss	- TUSG: Increased vascularity - Thyroid scan (Tc-99 m uptake): NR	- Low TSH (<0.008 μIU/mL), elevated FT4 (26.61 ng/dL)	- Anti-TSHR (4.24 IU/L) was positive - Anti-TG, anti-TPO: NR	NR	

Table 4 (continued)

Country (Case NO.)	Gender–age, years	Vaccine name (vaccine type)	Onset time of symptoms-primary clinical symptoms	Physical, histopathological examination of thyroid	Thyroid function tests (TFTs)	Other related laboratory tests	Medication and outcome	Ref
China (10)	F-40	Pfizer (mRNA-based)	- 5 days after 2nd dose - Palpitation and tachycardia	- TPE: Gland bruit with moderate diffuse goiter - TUSG: An elevated vascularity with a heterogeneous background in gland echogenicity - Thyroid scan (Tc uptake): Increased uptake in both lobes of the gland, high blood flow and large blood pool on dynamic scans	- Low TSH (<0.02 mIU/L), elevated FT3 (30.50 pmol/L) and FT4 (66.6 pmol/L)	- Anti-TPO (239.2 kIU/L), anti-TG (7.2 kIU/L) and TSI (420%) were positive	- Treatment with carbimazole and propranolol improved thyroid function	[58]
USA (11)[4]	F-38	Pfizer (mRNA-based)	- 5 days after 1st dose - Abdominal pain, fever, tachycardia	- TUSG: Thyroid pattern showed a diffuse enlargement with hyper-vascularity and heterogeneous echogenicity	- Low TSH (<0.008 µIU/mL), elevated T3 (10.3 nmol/L) and FT4 (108 pmol/L)	- Anti-TPO (1730 IU/mL), anti-TSHR (32 IU/L), and TSI (>40 IU/L) were positive	- Methimazole and propranolol -FT4 was normalized after 3 months	[59]
USA (12)	F-68	Moderna (mRNA-based)	- 7 days after 1st dose - Pruritic rash	- TUSG: Heterogeneous and hyper-vascularity gland along with 2 nodules	- Low TSH (0.011 µIU/mL), elevated T3 (4.6 nmol/L) and FT4 (30.9 pmol/L)	- Anti-TPO (1149 IU/mL) and anti-TSHR (22 IU/L) were positive	No medication was done, as the patient was asymptomatic After 6 months, TSH was normalized	
USA (13)	M-30	Pfizer (mRNA-based)	- 28 days after 2nd dose - Palpitations, tremor, weight loss, irritability	NR	- Low TSH (<0.005 µIU/mL), elevated T3 (161 pmol/L) and FT4 (22.9 pmol/L)	- Anti-TPO (15 IU/mL) was negative, while TSI (0.95 IU/L) was positive	- Methimazole and atenolol -TSH and FT4 were normalized after 6 weeks	
Thailand (14)	M-70	AstraZeneca (Vector-based)	- 2 days after 2nd dose - Weight loss, dyspnea, myalgia, and palpitation	- TPE: Thyroid was not enlarged	- Low TSH (<0.0036 mIU/L), elevated FT3 (>20 pg/mL) and FT4 (3.19 ng/dL)	- Anti-TSHR (3.23 IU/L) was positive - CRP (1.01 mg/L) was normal	- Methimazole -Favorite response was observed to treatment	[60]

Table 4 (continued)

Country (Case NO.)	Gender–age, years	Vaccine name (vaccine type)	Onset time of symptoms-primary clinical symptoms	Physical, histopathological examination of thyroid	Thyroid function tests (TFTs)	Other related laboratory tests	Medication and outcome	Ref
Italy (15)[5]	M-52	Pfizer (mRNA-based)	- 28 days after 2nd dose - Weight loss, myalgia, dyspnea and palpitation	- TPE: Minor diffuse thyromegaly with no tenderness - TUSG: Thyroid enlargement with heterogeneous echotexture and enhanced vascularization	- Low TSH (<0.004 mIU/L), elevated FT3 (15 ng/L) and FT4 (5.56 ng/dL)	- Anti-TPO (21 IU/mL), anti-TG (30 IU/mL), and TRAb (6.48 IU/L) were positive	-Methimazole and Atenolol - Symptoms were disappeared and TFTs were normalized	[61]
Belgium (16)[6]	F-34	Pfizer (mRNA-based)	- 10 days after 1st dose - Eyelids swelling, weight loss, tremor, sweating, dyspnea	TPE: Diffuse goiter	- Low TSH (<0.01 mIU/L), elevated FT3 (22.09 pmol/l) and FT4 (2.54 ng/dL)	- TRAb (40 IU/L) was positive	Treatment with thiamazole was started	[62]
USA (17)	F-71	Pfizer (mRNA-based)	- 14 days after 2nd dose - Tachycardia, breath shortness, sweating, dizziness, hand tremors, nausea	TUSG: Gland was diffusely enlarged to palpation	- Low TSH (<0.01 μ(IU/mL), elevated FT4 (7.2 ng/dL) and T3 (5.3 ng/mL)	- Anti-TG and anti-TPO were negative, while TSI was positive - Elevated CRP (6.9 mg/L) and ESR (126 mm/h)	The patient exhibited a good response to treatment with methimazole and atenolol	[63]
Spain (18)	F-71	Pfizer (mRNA-based)	- 60 days after 2nd dose - Weight loss, asthenia, atrial fibrillation	- TUSG: Enlarged thyroid, increased vascularity - Thyroid iodine scan: High uptake over both lobes	- Low TSH (<0.005 mUI/L), elevated FT4 (2.3 ng/dl)	- Anti-TG was normal (<0.9 UI/mL), while anti-TPO (30 UI/mL) and anti-TSHR (3.6 U/L) were positive - Normal CRP (5 mg/dl) and ESR (6 mm/h)	- Treatment was done using methimazole - Anti-TSHR remained positive 2 months later, although its level was reduced	[45]
Spain (19)	F-42	Pfizer (mRNA-based)	- 10 days after 1st dose - Weight loss, asthenia, palpitation	- TUSG: Enlarged thyroid, increased vascularity - Thyroid iodine scan: Diffuse markedly increased uptake over both lobes	- Low TSH (<0.005 mUI/L), elevated FT4 (2.9 ng/dl)	- Anti-TPO was normal (2.5 UI/mL), while anti-TSHR (4.39 U/L) was positive - Normal CRP (2.5 mg/dl) and ESR (8 mm/h)	- Treatment was done using methimazole - Anti-TSHR remained positive 2 months later, although its level was reduced	
Spain (20)	F-54	Moderna (mRNA-based)	- 10 days after 2nd dose - Weight loss, asthenia, palpitation	- TUSG: Enlarged thyroid, increased vascularity	- Low TSH (<0.005 mUI/L), elevated FT4 (4.7 ng/dl)	- Anti-TG (55 UI/mL), anti-TPO (30 UI/mL) and anti-TSHR 5.1 U/L) were positive - CRP (10 mg/dl) was in the upper limit and ESR (8 mm/h) was normal	- Treatment was done using methimazole - Anti-TSHR remained positive 2 months later, although its level was reduced	

Table 4 (continued)

Country (Case NO.)	Gender–age, years	Vaccine name (vaccine type)	Onset time of symptoms-primary clinical symptoms	Physical, histopathological examination of thyroid	Thyroid function tests (TFTs)	Other related laboratory tests	Medication and outcome	Ref
Spain (21)	F-46	Pfizer (mRNA-based)	- 50 days after 1st dose - Weight loss, palpitation, irritability	- TUSG: Enlarged thyroid, increased vascularity	- TFTs: Low TSH (<0.005 mUI/L), elevated FT4 (3.2 ng/dl)	- Anti-TG (90 UI/mL), anti-TPO (60 UI/mL) and anti-TSHR 3.2 U/L) were positive - ESR (7 mm/h) was normal	- Treatment was done using methimazole - Anti-TSHR remained positive 2 months later, although its level was reduced	

[1]The patient had schizophrenia. [2]The patient had a previous history of arterial hypertension and COVID-19. [3]The patient expressed Graves' disease with heart failure. [4]According to computed tomography (CT) angiogram carried out one prior, the patient had thyroid gland enlargement. [5]The patient had a history of vitiligo vulgaris and controlled type 2 diabetes mellitus. [6]The patient had a previous history of Graves' disease.

ESR Erythrocyte sedimentation rate; CRP: C-reactive protein, *TSH* Thyroid-stimulating hormone, *T3* Triiodothyronine, *T4* Thyroxine, *TSI* thyroid-stimulating immunoglobulin, *Tc* technetium, *TRAbs* Thyrotropin receptor antibodies, *FT3* Free T3, *FT4* Free T4, *TFTs* Thyroid function tests, *TPO* thyroid peroxidase, *TG* Thyroglobulin, *TSHR* Thyroid-stimulating hormone receptor, *TPE* Thyroid physical examination, *TUSG* Thyroid ultrasonography, *TSG* Thyroid scintigraphy

[a]Thyroid-related tests were performed 4 days after second dose

of leukocyte adhesion molecules [85]. Despite this similarity raised concern about the safety of this vaccine, there was no indication of the elevated risk of arthritis in people who received the Lyme vaccination [86, 87].

If thyroid autoimmunity is triggered by molecular mimicry between COVID-19 vaccines and thyroid antigens, particularly TPO, it remains to explain why a rise in Hashimoto's thyroiditis has not been reported following vaccination. This is likely due to lack of investigation and under-estimating, because SAT and GD are characterized by a rapid onset of clinical symptoms that facilitate their diagnosis. However, Hashimoto's thyroiditis has a chronic and slow course, and usually, hypothyroidism (and thus symptoms) occurs years after the appearance of thyroid-related autoantibodies [52]. To establish whether there is an increase also in Hashimoto's thyroiditis occurrence following SARS-CoV-2 vaccination, prospective studies measuring thyroid-related autoantibodies before and after vaccination as well as comparison with an unvaccinated control group should be conducted.

Bystander activation is an antigen non-specific process that results in the activation of autoreactive T cells [5, 88]. In bystander activation, host tissue damage due to immunopathologic responses or infection leads to the releasing of sequestered autoantigens, activating antigen-presenting cells (APCs) and autoreactive Th cells. After that, activated macrophages and autoreactive T cells produce cytokines, which result in the recruitment of more Th cells promoting local inflammation [5, 88]. Abnormal cytokine and chemokine production can lead to aberrant expression of major histocompatibility complex (MHC) class II molecules, contributing to the pathogenesis of viral diseases, probably through the presentation of autoantigens [84]. Imbalances in various T-cell subsets have been related to some thyroid disorders [89, 90].

Furthermore, COVID-19 vaccine-derived S protein can directly bind to ACE2-expressing thyroid cells, leading to thyroid dysfunction. This possible alternative mechanism may explain the occurrence of thyroid dysfunction following vaccination with all types of SARS-CoV-2 vaccines. In addition to the protective target antigen, vaccines may contain other components, such as adjuvants that potentiate the immune response to the antigen, stabilizers, and preservatives, and sometimes traces of antibiotics to avoid bacterial or/and fungal contaminations during the manufacturing process [5]. The vaccine adjuvants (such as aluminum and thimerosal) were linked to autoantibody levels, such as increased anticardiolipin antibodies after influenza vaccination in lupus patients, as well as anti-thyroid and anti-ovarian antibodies after HPV vaccination [86]. The findings presented here indicate that most cases of thyroid abnormalities, including SAT and GD, were observed after vaccination with mRNA-based vaccines. While the novel mRNA-based vaccines of COVID-19 do not contain adjuvants, the mRNA

Table 5 Characteristics of cases presenting other thyroid disorders following COVID-19 vaccination

Country (case no.)	Thyroid disorder	Gender–age (years)	Vaccine name (vaccine type)	Onset time of symptoms-primary clinical symptoms	Physical, histopathological examination of thyroid	Thyroid function tests (TFTs)	Other related laboratory tests	Medication and outcome	Ref
Spain (1)[1]	Silent thyroiditis	M-32	Pfizer (mRNA-based)	- 10 days after 1st dose - Weight loss, insomnia, nervousness	TUSG: Changes in the parenchyma were consistent with an inflammatory condition - TSG: Thyroid parenchyma activity was completely absent, indicating thyroiditis	- Low TSH (0.01 µIU/mL) and elevated FT4 (2.37 ng/dL),	- Anti-TG (42 IU/mL), Anti-TPO (186 IU/mL) were positive	- Treatment was not given, due to mild symptoms - After 8 weeks, overt hypothyroidism was found, thus treatment was started with levothyroxine	[28]
USA (2)[2]	Thyroid eye disease	F-50	Pfizer (mRNA-based)	- 3 days after 2nd dose- - Eye irritation, tears, orbital pain, proptosis of the eyes bilaterally	- Orbital imaging and thyroid-related tests were consistent with a thyroid eye disease	- Normal levels of TSH, T4, and FT3	- TSI (2.29 UI/mL) was positive	- Treatment with teprotumumab improved the congestive symptoms	[68]
Australia (3)[3]	Focal painful thyroiditis	F-35	Pfizer (mRNA-based)	- 4 days after 1st dose - Right-sided neck pain - After 2nd dose of vaccine, neck pain increased along with fatigue, fevers, and night sweats	- TUSG: Right lobe lesions - Pathology: Atypia, Aspirate was paucicellular with scattered follicular cells, macrophages, and thick colloid fragments - TUSG after 2nd dose: An ill-defined hypoechoic area with raised vascularity	- TSH (2.03 mIU/L) and FT4 (11.4 pmol/L) were normal	-NR	NR	[56]
South Korea (4)[4]	Painless thyroiditis with thyrotoxic periodic paralysis	M-33	Janssen (Vector-based)	- 10 days after vaccination - Both leg weakness	- TUSG: Heterogenous echogenicity, decreased vascularity - Thyroid scan (Tc-99 m uptake): 3.4	- Low TSH (0.012 µIU/mL) and elevated FT4 (37.39 ng/dL)	- Anti-TG (203.3 IU/mL) was positive - Anti-TPO (<15 IU/mL) and anti-TSHR (<1.1 IU/mL) were negative - Elevated CRP (5.16 mg/L) and ESR (37 mm/h)	NR	[40]

Table 5 (continued)

Country (case no.)	Thyroid disorder	Gender–age (years)	Vaccine name (vaccine type)	Onset time of symptoms-primary clinical symptoms	Physical, histopathological examination of thyroid	Thyroid function tests (TFTs)	Other related laboratory tests	Medication and outcome	Ref
Spain (5)	Atypical subacute thyroiditis	M-57	Moderna (mRNA-based)	- 10 days after 1st dose - No neck pain, no swelling, mild fever, asthenia, weight loss, palpitation	- TUSG: Heterogeneous echogenicity, diffuse hypoechoic areas, decrease vascularity	- Low TSH (<0.005 mUI/L) and elevated FT4 (5 ng/dl)	- Anti-TG (0.9 UI/mL), anti-TPO (7.9 UI/mL) and anti-TSHR (0.8 U/L) were negative - Elevated CRP (88 mg/dl) and ESR (30 mm/h)	- Treatment was done with NSAIDs - Follow-up at week 6 revealed a subclinical hypothyroidism and normalization of acute phase reactants, with no symptoms	[45]
Spain (6)	Co-occurrence of Graves's disease and SAT	F-69	Pfizer (mRNA-based)	- 10 days after 1st dose - Neck pain, mild fever, weight loss, palpitation, hand tremor	- TUSG: NR	- Low TSH (<0.005 mUI/L), and elevated FT4 (1.8 ng/dl)	- Anti-TG (0.9 UI/mL), anti-TPO (0.5 UI/mL) were negative, while anti-TSHR (3.8 U/L) was positive - Elevated CRP (120 mg/dl) and ESR (75 mm/h)	- Treatment was done with methimazole and NSAIDs - The patient was still being followed up	
South Korea (7)[5]	Concurrent Graves' disease and Subacute thyroiditis	M-39	Janssen (Vector-based)	- 14 days after vaccination - Neck pain and fever	- TUSG: Diffuse goiter - Thyroid scan (Tc-99 m uptake): 13.8	- Low TSH (<0.012 μIU/mL), elevated FT4 (36.98 ng/dL)	- Anti-TG (295.1 IU/mL) was positive, while anti-TPO (<15 IU/mL) and anti-TSHR (2.90 IU/mL) were negative - Elevated CRP (36.51 mg/dl) and ESR (74 mm/h)	NR	[40]
Italy (8)	Silent thyroiditis	M-34	Moderna (mRNA-based)	- 7 days after 1st dose - Palpitations and weight loss	- TUSG: Normal volume, with mild hypoechogenicity, diffuse heterogeneous echotexture and decreased blood flow signals, without thyroid nodules Thyroid scan (Tc-99 m uptake): Low	- Low TSH (<0.01 μUI/mL), elevated FT4 (24 pmol/L)	- Anti-TG (<0.9 UI/mL), anti-TPO (<9 UI/mL), and anti-TSHR (<0.8 U/L) were negative - Normal CRP (<0.06 mg/dl) and ESR (5 mm/h)	- No specific treatment was initiated - The TFTs were normalized 33 days after vaccination	[69]

Table 5 (continued)

Country (case no.)	Thyroid disorder	Gender–age (years)	Vaccine name (vaccine type)	Onset time of symptoms-primary clinical symptoms	Physical, histopathological examination of thyroid	Thyroid function tests (TFTs)	Other related laboratory tests	Medication and outcome	Ref
Italy (9)	Silent thyroiditis	F-29	Moderna (mRNA-based)	- 7 days after 1st dose - Palpitations and weight loss	- TUSG: Normal volume with mild hypoechogenicity, diffuse heterogeneous echotexture and decreased blood flow signals, with a small thyroid nodule in the left lobe Thyroid scan (Tc-99 m uptake): Low	- Low TSH (<0.03 µUI/mL), normal levels of FT3 (5.8 pmol/L) and FT4 (21.7 pmol/L)	- Anti-TG (<0.9 UI/mL), anti-TPO (< UI/mL), and anti-TSHR (<0.8 U/L) were negative - Normal CRP (<0.06 mg/dl) and ESR (10 mm/h)	- No specific treatment was initiated - The TFTs were normalized 29 days after vaccination	
Japan (10)	Focal painless thyroiditis	F-38	Pfizer (mRNA-based)	- 17 days after 1st dose - Palpitations	- TUSG: Enlarged gland, heterogeneous, hypoechogenic, and normal Doppler flow - TSG: Reduced uptake	- Low TSH (<0.005 µUI/mL), elevated FT4 (4.08 ng/dL) and FT3 (7.30 pg/mL)	- Anti-TG (299 IU/mL) and anti-TPO (350 IU/mL) were positive, while anti-TSHR (1.16 IU/L) was negative	- The patient did not receive the 2nd dose of the vaccine - After 5 months, TFTs were normalized without treatment	[70]
Japan (11)	Focal painless thyroiditis	F-59	Pfizer (mRNA-based)	- 10 days after 2nd dose	- TUSG: Thyroid was bilateral, heterogeneous, hypoechoic with normal blood flow - TSG: Reduced uptake	- Low TSH (0.01 µUI/mL), elevated FT4 (2.35 ng/dL) and FT3 (5.42 pg/mL)	- Anti-TG (430 IU/mL) was positive, while anti-TPO (<16 UI/mL) and anti-TSHR (0.98 IU/L) were negative	- Two months after vaccination,—TFTs were normalized without treatment	
Italy (12)[6]	Overt hypothyroidism	F-61	Pfizer (mRNA-based)	- 21 days after 2nd dose - Swelling of neck and face, without pain, asthenia, and weight gain	- TUSG: Enlargement of thyroid with a diffuse hypoechoic	- High TSH (89.7 mUI/mL), low FT3 (undetectable) and low FT3 (5.1 pmol/L)	- Anti-TG (7671 mIU/mL) and anti-TPO (>2000 mUI/mL) were positive, while anti-TSHR (1.2 IU/L) was negative	- Treatment with levothyroxine reduced thyroid volume and improved neck swelling, however, hypoechoic pattern of the gland, as well as body weight, slightly changed	[71]

[1]The patient had type 1 diabetes. [2]The patient had a previous history of managed Graves' disease without ophthalmopathy symptoms. [3]The patient had a previous history of left hemithyroidectomy for a benign nodule. [4]The patient had a history of asymptomatic COVID-19 infection 3 months before to first vaccine dose. [5]The patient had a history of subclinical hypothyroidism. [6]The patient smoked 15 cigarettes daily without previous thyroid disease or other autoimmune. Abbreviations: ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; TSH: Thyroid-stimulating hormone; T3:Triiodothyronine; T4: Thyroxine. TSI: thyroid-stimulating immunoglobulin; Tc: technetium; TRAbs: Thyrotropin receptor antibodies; FT3: Free T3; FT4: Free T4; TFTs: Thyroid function tests; TPO, thyroid peroxidase; TG: Thyroglobulin; TSHR: Thyroid-stimulating hormone receptor; TPE: Thyroid physical examination; TUSG: Thyroid ultrasonography; TSG: Thyroid scintigraphy

could act as an adjuvant due to its intrinsic immunostimulatory properties [91]. Indeed, the possible recognition of mRNA by endosomal Toll-like receptors (such as TLR7 and TLR8) and cytoplasmic sensors such as retinoic acid-inducible gene I (RIG-I) [92, 93] potentiate the inflammatory reactions that amplify the autoimmune responses in genetically susceptible people.

The post-vaccination SAT and GD occurred with a greater rate in women compared to men. Like most autoimmune diseases, these observations can be attributed to the immunological effects of sex hormones. For example, testosterone promotes, while estrogen reduces the regulatory T (Treg)-cell-related activity [94]. The association of the vaccine-induced autoimmunity and human leukocyte antigen (HLA) gene has been also indicated. Furthermore, genetic polymorphisms in the cytokine genes may cause overexpression of cytokines and hyper-inflammatory responses, resulting in unfavorable consequences [86, 95, 96].

Conclusion

The reports concerning the incidence rate of vaccination-induced autoimmune responses may be under-estimated [86]. Because an effective monitoring system is missing, and the vaccination status of the majority of patients with newly diagnosed thyroid dysfunction is not checked. The world is currently undertaking the greatest mass vaccination, and cases of thyroid abnormalities will undoubtedly arise, either as a result of the vaccine-associated and/or vaccine-independent processes. Thus, prospective studies using vaccinated and unvaccinated groups should be conducted to establish a valid risk/benefit assessment and reliable figures of thyroid disorders. Fortunately, a favorable outcome was observed in nearly all cases of COVID-19 vaccination-associated thyroid dysfunction after treatment.

Globally, there is no exact information regarding the coverage of each type of COVID-19 vaccine. As of February 22, 2022, the numbers of administered doses based on the vaccine type in European countries are as follows: Pfizer: 592.37 million doses, Moderna: 143.35 million doses, AstraZeneca: 67.39 million doses, Johnson & Johnson: 18.5 million doses, Sinopharm: 2.29 million doses, and Sputnik V: 1.85 million doses [97]. Therefore, the increased incidence of thyroid disorders after vaccination with a particular vaccine may be attributed to the higher coverage of that vaccine. In addition, post-vaccination thyroid complications may be more monitored in some countries. It should be noted that reports of thyroid disorders following vaccination do not prove causality. More longitudinal studies using control groups are necessary to paint a clearer picture of the subject. Physicians should be knowledgeable about the typical and atypical clinical manifestations of these thyroid disorders to diagnose and manage possible cases and mitigate adverse events.

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Declarations

Conflict of interest The authors have no conflict of interest.

Research involving human participants and/or animals Not applicable.

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