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REVIEW

Autoimmune and inflammatory thyroid diseases following vaccination with SARS-CoV-2 vaccines: from etiopathogenesis to clinical management

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Abstract

Since the Covid-19 pandemic emerged in 2019, several adenoviral-vectored, mRNA-based and inactivated whole-virus vaccines have been developed. A massive vaccination campaign has been undertaken around the world, and an increasing number of SARS-CoV-2 vaccine-induced thyroid diseases have been described in the literature. Subacute thyroiditis has been reported in 52 patients, mean age 45.5 ± 1.8 years, mainly in women ($n = 39$). Graves' disease is more frequent in women ($n = 22$) than in men ($n = 10$), mean age 46.2 ± 2.6 years, reported as new onset, recurrent or exacerbation of well-controlled hyperthyroidism. The mean time to symptoms onset is 9.0 ± 0.8 days in subacute thyroiditis, and 15.1 ± 2.6 days in Graves' patients. Rare patients ($n = 6$) present silent or painless autoimmune thyroiditis. Thyroid function and autoimmune tests, inflammatory markers, thyroid echography with colour flow Doppler, radio-activity uptake on thyroid scan, medical treatment and follow-up are described and compared in patients with SARS-CoV-2 vaccine-induced thyroid diseases. The underlying pathogenic mechanisms of vaccine-induced thyroid diseases, molecular mimicry (various SARS-CoV-2 proteins sharing a genetic homology with a large heptapeptide human protein) or autoimmune/inflammatory syndrome induced by adjuvants (ASIA) are discussed in the context of predisposition or genetic susceptibility. The benefits of SARS-CoV-2 vaccination far outweigh the potential vaccine-induced adverse effects, but clinicians should be aware of possible autoimmune and inflammatory thyroid diseases, and can advise patients to seek medical assistance when experiencing anterior neck pain, fever or palpitations following SARS-CoV-2 vaccines. Further studies are warranted to investigate the etiopathogenesis and to clarify the factors which predispose patients to SARS-CoV-2 vaccine-induced thyroid diseases.

Keywords SARS-CoV-2 · Vaccines · Graves' disease · Subacute thyroiditis · Autoimmune thyroiditis

Introduction

Since the emergence of the new Coronavirus (Covid-19) pandemic in December 2019, several vaccines have been approved and rapidly developed in an attempt to protect populations from Covid-19 infection. A massive vaccination campaign using several types of vaccines against SARS-CoV-2 has been undertaken around the world with benefits to morbidity and mortality, but an increasing number of autoimmune and inflammatory-related side effects are described (thrombotic thrombocytopenia, Guillain Barré syndrome, myocarditis/pericarditis, type 1 diabetes mellitus, premature ovarian failure, adrenal insufficiency). It is noteworthy that several thyroid disorders such as Graves' disease, subacute thyroiditis and silent (painless) thyroiditis have been reported following the first or second dose of SARS-CoV-2 vaccines. Reports of such potential adverse events have been given in patients from countries in Asia, Europe, South and North America, and these are becoming more frequent in recent weeks.

Several pharmaceutical companies have developed SARS-CoV-2 vaccines:

adenoviral-vectored vaccine (Oxford-Astra Zeneca, Johnson and Johnson Jansen),

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mRNA-based vaccine (Pfizer-BioNTech, Moderna), inactivated whole-virus vaccine (Coronovac, Sinovac Life Sciences, Sinopharm BIPP2).

Adenoviral-vectored and mRNA vaccines encoding the SARS-CoV-2 spike protein antigen and inactivated whole-virus vaccine elicit antibodies and T cell response to protect against Covid-19. Most vaccines contain adjuvants which are used to increase the immunogenicity and the response to vaccination. It is suggested that in individuals who are genetically susceptible, SARS-CoV-2 vaccines can induce autoimmune and inflammatory adverse reactions by activating autoimmune cascades and pathways.

Methods

The systematic review of the literature was conducted on original articles published from July 2021 to the end of January 2022, via the PubMed online databases using the following keywords: thyroid, Graves' disease, subacute thyroiditis, chronic thyroiditis, SARS-CoV-2 and vaccines.

Case reports and cases series recording data on thyroid diseases (Graves' disease, subacute or chronic thyroiditis) in patients after SARS-CoV-2 vaccination were eligible for inclusion. Articles that were not written in English were excluded.

For each included article we recorded reference data (authors, journal, year of publication), and for each patient we collected demographic data (sex, age), previous history of autoimmune or thyroid disease, type of administered vaccines (mRNA vaccine, inactivated virus or vector vaccine), timing of thyroid disease onset following vaccination, signs and symptoms at presentation, laboratory tests (TSH, freeT4, anti-TPO, anti-Tg, anti-TSH receptor antibodies, C-reactive protein, erythrocyte sedimentation rate) and other diagnostic examens (ultrasonography with colour flow doppler, thyroid scintigraphy), specific medical therapies and clinical or hormonal follow-up.

Patients with SARS-CoV-2 vaccine-induced thyroid diseases

Subacute thyroiditis

Subacute thyroiditis usually occurs following viral upper respiratory tract infection, and several patients have been described as presenting with this following Covid-19 infection. This self-limited inflammatory and benign thyroid disease usually follows a triphasic pattern: an initial thyrotoxic phase is characterised by severe pain, swelling and a tender thyroid gland with follicular destruction and release of preformed thyroid hormones responsible for thyrotoxicosis, with signs of systemic inflammation and high inflammatory markers. Then granulomatous thyroid tissue can be associated with transient hypothyroidism, and followed by spontaneous resolution with a recovery phase.

The first cases of subacute thyroiditis associated with SARS-CoV-2 vaccines were described by Iremli et al. [1] in 3 female patients, and cases or case series continued to be reported, with there being 52 patients at the time of writing this manuscript (Table 1) [1–23]. The median age of the patients is 45.5 ± 1.8 years, ranging from 26 to 75, and subacute thyroiditis is more prevalent in women ($n = 39$, 75%) than in men ($n = 13$, 25%). Seventeen percent of patients have a personal history of thyroid disease (nodular thyroid disease $n = 5$, subacute thyroiditis $n = 2$, Hashimoto' thyroiditis $n = 1$). Patients develop subacute thyroiditis after receiving mRNA (60%), inactivated whole-virus (25%) and adenoviral-vectored (13.5%) vaccines, either after the first (62%) or the second (38%) dose. The mean time from vaccination to symptom onset is 9.0 ± 0.8 days, with a range of 1–21. The most frequent symptom is neck pain (97%) followed by signs of thyrotoxicosis (palpitations 71%, weight loss 29%, night sweats 12.5%, tremor 12.5%) and signs of systemic inflammation (fever 54%, fatigue 34.5%, headaches 11.5%, myalgia 7%).

Thyrotoxicosis is confirmed by increased thyroid hormones (free T4 = 30.0 ± 2.8 pmol/L, free T3 = 34.3 ± 10.8 pmol/l) with decreased TSH (0.29 ± 0.10 mU/L) concentrations. In all patients except one (concurrent subacute thyroiditis and Graves' disease) anti TSH-receptor antibodies are negative, and TPO-antibodies are present in only 4 (9.5%) patients. Erythrocyte sedimentation rate (53 ± 3 mm/hour) and C-reactive protein (87 ± 14 mg/L) are significantly increased ($p < 0.02$) compared to SARS-CoV-2 vaccine-induced Graves' disease. Ultrasound sonography with colour flow Doppler, in the majority of patients reveals normal or increased heterogeneous thyroid gland with hypoechoic areas and decreased blood flow, and decreased uptake on thyroid scan. Finally, at the inflammatory phase of the subacute thyroiditis, post-surgical pathology (destroyed follicles, presence of macrophages and inflammatory cells) [6] or cytology (mononuclear lymphocytes infiltrate, presence of macrophages and multinucleated giant cells) examen after fine needle aspiration [14, 17, 20, 21] are compatible with a diagnosis of subacute thyroiditis.

SARS-CoV-2 vaccine-induced subacute thyroiditis appears to follow a clinical course and responds to conventional treatment in an identical way to classic subacute thyroiditis. Patients with palpitations or tachycardia are given beta-adrenergic blockers (31%). During the inflammatory phase, patients were initially given non-steroidal anti-inflammatory drugs (52%) and/or oral glucocorticoids (48%), which were considered when the patient presented

Table 1 Clinical characteristics, laboratory results and imaging findings of patients with SARS-CoV-2 vaccine-induced subacute thyroiditis

N°	Author (Ref)	Gender	Age	Type of vaccine	Dose	Time (days)	Neck pain	TSH	FT4	ESR	CRP	Thyroid ultrasound, Colour flow Doppler	Thyroid scintigraphy	Treatment	Follow-up
1	Iremli [1]	F	35	Inactivated virus	2nd	4	Y	0.47	14.1	53	100.5	Bilateral focal hypoechoic area, decreased blood flow	ND	Methylprednisolone, propanolol	Disappeared within 1 day, recovery 4 weeks
2	Iremli [1]	F	34	Inactivated virus	1st	4	Y	0.01	5.2	19	6	Bilateral focal hypoechoic area, decreased blood flow	ND	Methylprednisolone, propanolol	Myalgia, neck pain during taperring methylprednisolone, recovery 10 weeks
3	Iremli [1]	F	37	Inactivated virus	2nd	7	Y	0.9	13.85	25	2.4	Bilateral focal hypoechoic area, decreased blood flow	ND	Rarely paracetamol	No treatment, recovery 8 weeks
4	Oyibo [2]	F	55	Adenovirus vectored	1st	21	Y	0.09	25.2	51	87	Enlarged, heterogenous thyroid gland		Propanolol, ibuprofen, paracetamol	Hypothyroidism at 6 weeks treated by LT4, recovery 12 weeks
5	Franquemont [3]	F	42	mRNA	1st	5	Y	<0.01	58.95	62	NA			Prednisone, propanolol	
6	Schimmel [4]	F	57	mRNA	2nd	1	Y	0.008	24.7	NA	NA	Enlarged, heterogenous, hypervascular right lobe thyroid		Ibuprofen, propanolol, prednisone	
7	Saygili [5]	F	38	Inactivated virus	2nd	14	Y	0.008	59.8	78	87.6	Increased size, hypoechoic area		Naprozen sodium, propanolol	Hypothyroidism at 1 month, levothyroxine treatment
8	Sigstad [6]	F	30	mRNA	1st	6		Normal	13	NA	NA	Thyroiditis, hypoechoic nodule			
9	Jeeyavudeen [7]	F	NA	mRNA	2nd	14	Y	<0.01	27	NA	23		Minimal isotope uptake	NSAID	Resolution symptoms 6 weeks, euthyroid 8 weeks
10	Soltanpoor [8]	F	34	Inactivated virus	1st	5	Y	0.05		60	9.8	Heterogeneity, decreased vascularity	Moderate to severely decreased uptake	Prednisone, propanolol	Euthyroid state at 7 weeks
11	Ratnayake [9]	M	75	Adenovirus vectored	1st	14	Y	0.01	28.2	NA	NA		Marked reduction of uptake	Ibuprofen	Normal thyroid function at 1 month
12	Sozen [10]	M	41	mRNA	2nd	3	Y	0.01	40.9	32	124	Heterogeneous, hypoechogenicity, decreased blood flow		Acetylsalicylic acid, propanolol	Transient hypothyroiidsm, complete remission, eythyroid
13	Sozen [10]	F	40	mRNA	2nd	6	Y	0.18	20.34	80	34	Heterogeneity, hypoechoic areas, decreased blood flow		Acetylsalicylic acid, propanolol	Control at 1 month
14	Sozen [10]	M	40	mRNA	1st	4	Y	1.1	19.95	28	15	Heterogenous, hypoechoic areas		Ibuprofen	Control at 2 weeks
15	Sozen [10]	F	26	mRNA	1st	20	Y	0.01	26	34	27	Heterogeneous, hypoechogenicity, decreased blood flow	Suppressed thyroid gland	Acetylsalicylic acid, propanolol	Control at 1 month, euthyroid
16	Sozen [10]	F	44	mRNA	2nd	9	Y	0.24	20.33	44	18	Heterogeneity, hypoechoic areas, decreased blood flow		Ibuprofen	Control at 1 month
17	Kyriacou [11]	F	40	mRNA	2nd	1	Y	0.11	33.74	67	174.3	Heterogeneity, hypoechoic areas, decreased blood flow		Prednisone, propanolol	Resolution symptoms in 2 days, euthyroid TSH 2,74 1 month
18	Patel [12]	M	48		2nd	7	Y	0.01	46.34	Increased	Increased	Heterogeneous, hypoechogenicity, goiter		NSAID, prednisone during 1 week	Resolution symptoms in 1 day
19	Sahin tekin [13]	M	67	Inactivated virus	2nd	17	Y	0.005	36.9	67	5.9	Hypoechogenicity, heterogenous, pseudonodular areas		Ibuprofen	Relief of symptoms in few days
20	Bornemann [14]	F	26	Adenovirus vectored	1st	16	Y	1.75	11.97	NA	29.4	Heterogenous, hypoechoic areas, decreased blood flow		Ibuprofen, prednisolone	

Table 1 (continued)

N°	Author (Ref)	Gender	Age	Type of vaccine	Dose	Time (days)	Neck pain	TSH	FT4	ESR	CRP	Thyroid ultrasound, Colour flow Doppler	Thyroid scintigraphy	Treatment	Follow-up
21	Bornemann [14]	F	49	mRNA	1st	14	Y	0.01	12.1	NA	21.9	Normal size, hypoechoic areas, decreased vascularity		Ibuprofen, prednisolone	Resolution symptoms 2 weeks, euthyroid 6 weeks TSH 0,83 Symptoms improved in 2 weeks
22	Lee [15]	F	39	Adenovirus vectored	2nd	4	Y	0.113	31.4	63	28.6	Ill defined, hypoechoic lesion	Decreased uptake		
23	Lee [15]	F	73	Adenovirus vectored	1st	11	Y	0.012	94.7	85	34.6	Ill defined, hypoechoic lesion			
24	Lee [15]	M	39	Adenovirus vectored	1st	14	Y	0.012	36.98	74	36.5	Ill defined, hypoechoic lesion	Thyroid scan uptake increased		
25	Siolos [16]	F	51	mRNA	1st	4	Y	0.08	24.84	103	135		Markedly decreased thyroid uptake	Prednisolone	Resolution fever and neck pain in 2 days
26	Pujol [17]	F	38	mRNA	1st	8	Y	<0.008	23.94	NA	NA	Enlarged right lobe, diffuse hypoechogenicity	Very low uptake	Ibuprofen, propanolol, prednisone	Improvement of symptoms in 1 week
27	Pandya [18]	M	37	mRNA	1st	15	Y	<0.01	89.58	51	NA	Enlarged and heterogenous thyroid gland	Decreased uptake at 4 and 24 hr	Ibuprofen, propanolol, prednisone	
28	Pandya [18]	M	35	mRNA	1st	10	Y	0.07	39.13	NA	NA	Enlarged and heterogenous thyroid gland		Ibuprofen, propanolol	
29	Pandya [18]	F	41	mRNA	2nd	20		0.019	32.43	NA	NA	Enlarged and heterogenous thyroid gland	Decreased uptake	Ibuprofen, diltiazen	
30	Pla Pleris [19]	M	57	mRNA	1st	<14	No	<0.005	64.36	30	88	Heterogeneous echogenicity, diffuse hypoechoic area, decreased vascularity	NA	NSAID	Improvement in 2 weeks, subclinical hypothyroidism
31	Pla Pleris [19]	M	67	mRNA	1st	<14	Y	<0.005	45.05	60	120	Unstructured thyroid, diffuse hypoechoic area, decreased vascularity	Decreased uptake	NSAID	Improvement in 2 weeks, subclinical hypothyroidism at 4 weeks
32	Pla Pleris [19]	M	47	mRNA	1st	<14	Y	0.005	33.46	70	92	Unstructured thyroid, diffuse hypoechoic area, decreased vascularity	Decreased uptake	NSAID	Improvement of symptoms in 2 weeks, normal thyroid function at 5 weeks
33	Pla Pleris [19]	F	69	mRNA	1st	<14	Y	<0.005	23.17	75	120	Enlarged thyroid gland, heterogeneous echogenecity, diffuse hypoechoic pattern	NA	Methylprednisolone, NSAID	
34	Das [20]	F	47	Adenovirus vectored	1st	14	Y	0.06		NA	NA	Bulky thyroid with bilateral hypoechoic nodules	No tracer uptake	Propanolol,	Improvement and complete rsolution and normal TSH at 8 weeks
35	Raven [21]	F	35	mRNA	1st	4	Y	2.03	11.4	NA	NA	11 mm right thyroid nodule	NA	No treatment	Resolution of pain in 2 weeks
36	Chatzi [22]	F	35	mRNA	1st	12	Y			75	498	Increased gland, heterogeneous appearance, hypoechogenic regions	Low uptake	Prednisolone	
37	Chatzi [22]	F	32	mRNA	2nd	4	Y			40	10	Increased gland, heterogeneous appearance, hypoechogenic regions	Low uptake	Prednisolone	
38	Oguz [23]	F	42	mRNA	1st	4		<0.015	51.4	74	44.4	Patchy heterogenous hypoechoic areas in right lobe	Partially suppressed thyroid uptake	NSAID	Remission 14 weeks
39	Oguz [23]	F	48	Inactivated virus	2nd	1		0.031		48	58	Patchy heterogenous, hypoechoic areas	NA	Prednisolone	Remission 5 weeks

Table 1 (continued)

N°	Author (Ref)	Gender	Age	Type of vaccine	Dose	Time (days)	Neck pain	TSH	FT4	ESR	CRP	Thyroid ultrasound, Colour flow Doppler	Thyroid scintigraphy	Treatment	Follow-up
40	Oguz [23]	F	47	mRNA	1st	10		0.54	13.42	55	48.5	Patchy heterogenous, hypoechoic areas	NA	Paracetamol	Remission 13 weeks
41	Oguz [23]	F	72	mRNA	2nd	15			11.81	10	7.7	Patchy heterogenous, hypoechoic areas in the right lobe	NA	No treatment	Remission 5 weeks
42	Oguz [23]	M	50	Inactivated virus	1st	1		0.127	11.4	41	10.2	Ill-edged heterogenous hypoechoic area in right lobe	NA	NSAID	Remission 6 weeks
43	Oguz [23]	F	61	Inactivated virus	2nd	15		4.44	10.99	34	11.6	Patchy heterogenous, hypoechoic areas	NA	Methylprednisolone	Remission 20 weeks
44	Oguz [23]	F	36	Inactivated virus	2nd	4		0.47	19.11	53	105	Patchy heterogenous, hypoechoic areas, decreased vascularisation	NA	Methylprednisolone	No remission
45	Oguz [23]	F	38	Inactivated virus	2nd	7		0.018	26.1	44	3	Patchy heterogenous, hypoechoic areas, decreased vascularisation	NA	No treatment	Remission 11 weeks
46	Oguz [23]	F	38	mRNA	1st	10		<0.01	51.48	55	136.3	Patchy heterogenous, hypoechoic areas	NA	NSAID	Remission 4 weeks
47	Oguz [23]	F	38	Inactivated virus	1st	13		0.032	12.23	42	19	Patchy heterogenous, hypoechoic areas	NA	Paracetamol, NSAID	Remission 12 weeks
48	Oguz [23]	F	43	mRNA	2nd	7		0.01	37.7		429	Patchy heterogenous, hypoechoic areas, decreased vascularisation	Low thyroid uptake (24 h RAIU 1%)	Methylprednisolone, NSAID	Remission 11 weeks
49	Oguz [23]	F	60	mRNA	1st	3		0.6	14	33	52	Patchy heterogenous, hypoechoic area in left lobe	NA	No treatment	Not in remission
50	Oguz [23]	F	46	mRNA	1st	1		0.43	14.08	60	17	Patchy heterogenous, hypoechoic areas	NA	NSAID, methylprednisolone	Remission 18 weeks
51	Oguz [23]	F	34	Inactivated virus	1st	4		0.03	31.65	18	6	Patchy heterogenous, hypoechoic areas, decreased vascularisation	NA	Methylprednisolone and then methimazole after GD diagnosis	Not in remission
52	Oguz [23]	M	71	mRNA	1st	10		0.038	17.27	67	36.5	Patchy heterogenous, hypoechoic areas, decreased vascularisation	NA	Prednisolone	Not in remission

Age in years, Time in days, TSH in mU/L, and FT4 in pmol/l

Gender *F* female, *M* male, *Y* yes, *N* not present, *ESR* Erythrocyte sedimentation rate (mm/h), *CRP* C-reactive protein (mg/l), *NSAID* non-steroidal anti-inflammatory drug, *NA* Not available

moderate to severe cervical pain or when there was no response to initial treatment with non-steroidal anti-inflammatory drugs. Ten percent of patients are followed with no medical treatment. Symptom resolution is observed in a few weeks, and transient hypothyroidism is observed in 9.6% of patients, subsequently treated by levothyroxine when they develop symptomatic, prolonged hypothyroidism. In the vast majority of patients, thyroid function tests return to the normal range and they do not relapse. The median recovery time of vaccine-induced subacute thyroiditis is 7 weeks ranging from 2 to 20 weeks.

Graves' disease

Graves' disease is a Th1-mediated immune disease caused by the stimulation of the follicular thyroid cells by anti-TSH receptor antibodies. Graves' disease is the most common cause of hyperthyroidism in young adults, mainly in women. After SARS-CoV-2 vaccination, the mean age of Graves' disease patients is 46.2 ± 2.6 years, ranging from 28 to 73 (Table 2) [15, 17, 19, 21, 23–35]. Graves' hyperthyroidism is more frequent in women ($n = 22$) than in men ($n = 10$). Seven patients have a personal history of thyroid disease, autoimmune hypothyroidism ($n = 3$) or past history of Graves' disease ($n = 3$). Graves' hyperthyroidism following SARS-CoV-2 vaccination is reported as:

- new onset or newly diagnosed Graves' disease with no previous history of thyroid disease [24, 35], after recovering from a mildly symptomatic Covid-19 infection [28], or in a patient associated with the conversion of pre-existing type 2 diabetes mellitus into type 1 immune diabetes [30],
- exacerbation of well-controlled hyperthyroidism on low-dose thioamide treatment [31],
- recurrent hyperthyroidism following a long-period of remission after medical treatment [25],
- after long standing stable hypothyroidism on thyroxine replacement [29],
- following an episode of subacute thyroiditis [15, 19, 23],
- a thyroid storm [35].

Newly diagnosed or recurrent Graves' hyperthyroidism is reported following adenoviral-vectored (28%) and mRNA (72%) SARS-CoV-2 vaccines following the first dose (62%), the second dose (34%) or a booster dose (3%) of Covid-19 vaccines. No patient received an inactivated whole-virus vaccine. The mean time from vaccination to thyrotoxicosis onset is 15.1 ± 2.6 days, with a range of 1 to 60 days. Patients present palpitations (53%), weight loss (34%), tremor (22%), sweating (12.5%), and heat intolerance (3%).

After SARS-CoV-2 vaccination, thyrotoxicosis is confirmed by increased free thyroid hormones concentrations (free T4 = 43.3 ± 4.0 pmol/L, free T3 = 39.0 ± 20.1 pmol/L) and low TSH (0.002 ± 0.0008 mU/L) concentrations. All patients with Graves' hyperthyroidism except two have positive anti-TSH-receptor antibodies or thyroid stimulating immunoglobulins, and anti-TPO antibodies are positive in 73% of patients. Most patients have an increased vascularity of normal sized or enlarged thyroid gland during thyroid ultrasound with Colour flow Doppler, with a diffuse and markedly increased uptake of the radiotracer activity during thyroid scintigraphy.

In classic Graves' disease, treatment should control the thyrotoxic symptoms and decrease the thyroid hormone synthesis either with thioamides, radioiodine ablation or surgical thyroidectomy. After SARS-CoV-2 vaccination, 32% patients have symptomatic treatment with beta-adrenergic blockers and 89% require antithyroid drugs, while 11% patients receive no treatment. Rapid improvement of signs and symptoms of thyrotoxicosis is observed in most patients, response to standard or low-dose medical treatment is good with rapid restoring of normal thyroid hormone concentrations in under 8 weeks, and a decrease or normalisation of anti-TSH receptor antibodies in 2 or 3 months. A rare recurrence of hyperthyroidism is observed in patients with Graves' disease following Covid-19 vaccination [23, 32].

Silent autoimmune thyroiditis

Autoimmune thyroiditis (Hashimoto' thyroiditis, lymphocytic thyroiditis) is the most common form of thyroiditis with lymphocytic infiltration of the thyroid gland, and is characterised by the presence of high serum thyroid antibodies (anti-thyroperoxidase, anti-thyroglobulin) concentrations and heterogenous goiter, while TSH concentration is variable and in most patients within the normal range. Silent or painless thyroiditis, a variant form of autoimmune thyroiditis, can be exhibited through thyrotoxicosis, often followed by a transient hypothyroidism and then a full recovery to normal thyroid function.

Few patients (3 women, 3 men) with variable forms of autoimmune thyroiditis are reported after SARS-CoV-2 vaccines (Table 3) [15–17, 36, 37]. Patients have a personal (type 1 diabetes mellitus) or family history (Hashimoto's thyroiditis) of autoimmune diseases. The mean age is 33 ± 1 year, and the time from vaccination to onset of symptoms ranges from 1 to 21 days. Silent autoimmune thyroiditis following mRNA SARS-CoV-2 vaccines [17, 37] or following adeno-vectored vaccine [16] are reported, whereas painless thyroiditis with thyrotoxic periodic paralysis is described following inactivated virus vaccine in one patient [15]. Thyrotoxicosis ($n = 5$) is observed after the first dose

Table 2 Clinical characteristics, laboratory results and imaging findings of patients with SARS-CoV-2 vaccine-induced Graves' disease

N°	Author (Ref)	Gender	AGE	Type of vaccine	Dose	Time (days)	TSH	FT4	TPO-Ab	Tg-Ab	TSHr-Ab	Thyroid ultrasound, Colour flow Doppler	Thyroid scintigraphy	Treatment	Follow-up
1	Vera Lastra [24]	F	40	mRNA	1st	2	<0.001	45.95	Y	Y	Y	Enlarged thyroid gland, hypervascularity	NA	Propanolol, diltiazem, ivabradine, thiamazol	Good response
2	Vera Lastra [24]	F	28	mRNA	1st	3	<0.001	23.68	Y	N	Y		Diffuse toxic goiter	Propanolol, thiamazol	
3	Zettinig [25]	F	71	mRNA	2nd	35		45.82			Y	Multiple anechogenic areas, increased vascularisation	Patchy inhomogenous tracer distribution, midly increased uptake	Thyreostatic treatment	Normal thyroid function
4	Zettinig [25]	M	46	mRNA	1st	15		20.98			Y	Slightly enlarged, hypo and anechogenic areas, increased vascularisation	Patchy inhomogenous tracer distribution, normal uptake	Thyreostatic treatment	Normal thyroid function
5	Lee [15]	F	46	Adenovirus vectored	1st	1	0.01	33.92	Y	Y	Y	Increased vascularity	Increased uptake (38.6%)		
6	Lee [15]	F	73	Adenovirus vectored	2nd	14	<0.008	73.8	Y	NA	Y	Increased vascularity	Increased uptake (54.2%)		
7	Lee [15]	M	34	Adenovirus vectored	1st	14		26.61	NA	NA	Y	Increased vascularity			
8	Lee [15]	M	39	Adenovirus vectored	1st	14	<0.01	36.98	NA	Y	Y	Diffuse goiter, ill-defined, hypoechoic lesion in left lobe	Increased uptake (13.8%)		
9	Sriphrapradang [26]	M	70	Adenovirus vectored	2nd	2	0.003	41.06	NA	NA	Y			Methimazole	
10	Pujol [17]	F	38	mRNA	1st	12	0.008	25.87	Y	Y	Y	Diffuse hypoechogenicity, increased vascularity	Hyperfunctionning diffuse goiter	Methimazole	
11	Goblirsch [27]	F	71	mRNA	2nd		<0.01	92.68	N	N	Y	Multinodular goiter		Methimazole	Euthyroidism at 1 month
12	Hamouche [28]	M	32	mRNA	1st	22	<0.005	69.63	Y	Y	Y	Heterogenous thyrous	Increased uptake (72%)	Methimazole, propanolol, prednisone (7 days)	Euthyroidism at 8 weeks
13	Lui [29]	F	40	mRNA	2nd	39	<0.02	66.6	Y	Y	Y	Heterogenous echogenicity, increased vascularity	Diffuse markedly increased uptake	Stop LT4, carbimazole, propanolol	Improvement of thyroid function
14	Patrizio [30]	M	52	mRNA	2nd	28	<0.004	71.57	Y	±	Y	Enlarged thyroid, heterogenous echotexture, increased vascularisation		Methimazole, atenolol	Normalisation of thyroid hormones
15	Sriphrapradang [31]	F	30	Adenovirus vectored	3rd	4	0.006	16.6			Y			Methimazole	
16	Pierman [32]	F	34	mRNA	1st	10	0.01	32.69	NA	NA	Y			Thiamazol	
17	Yamamoto [33]	F	64	mRNA	1st	4	<0.008	42.73	NA	NA	Y	Goiter, increased vascularisation		Thiamazole, potassium iodine, corticosteroid, furosemide, carvedilol	Normalisation of thyroid hormones in 23 days
18	Di Filippo [34]	M	32	Adenovirus vectored	2nd	10	0.005	38.1			Y	Enlarged thyroid gland, pseudonodules, hypervascularisation		Propanolol, thiamazole then propylthiouracil (rush)	Euthyroidism in 3 months, decreased anti-TSHr antibodies
19	Di Filippo [34]	M	35	Adenovirus vectored	1st	5	<0.004	63.84			Y	Enlarged thyroid gland, hypervascularisation		Propanolol, thiamazol	Good clinical and hormonal response, normal antiTSHr antibodies at 3 months

Table 2 (continued)

N°	Author (Ref)	Gender	AGE	Type of vaccine	Dose	Time (days)	TSH	FT4	TPO-Ab	Tg-Ab	TSHr-Ab	Thyroid ultrasound, Colour flow Doppler	Thyroid scintigraphy	Treatment	Follow-up
20	Pla Peris [19]	F	71	mRNA	2nd	60	<0.005	29.6	Y	N	Y	Enlarged thyroid, increased vascularity	Diffuse markedly increased uptake	Methimazole	Decreased Ac anti-TSHr after 2 months
21	Pla Peris [19]	F	42	mRNA	1st	<14	<0.005	37.32	N	NA	Y	Enlarged thyroid, increased vascularity	Diffuse markedly increased uptake	Methimazole	Decreased Ac anti-TSHr after 2 months
22	Pla Peris [19]	F	54	mRNA	2nd	<14	<0.005	60.5	Y	Y	Y	Enlarged thyroid, increased vascularity	NA	Methimazole	
23	Pla Peris [19]	F	46	mRNA	1st	50	<0.005	41.19	Y	Y	y	Enlarged thyroid, increased vascularity	NA	Methimazole	
24	Pla Peris [19]	F	69	mRNA	1st	<14	<0.005	23.17	N	N	Y	Enlarged thyroid gland, heterogeneous echogenicity, diffuse hypoechoic pattern	NA	Methimazole, non-steroidal antiinflammatory drugs	
25	Raven [21]	F	35	Adenovirus vectored	1st	5	<0.02	64	Y	Y	Y	Diffuse heterogeneous thyroid, marked increased vascularity		Carbimazole	
26	Weintraub [35]	F	38	mRNA	1st	5	<0.008	108	Y	NA	Y	Diffusely enlarged gland, heterogeneous echogenicity, increased vascularity		Methimazole, propanolol	Normal FT4 at 3 months
27	Weintraub [35]	F	63	mRNA	2nd	4	0.011	30.9	Y	NA	Y	Heterogeneous hypervascular thyroid gland	At 6 months: high radiotracer activity in both lobes, uptake at 24 h: 41%	No treatment	
28	Weintraub [35]	M	30	mRNA	2nd	28	<0.005	22.9	N	N	Y			Methimazole, atenolol	At 6 weeks, normal FT4, improvement of irritability and restless sleep
29	Oguz [23]	F	40	mRNA	1st	2	<0.015	27.92	Y	Y	Y	Diffuse hyperplasia, increased vascularisation	Diffusely increase radiotracer uptake	Methimazole	Not in remission
30	Oguz [23]	M	29	mRNA	1st	15	<0.015	12.15	N	N	N	Diffuse hyperplasia, increased vascularisation	24-h RAIU: 27%	No treatment	Remission 10 weeks
31	Oguz [23]	F	43	mRNA	1st	9	0.015	33.1	N	N	N	Diffuse hyperplasia, increased vascularisation	24-h RAIU: 61%	Methimazole	Not in remission
32	Oguz [23]	F	43	mRNA	1st	14	0.01	25.5	Y	Y	Y	Diffuse hyperplasia, increased vascularisation	24-h RAIU: 23%	Stop levothyroxine	Hypothyroidism at 20th week

Age in years, Time in days, TSH in mU/L, and FT4 in pmol/l

Gender *F* female, *M* male, *Y* yes, *N* not present, *TPO-Ab* TPO antibody, *Tg-Ab* Tg antibody, *TSHr-Ab* TSH receptor antibody, *NA* not available

Table 3 Clinical characteristics, laboratory results and imaging findings of patients with SARS-CoV-2 vaccine-induced chronic autoimmune thyroiditis

N°	Author (Ref)	Gender	Age	Type of vaccine	Dose	Time (days)	Neck pain	TSH	FT4	TPO-Ab	Tg-Ab	ESR	CRP	Thyroid ultrasound, Colour flow Doppler	Thyroid scintigraphy	Treatment	Follow-up
1	Leber [36]	F	32	Inactivated	2nd	1	Y	13.2	Normal	Y	Y					Methylprednisolone for 5 days	Normal TSH after corticosteroid treatment
2	Lee [15]	M	33	Inactivated	1st	10	N	0.012	37.4	N	Y	37	5.16	Heterogenous echogenicity, decreased vascularity	Low thyroid scan uptake		
3	Pujol [17]	M	32	mRNA	1st	10	NA	0.01	30.5	Y	Y	NA	NA	Inflammatory process	Absence of uptake	No treatment	At 8 weeks: TSH = 116 mU/L Levothyroxine treatment
4	Siolos [16]	F	39	Adenovirus vectored	1st	21	N	<0.03	20.47	Y	Y	17	1		Markedly decreased thyroid uptake	No treatment	Euthyroid state at 8 weeks
5	Capezzone [37]	M	34	mRNA	1st	7	N	0.01	24	N	N	5	<0.6	Normal volume, mild hypoechogenicity, diffuse heterogenous echotexture, decreased blood flow	Decreased thyroid uptake	No treatment	Normal TSH after 4 weeks
6	Capezzone [37]	F	29	mRNA	1st	7	N	0.003	21.7	N	N	10	<0.6	Normal volume, mild hypoechogenicity, diffuse heterogenous echotexture, decreased blood flow	Decreased thyroid uptake	No treatment	Normal TSH after 4 weeks

Age in years, Time in days, TSH in mU/L, and FT4 in pmol/l

Gender *F* female, *M* male, *Y* yes, *N* not present, *ESR* Erythrocyte sedimentation rate (mm/h), *CRP* C-reactive protein (mg/l), *TPO-Ab* TPO antibody, *Tg-Ab* Tg antibody, *NA* not available

and hypothyroidism ($n = 1$) after the second dose of vaccine. In thyrotoxic patients, mean free T4 concentration is 33.2 ± 1.3 pmol/L, lower than in patients with Graves' disease or subacute thyroiditis ($p < 0.01$). Four patients have anti-TPO or anti-thyroglobulin antibodies, and markedly decreased thyroid uptake at the thyroid scan is observed in all thyrotoxic patients. Thyrotoxic patients are followed with no medical treatment and euthyroid state is restored after 4 to 8 weeks, with transient subclinical hypothyroidism in one patient.

Comments

(a) Post-vaccination Graves' disease was associated with mRNA or adenovirus-vectored type vaccines, while inactivated vaccine seems to be safe to induce Graves' hyperthyroidism. Among several explanations (variable used doses, humoral-mediated and cell-mediated immunity response), one may be that mRNA and adenovirus-vectored type vaccines have higher immunogenicity than inactivated SARS-CoV-2 vaccine [38], and induce stimulatory anti-TSH receptor antibodies.

(b) The overall prevalence of thyroid-eye disease among patients with Graves' disease is up to 40% [39], but signs of thyroid-eye disease after Covid-19 vaccination are rare: one patient presents with a swelling of the eyelids at diagnosis [32], an active thyroid-eye disease is reported in a patient on chronic levothyroxine treatment for post-radioiodine hypothyroidism [40], and one patient develops moderate to severe ophthalmopathy after 10 weeks of medical treatment [27].

(c) Development of Graves' disease and subacute thyroiditis may occur within a few days of the vaccination, suggesting that the patient had mild or subclinical autoimmune or inflammatory diseases that were aggravated by SARS-CoV-2 vaccines. On the other hand, rapid onset of symptoms is the time when the viral protein concentration reaches its peak in one or two days triggering an autoimmune response.

(d) Clinical course of focal painful thyroiditis may be mild [21], and symptoms related to subacute thyroiditis may be identified as being post-vaccination symptoms, and consequently the diagnosis of subacute thyroiditis may be overlooked.

(e) Co-occurrence of subacute thyroiditis and Graves' disease is rare in the literature, but is observed in some patients following Covid-19 vaccination. Subacute thyroiditis at the inflammatory phase may release thyroid antigens with subsequent development of stimulatory TSH-receptor antibodies, promoting consequently the thyrotoxicosis of autoimmune hyperthyroidism [41, 42].

(f) At the thyrotoxic phase, free T4 concentrations are higher in patients with Graves' disease than in subacute

thyroiditis ($p = 0.001$) and in thyrotoxic patients after silent or painless autoimmune thyroiditis ($p < 0.001$).

(g) In patients with autoimmune thyroiditis, the appearance of an episode of thyrotoxicosis within a few days of the first dose of vaccination may suggest that the patient had a (chronic) autoimmune thyroiditis which was aggravated by the SARS-CoV-2 vaccines, or that thyroid dysfunction may be mild or moderate, and consequently this diagnosis of painless or autoimmune thyroiditis may be overlooked.

(h) No relapses or exacerbation of symptoms or signs of thyrotoxicosis are observed in the majority of the patients with Graves' disease or subacute thyroiditis after a repeated or a booster dose of SARS-CoV-2 vaccination [23].

Pathophysiological mechanisms of thyroid diseases after SARS-CoV-2 vaccines

SARS-CoV-2 vaccination may induce autoimmune and inflammatory thyroid dysfunctions, and may precipate differents forms of thyrotoxicosis (autoimmune hyperthyroidism or Graves' disease, overt subacute thyroiditis and atypical autoimmune thyroiditis, or concurrence of subacute thyroiditis and Graves' disease). Investigation is needed to clarify the etiology of the thyrotoxicosis in order to start adapted treatment or management. The underlying pathogenic mechanisms of SARS-CoV-2 vaccine-induced thyroid disorders are as yet unclear and are a subject of discussion:

(a) Molecular mimicry: Adenoviral-vectored and mRNA vaccines encode and inactivated whole-virus vaccines contain the SARS-CoV-2 spike protein, and various SARS-CoV-2 proteins (spike protein, nucleoprotein and membrane proteins) share a genetic similarity or homology with a large heptapeptide human protein including thyroid peoxidase peptide sequences [43]. Therefore, SARS-CoV-2 proteins in vaccines can cross react with thyroid target proteins and cause autoimmune thyroid diseases. After polyclonal activation of B lymphocytes by vaccination, antibodies directed against SARS-CoV-2 proteins might cross react with thyroid antigens located on the follicular cells of the thyroid, and may promote mitochondrial damage and cause thyroid dysfunctions. Therefore, molecular mimicry is a potential mechanism underlying the autoimmune reactions after SARS-CoV-2 vaccination, and has been proposed to cause autoimmune thyroid disorders such as Graves' hyperthyroidism after SARS-CoV-2 vaccination.

(b) Autoimmune/inflammatory syndrome induced by adjuvants (ASIA): ASIA, described in 2011 by Shoenfeld and Agmon-Levin [44], is the consequence of the dysregulation of immune system following exposure to adjuvants. Adjuvants enhance the immunogenicity of vaccines, increase both innate and adaptive immune response, and can induce the formation of autoantibodies or localised/systemic inflammation. The SARS-CoV-2 vaccines contain several excipients such as aluminium hydroxide or aluminium salts (Coronavac vaccine), polysorbate 80 (Astra-Zeneca vaccine) or polyethylene glycol (PEG) lipid conjugates that stabilise the lipid nanoparticles and may act as adjuvants in mRNA vaccine (Pfizer BioNTech) and oil-in-water emulsion type that may trigger autoimmune or allergic reaction following SARS-CoV-2 vaccines. Autoimmune endocrine diseases such as type 1 diabetes mellitus, primary ovarian failure, adrenal insufficiency and autoimmune thyroid diseases have been reported to be related to ASIA syndrome after human papillomavirus, influenza, hepatitis B vaccination [45–50] and recently after Covid-19 vaccines.

(c) Genetic predisposition or susceptibility: despite a mass immunisation campaign against Covid-19 infection, thyroid adverse effects such as subacute thyroiditis, Graves' disease and silent autoimmune thyroiditis appear to be rare, suggesting they are probably under-reported adverse effects of Covid-19 vaccines or are usually occurring with individual predisposition or genetic susceptibility. In genetically susceptible individuals, T lymphocytes are excessively sensitised to the TSH receptor antigen and vaccines, activating B lymphocytes, may produce and secrete autoantibodies against the TSH receptor and cause Graves' hyperthyroidism [51, 52]. Moreover, molecular mimicry between human leucocytes antigen (HLA) genes and SARS-CoV-2 antigens can predispose individuals to Graves' disease as SARS-CoV-2 products altering the HLA structure and function. On the other hand, certain types of HLA (HLAB35) are considered for susceptibility to subacute thyroiditis, activation of the antigen-HLAB35 complex, leading to immune-mediated destruction of the thyroid follicular cells [53]. Interestingly, a report on two sisters who present subacute thyroiditis a few days after receiving a Covid-19 mRNA vaccine has been recently described [22], and the potential role of genetic predisposition remains to be investigated further. However, no potential risk factors (personal or familial autoimmune disease, pregnancy, postpartum) or predictors (smoking, stress, drugs, hypovitaminosis D) have been reported to have an influence on the occurrence of the majority of autoimmune or inflammatory thyroid diseases following SARS-CoV- 2 vaccination.

Conclusion

Although the benefits of SARS-CoV-2 vaccination are undeniable and far outweigh the potential side effects, clinicians should be aware of possible autoimmune and inflammatory thyroid adverse effects following Covid-19 vaccination. Vaccination against SARS-CoV-2 should be

highly recommended, and it is the priority in the fight against Covid-19.

During this massive vaccination campaign, autoimmune and inflammatory thyroid diseases following vaccination with SARS-CoV-2 vaccines appear to be rare, but the potential cases are being reported more frequently. Clinicians can advise patients to seek medical assistance if they are experiencing anterior neck pain, fever or palpitations so that they are treated properly and in a timely fashion. Patients with prior personal or family history of autoimmune thyroid and non-thyroidal diseases may require post-vaccine monitoring and management.

Further clinical studies are warranted to clarify the clinical features, predisposing factors, clinical management and prevention of autoimmune and inflammatory thyroid diseases after SARS-CoV-2 vaccination. At the same time, further research is needed to investigate the etiopathogenesis of thyroid dysfunctions following vaccination against SARS-CoV-2.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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