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ORIGINAL ARTICLE

Graves' orbitopathy post-SARS-CoV-2 vaccines: report on six patients

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Abstract

Context Autoimmune and inflammatory thyroid diseases (Graves' disease, subacute thyroiditis, chronic autoimmune thyroiditis) have been reported following SARS-CoV-2 vaccines but Graves' orbitopathy (GO) post-COVID-19 vaccination is uncommon.

Methods We describe six new patients seen in Endocrinology Departments with Outpatient Clinics for GO following SARS-CoV-2 vaccines in France.

Results After COVID-19 vaccination, GO was observed in six patients (three men, three women, mean age 53 ± 6 years) with a personal past history of Graves' disease (5/6) or orbitopathy (4/6). New-onset ($n=2$) or recurrence ($n=4$) of GO was observed following mRNA vaccines after the first (3/6) or second (3/6) dose, with the mean time from vaccination to GO at 23.8 ± 10.4 days. In one patient, thyrotoxicosis was confirmed by increased free T4 and low TSH concentrations while others had normal TSH levels, during chronic levothyroxine treatment in three patients. Four patients had significant anti-TSH receptor antibodies levels. According to the severity and activity of GO, the patients were treated using selenium ($n=2$), intravenous glucocorticoids ($n=2$), teprotumumab ($n=1$), tocilizumab ($n=2$) and orbital decompression ($n=1$) with a significant improvement in GO signs and symptoms observed by most patients.

Conclusion In this study, we report the main data from six new patients with GO following SARS-CoV-2 vaccines. Clinicians need to be aware of the risk of new-onset or recurrent GO in predisposed patients with autoimmune thyroid diseases after COVID-19 vaccination. This study should not raise any concerns regarding SARS-CoV-2 vaccination since the risk of COVID-19 undoubtedly outweighs the incidence of uncommon GO after SARS-CoV-2 vaccination.

Keywords Graves' orbitopathy · Graves' disease · COVID-19 · SARS-CoV-2 · Vaccine · Autoimmunity

Introduction

Graves' disease is the most frequent cause of hyperthyroidism due to the stimulation of the TSH-receptor on follicular thyroid cells by autoimmune antibodies which results in thyrotoxicosis, goitre and extra-thyroidal manifestations (Graves' orbitopathy, pretibial myxoedema). Graves' hyperthyroidism is characterized by a Th-1 response with a high number of Th-1 CD4 cells and interferon secretion but usually affects genetically predisposed patients in the presence of triggering factors (stress, smoking, infection, post-partum, radioiodine treatment). The overall prevalence of Graves' orbitopathy (GO) among patients with Graves' disease is up to 40%, with 3–5% going on to develop severe Graves' ophthalmopathy [1].

An increasing number of autoimmune and inflammatory-related side effects are being reported following COVID-19 vaccination (thrombotic thrombocytopenia, Guillain–Barré

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syndrome, myocarditis/pericarditis, type 1 diabetes mellitus, premature ovarian failure, adrenal insufficiency). Moreover, autoimmune and inflammatory-related thyroid disorders such as Graves' disease, subacute thyroiditis and silent (painless) thyroiditis have been described following SARS-CoV-2 vaccines [2–5] but autoimmune and inflammatory orbital adverse complications are uncommon post-COVID-19 vaccination [6].

In the present study, we describe 6 new patients with GO following SARS-CoV-2 vaccines.

Methods

The 6 patients were seen in the Tertiary Endocrinology Department with Outpatient Clinic for GO with new-onset, recurrent or worsening GO following SARS-CoV-2 vaccination. For every patient, we collected information on demographic data (sex, age), previous history of autoimmune or thyroid disease, type of administered vaccines (mRNA vaccine, inactivated virus or vector vaccine), timing of GO, onset or recurrence following vaccination, signs and symptoms at presentation, laboratory tests (TSH, free T4, anti-TSH receptor antibodies) and other diagnostic examinations (CT scan or MRI scan of the orbits), specific medical or surgical therapies and ophthalmic follow-up.

Patients

(a) A 70-year-old female was treated with oral prednisolone (7.5 mg/day) for frozen shoulder syndrome. Her past thyroid history included Graves' disease with total thyroidectomy and daily substitutive levothyroxine therapy (137 µg) as well as stable GO after 4 intravenous infusions of tocilizumab. Eighteen weeks after the last infusion of tocilizumab, she received the second dose of the mRNA vaccine. Sixty days later, the woman presented spontaneous and orbital pain upon eye movement, conjunctival irritation and eyelid oedema. Clinical Activity Score (CAS) was 4/7 and an orbital MRI confirmed bilateral proptosis with oedema of the medial and inferior rectus muscles which was indicative of active moderate-to-severe GO. Laboratory investigations confirmed normal thyroid function with normal TSH and free T4 concentrations during stable levothyroxine treatment, and elevated levels of anti-TSH receptor antibodies (> 40 IU/L). In the context of recurrent GO during oral glucocorticoid therapy, the woman was treated with tocilizumab (8 mg/kg monthly intravenous infusions) and reported a significant and rapid (2 weeks) clinical improvement with decreased anti-TSH receptor antibodies levels (25 IU/L) after 5 infusions of tocilizumab.

(b) A 43-year-old male patient had a personal medical history of type-1 diabetes mellitus, psoriasis, Graves' disease treated with carbimazole (10 mg/day) and sight-threatening GO of the right eye refractory to intravenous glucocorticoids treated by 4 IV infusions of tocilizumab (8 mg/kg) with complete recovery of the dysthyroid optic neuropathy (DON). Forty-five days after the last infusion of tocilizumab, the patient received the first dose of the Moderna mRNA vaccine. The patient reported spontaneous orbital pain and diplopia the next day then decreased visual acuity after the second dose of the COVID-19 vaccine. The CAS was 7/7 and the patient presented sight-threatening GO in relation to recurrent DON on the right eye. During carbimazole therapy, TSH levels were slightly elevated with low free T4 concentrations and absence of anti-TSH receptor antibodies. The patient was once again treated with tocilizumab (8 mg/kg). Significant improvement in inflammatory symptoms (CAS = 1/7) was observed after the first infusion of tocilizumab with recovery of visual acuity after 4 IV infusions.

(c) A 73-year-old male patient with a personal medical history of atrial fibrillation and prostate cancer presented a Graves' disease treated with carbimazole. Twenty-one days after the first dose of the Pfizer mRNA vaccine, he experienced conjunctival irritation and diplopia. The CAS was 3/7 and an orbital MRI showed oedema of the lower rectus muscle in the right eye favouring mild GO. TSH levels were normal and anti-TSH receptor antibodies were normal. The patient was treated with selenium as well as intravenous methylprednisolone infusions and reported an improvement in symptoms affecting the right eye after the first infusion with absence of inflammatory signs or symptoms after 6 infusions of 500 mg methylprednisolone.

(d) A 45-year-old woman had a past medical history of hyperparathyroidism, sickle cell anaemia, total thyroidectomy in the context of Graves' hyperthyroidism managed with substitutive levothyroxine therapy, GO treated by intravenous infusions of glucocorticoids and subsequent bilateral orbital decompression for inactive GO. During the week following the second dose of the Moderna mRNA vaccine, she presented an eyelid oedema, conjunctival irritation, spontaneous and orbital pain upon eye movement without diplopia. The CAS was 4 and the woman had active moderate-to-severe GO. On stable levothyroxine treatment, TSH levels were in the normal range and anti-TSH receptor antibodies were elevated. The woman received lubricants and reported a spontaneous improvement in orbital inflammation in 5 months.

(e) A 48-year-old male patient with a medical history of obesity, type-2 diabetes mellitus and schizophrenia had presented Graves' disease treated with total thyroidectomy and subsequent substitutive levothyroxine therapy as well as sight-threatening unilateral right GO with DON and total recovery after steroids and orbital decompression. Eleven months after surgical decompression, the patient received the second dose of the Moderna mRNA vaccine. One month later, the patient experienced left conjunctival irritation, orbital pain with rapid decreased visual acuity. During the ophthalmic evaluation, the CAS was 5/7 and the patient presented contralateral DON. The thyroid function test showed thyrotoxic phase with increased free T4 and low TSH concentrations justifying decreased levothyroxine dosage, and anti-TSH receptor antibodies were elevated (28 IU/L). CT scan of the orbits visualised significant and bilateral proptosis with enlargement of the extraocular muscles. In the absence of response to intravenous methylprednisolone (1 gr/day × 3), the patient underwent trans-ethmoidal and transsphenoidal orbital decompression of the left eye and subsequent intravenous infusion of teprotumumab. Ophthalmic follow-up showed normal visual acuity and absence of inflammatory signs (CAS 0/7) after the first infusion of teprotumumab [7] with a significant decrease in anti-TSH receptor antibodies (9 IU/L) three months later.

(f) A 39-year-old woman with a family history of thyroid disease presented an oedema of the upper eyelid and proptosis of the left eye with photophobia, conjunctival irritation without diplopia 7 days after the first dose of the Pfizer mRNA vaccine. The CAS was 2/7. No aggravation after the second dose of the COVID-19 vaccine was observed. The TSH level was at the lower limit of the normal range with elevated anti-TSH receptor antibodies. The orbital MRI revealed enlargement and an inflammatory aspect of the left lower rectus muscle. The woman presented mild GO, was treated with selenium (200 µg/day) and the CAS was unchanged at 6-month follow-up.

Main clinical, hormonal and radiological data as well as treatment and ophthalmic follow-up from the 6 patients are presented in Table 1.

At the time of writing the article, GO following SARS-CoV-2 vaccines had been previously described in 12 patients [8–14] and the main data are reported in Table 2.

Discussion

After SARS-CoV-2 vaccination, GO was observed in 6 new patients (3 men, 3 women, mean age was 53 ± 6 years, ranging from 39 to 73 years). Most patients had a past personal history of Graves' disease (5/6) or GO (4/6). Newly diagnosed or recurrent GO were reported following mRNA COVID-19 vaccines after the first (3/6) or second (3/6) dose with the mean time from COVID-19 vaccination to onset or worsening of GO at 23.8 ± 10.4 days, ranging from 1 to 60. In one patient, thyrotoxicosis was confirmed by high free T4 and low TSH concentrations while others (5/6) had normal TSH levels during chronic levothyroxine treatment in 3 patients. Autoimmune GO was associated with the presence of anti-TSH receptor antibodies in most patients (4/6). According to the activity and severity of GO, patients were treated using selenium ($n = 2$), intravenous glucocorticoids ($n = 2$) or immunosuppressive drugs (tocilizumab $n = 2$), anti IGF1 receptor monoclonal antibody (teprotumumab $n = 1$) and orbital decompression ($n = 1$) with significant improvement in signs and symptoms experienced by most patients.

In all reported patients with GO following COVID-19 vaccination, no triggering events (increased TSH concentrations, changes in smoking status, pregnancy, recent surgeries, radioiodine treatment) were observed in their medical history other than COVID-19 vaccination and the timing between the new-onset or reactivation of GO and SARS-CoV-2 vaccines was similar to that stated in previous reports of autoimmune and inflammatory diseases following COVID-19 vaccination [2]. Considering the high vaccination coverage, it is possible that the relationship between the occurrence of GO and COVID-19 vaccination was coincidental. However, the temporal sequence of the new onset, recurrence or worsening of GO was potentially prompted by exposure to the SARS-CoV-2 vaccines with the COVID-19 vaccination serving as a triggered event in predisposed patients with Graves' disease and/or GO. In the absence of reports on the total number of patients with GO following SARS-CoV-2 vaccination in a defined population, estimating the incidence of this orbital side effect is difficult.

Autoimmune hyperthyroidism can occur after several vaccines (hepatitis B, human papilloma virus, H1N1) [15–19] and autoimmune thyroid diseases may develop in the hyperimmune environment created after the SARS-Cov-2 immunisation. The exact pathogenetic mechanisms underlying new onset, recurrence or exacerbation of GO following SARS-CoV-2 vaccines are not fully understood and several hypotheses could be put forward:

(a) Molecular mimicry: various SARS-CoV-2 proteins (spike proteins, nucleoproteins and membrane proteins)

Table 1 Main clinical, hormonal and radiological data as well as treatment and ophthalmic follow-up in 6 new patients with GO post-SARS-CoV-2 vaccines

N	Sex	Age	Family history	Personal history	Past thyroid disease	Treatment	Name of vaccine	Type of vaccine	Dose	Time (days)	History of GO	Signs of ophthalmopathy	CAS	Severity of GO	TSH (mIU/L)	FT4 (pmol/l)	TSHr-Ab	Radiological signs	Treatment	Follow-up
1	F	70	N	Adhesive capsulitis (frozen shoulder)	Graves' disease treated by thyroidectomy, Graves' orbitopathy treated with tocilizumab, pretibial myxoedema	Levothyroxine, prednisolone	Pfizer	mRNA	2nd	60	Recurrence after 7 years	Spontaneous and orbital pain with eye movement, oedema	4	Moderate-to-severe GO	1.65	20	> 40	Bilateral proptosis, oedema of medial and inferior rectus muscles	Prednisolone, tocilizumab	Significant clinical improvement, decreased anti-TSH receptor Ab (25 IU/L)
2	M	43	N	Diabetes mellitus type 1, psoriasis	Graves' disease, dysthyroid optic neuropathy treated with tocilizumab with complete recovery	Insulin therapy, carbimazole, inhibitor proton pump	Moderna	mRNA	1st	1	Recurrence after 11 months	Spontaneous orbital pain, diplopia, abnormal visual acuity after the 2nd dose	7	Sight-threatening GO (dysthyroid optic neuropathy)	4.04	6.2	N	NA	Tocilizumab (8 mg/kg × 4)	Significant improvement in symptoms, normal visual acuity after tocilizumab
3	M	73	N	Prostate cancer, atrial fibrillation	Graves' disease	Carbimazole, beta blockers, apixaban	Pfizer	mRNA	1st	21	new	Conjunctival irritation, diplopia	3	Mild GO	2.4	***	N	Oedema of lower rectus muscle in the right eye	Selenium, IV methylprednisolone	Improvement in inflammation of lower rectus muscle in the right eye
4	F	45	N	Hyperparathyroidism, sickle cell anaemia	Total thyroidectomy, Graves' orbitopathy treated with steroid therapy (EUGOGO protocol) and orbital decompression	Levothyroxine	Moderna	mRNA	2nd	NA	Recurrence after 18 months	Spontaneous and orbital pain with eye movement, conjunctival irritation, eyelid oedema	4	Moderate-to-severe GO	0.76	NA	151 IU/L	NA	Lubricants	Improvement in orbital inflammation at 5 months

Table 1 (continued)

N	Sex	Age	Family history	Personal history	Past thyroid disease	Treatment	Name of vaccine	Type of vaccine	Dose	Time (days)	History of GO	Signs of ophthalmopathy	CAS	Severity of GO	TSH (mIU/L)	FT4 (pmol/l)	TSHr-Ab	Radiological signs	Treatment	Follow-up
5	M	48	N	Diabetes mellitus, obesity, schizophrenia	Total thyroidectomy, dysthyroid optic neuropathy in 2020	Levothyroxine, metformin, propanolol, risperidone, diazepam	Moderna	mRNA	2nd	30	Recurrence after 12 months	Orbital pain, conjunctival irritation, decreased visual acuity	5	Sight-threatening GO (dysthyroid optic neuropathy)	<0.01	21	28 IU/L	CT: significant and bilateral proptosis, enlargement of orbital muscles	IV methylprednisolone, bilateral orbital decompression, teprotumumab	Normal visual acuity and CAS 0/7 after 1 IV infusion of teprotumumab, anti-TSH receptor 9 IU/L
6	F	39	Y	N	N	No treatment	Pfizer	mRNA	1st	7	New	Left proptosis, conjunctival irrtation	2	Mild GO	0.30	NA	5 IU/L	Enlargement and inflammatory aspect of extraocular muscles (lower rectus muscle)	Selenium	
		53 ± 6								23.8 ± 10.4			4.2 ± 0.7		1.53 ± 0.62	15.7 ± 4.8				

Footnote: Sex *F* female, *M* male. Age (years). Time (days). *Y* yes, *N* not present. TSH (mU/L). FT4 (pmol/l). TSHr-Ab: TSH receptor antibody. *NA* not available

Table 2 Main clinical, hormonal and radiological data as well as treatment and ophthalmic follow-up in 12 patients with GO post SARS-CoV-2 vaccines from literature

N	Ref	Sex	Age	Family history	Personal history	Past thyroid disease	Treatment	Name of vaccine	Type of vaccine	Dose	Time (days)	History of G0	Signs of ophthalmopathy	CAS	Severity of GO	TSH (mIU/L)	FT4 (pmol/l)	TSHr-Ab	Radiological signs	Treatment	Follow-up
1	8	F	50	NA	NA	Graves' disease treated with I131	Levothyroxine	Pfizer	mRNA	2nd	3	New	Eye irritation, tearing, orbital pain, bilateral proptosis	5/7	Moderate-to-severe GO	Normal		Y	CT: enlargement of inferior and medial recti muscles	Teprotumumab	After 2 doses: improvement in congestive symptoms, significant reduction in proptosis
2	9	F	34	NA	NA	Graves' disease treated with thiamazole	No treatment	Pfizer	mRNA	1st	10	New	Swelling and oedema of the eyelids	NA	Mild GO	0.01	32.69	Y	NA	Thiamazole	NA
3	10	F	71	NA	Breast cancer, struma ovarii	Multinodular goiter	No treatment	Pfizer	mRNA	2nd	> 70	New	NA	NA	Moderate-to-severe GO 10 weeks after treatment of Graves' disease	< 0.02	92.67	Y	NA	Methimazole	NA
4	11	F	51	NA	Diabetes mellitus, hypertension	N		Pfizer	mRNA	2nd	4	New	Proptosis, irritation, dryness	3/7	Active and mild GO	< 0.01	47.88	Y	NA	Methimazole, propanolol, then thyroidectomy	Significant clinical regression after thyroidectomy
5	12	F	58	NA	NA	Graves' disease treated with I131	No treatment	Pfizer	mRNA	2nd	3	Worsening of 3-year GO	Chemosis, redness of eyelids, periorbital oedema, pain, diplopia, foreign object sensation	6/10	Moderate-to-severe GO	1.17	16.22	Y	NA	Planned teprotumumab	NA

Table 2 (continued)

N	Ref	Sex	Age	Family history	Personal history	Past thyroid disease	Treatment	Name of vaccine	Type of vaccine	Dose	Time (days)	History of G0	Signs of ophthalmopathy	CAS	Severity of GO	TSH (mIU/L)	FT4 (pmol/l)	TSHr-Ab	Radiological signs	Treatment	Follow-up
6	12	M	43	NA	NA	Graves' disease, Graves' orbitopathy treated with steroid and external orbital radiation	No treatment	Pfizer	mRNA	NA	14	Recurrence of GO	Proptosis, diplopia, keratopathy, dysthyroid optic neuropathy	NA	Sight-threatening GO	2.31	9.78	Y	NA	NA	NA
7	13	F	66	NA	NA	Graves' disease treated with I131, Graves' orbitopathy treated with bilateral orbital decompression	No treatment	Moderna	mRNA	2nd	21	Recurrence after 15 years	Bilateral periorbital oedema, proptosis, pain with eye movement	6/10	Moderate-to-severe GO	0.04	21.88	Y	Oedema and enlargement of the inferior rectus muscles	Teprotumumab	Improvement in symptoms at 5 months
8	13	F	53	NA	NA	N	Methimazole	Pfizer	mRNA	1st	1	New	Periorbital oedema, proptosis, upper and lower eyelid retraction in the right eye	NA	Moderate-to-severe GO	0.99	11.58	Y	Mild oedema, enlargement of bilateral inferior rectus muscles and lacrimal gland	Teprotumumab	Improvement in symptoms at 8 months

Table 2 (continued)

N	Ref	Sex	Age	Family history	Personal history	Past thyroid disease	Treatment	Name of vaccine	Type of vaccine	Dose	Time (days)	History of G0	Signs of ophthalmopathy	CAS	Severity of GO	TSH (mIU/L)	FT4 (pmol/l)	TSHr-Ab	Radiological signs	Treatment	Follow-up
9	13	F	45	NA	NA	Hashimoto's thyroiditis with TED	No treatment	Moderna	mRNA	1st	21	Recurrence after 5 years	Proptosis, mild bilateral lower eyelid oedema, worsening of eyelid swelling after the 2nd dose	NA	Mild-to-moderate GO	NA	NA	NA	NA	No treatment	Spontaneous reduction in eyelid swelling at 4 months
10	14	F	37	NA	NA	NA	No treatment	NA	mRNA	2nd	21	New	NA	NA	Mild-to-moderate GO	0.01	72	Y	NA	Carbimazole, propanolol	NA
11	14	F	34	NA	NA	NA	No treatment	NA	mRNA	1st	26	New	NA	NA	Mild-to-moderate GO	0.01	68	Y	NA	Carbimazole, propanolol	NA
12	14	M	59	NA	NA	Graves' disease	No treatment	NA	mRNA	1st	21	New	NA	NA	Mild-to-moderate GO	0.01	49	Y	NA	Carbimazole, propanolol	NA
mean ± SE			50 ± 3								18 ± 5					0.5 ± 0.23	42.2 ± 9.0				

Footnote: Sex *F* female, *M* male. Age (years). Time (days). *Y* yes, *N* not present. TSH (mU/L). FT4 (pmol/l). TSHr-Ab: TSH receptor antibody. *NA* not available

share a genetic similarity or homology with human proteins [20]. After polyclonal activation of B lymphocytes by COVID-19 vaccines, antibodies directed against SARS-CoV-2 proteins might cross-react with thyroid antigens located on the follicular cells of the thyroid and the cells of periorbital tissues to cause Graves' hyperthyroidism and autoimmune GO, respectively, in rare patients.

(b) Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) is the consequence of the dysregulation of the 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. Autoimmune thyroid diseases have been reported to be related to ASIA syndrome after human papillomavirus, influenza, hepatitis B vaccination [21–26] and most recently after COVID-19 vaccines [2, 5, 27–29]. In the BNT162b2 mRNA vaccine, polyethylene glycol (PEG) conjugates stabilise the lipid nanoparticles and may act as adjuvants to trigger an autoimmune reaction following SARS-CoV-2 vaccination.

(c) Autoimmune hyperthyroidism and TED are related to stimulating anti-TSH receptor antibodies and produced secondary to a Th-1 immune response in which interferon gamma plays a key role [30]. As COVID-19 vaccines lead to a production of Th-1 cells, a similar mechanism could be involved in vaccine-induced Graves' hyperthyroidism or orbitopathy.

Despite a mass immunisation campaign against COVID-19 infection, autoimmune thyroid adverse effects such as Graves' disease and GO appear to be rare, suggesting they are probably under-reported side effects of COVID-19 vaccination or usually occur 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 autoantibodies against the TSH receptor thereby causing Graves' hyperthyroidism and GO [31, 32]. On the other hand, inflammatory recurrence of GO in some patients is also a possibility after previous immunomodulating treatments unrelated to SARS-CoV-2 vaccination. Therefore, systematic reporting of patients with GO following COVID-19 vaccination will add information on the frequency and potential mechanism(s) between SARS-CoV-2 vaccines and autoimmune GO.

After clinical and ophthalmic assessment, all grades of severity (mild, moderate-to-severe, sight-threatening) were observed in patients with GO following SARS-CoV-2 vaccination [33]. In patients with mild GO, local (lubricants) and lifestyle measures were sufficient and 2 patients had also selenium (200 µg/day) therapy. In patients with moderate-to-severe GO, immunomodulatory therapy was indicated (intravenous glucocorticoids, tocilizumab) or anti IGF1 receptor monoclonal antibody (teprotumumab), and associated with a significant improvement in most patients. For patients with sight-threating GO, urgent treatment was instituted with close monitoring of response to immunosuppressive therapies and restoration of visual acuity. The response to immunomodulatory therapy in patients with GO following COVID-19 vaccination may be related to the rapidity of treatment in such patients with a past history of autoimmune thyroid diseases or to a possible brief autoimmune reaction following SARS-CoV-2 vaccination. Finally, vitamin D supplements inhibit Th-1 type immune activity and induce suppression of B cells while selenium supplements decrease the B cell-activating factor. Therefore, these class 2 micronutrient (vitamin D, selenium) supplements have the potential to reduce and modulate autoimmune thyroid activity as well as protect against activation or relapse of autoimmune adverse events due to SARS-CoV-2 vaccination, particularly in predisposed patients with a past history of Graves' disease and/or GO [34].

Conclusion

All vaccinations are risky but the benefits of SARS-CoV-2 vaccines outweigh any theoretical risks of immunisation. COVID-19 vaccines may be recommended to all patients who are eligible for COVID-19 vaccination or booster doses, including those with autoimmune-mediated diseases such as Graves' hyperthyroidism and GO. Clinicians should remain vigilant for recurrence or aggravation in patients with a known history of Graves' disease or GO following SARS-CoV-2 vaccination. In such patients with a prior history of thyroid or orbital autoimmune diseases, a baseline pre-COVID-19 vaccine examination and ophthalmic monitoring is required to diagnose rapidly autoimmune hyperthyroidism or orbitopathy. Concomitantly, class 2 micronutrient (vitamin D, selenium) supplements can be prescribed to prevent more severe forms of GO in patients with a past history of Graves' disease and/or orbitopathy.

Author contributions All authors have been involved in the medical care of the patients. Material preparation, data collection and analysis were performed by all the Authors. The first draft of the manuscript was written by PC and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript to be published and agreed to be accountable for all aspects of the study.

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Declarations

Conflict of interest The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Ethical standards Informed consent was obtained from the patients and the work conforms with the 1964 Declaration of Helsinki Good Clinical Practice Guidelines.

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References

1. Bahn RS (2010) Graves' ophthalmopathy. N Engl J Med 362:726–738. https://doi.org/10.1056/NEJMra0905750
2. Caron P (2022) Autoimmune and inflammatory thyroid diseases following vaccination with SARS-CoV-2 vaccines: from etiopathogenesis to clinical management. Endocrine. https://doi.org/10.1007/s12020-022-03118-4
3. Caironi V, Pitoia F, Trimboli P (2022) Thyroid inconveniences with vaccination against SARS-CoV-2: The size of the matter. A systematic review. Front Endocrinol (Lausanne). 13:900964. https://doi.org/10.3389/fendo.2022.900964
4. Lui DTW, Lee CH, Cheung CYY, Cheung Mak JH, Fong CHY, Lui BWC, Cheung VSY, Chow WS, Lee ACH, Tam AR, Pang P, Ho TY, Tan KCB, Woo YC, Hung IFN, Lam KSL (2022) Impact of COVID-19 vaccines on thyroid function and autoimmunity and impact of thyroid autoimmunity on antibody response. J Clin Endocrinol Metab. https://doi.org/10.1210/clinem/dgac355
5. Ippolito S, Gallo D, Rossini A, Patera B, Lanzo N, Fazzino GFM, Piantanida E, Tanda ML (2022) SARS-CoV-2 vaccine-associated subacute thyroiditis: insights from a systematic review. J Endocrinol Invest 45:1189–1200. https://doi.org/10.1007/s40618-022-01747-0
6. Nyankerh CNA, Boateng AK, Appah M (2022) Ocular complications after COVID-19 vaccination, vaccine adverse event reporting system. Vaccines (Basel) 10(6):941. https://doi.org/10.3390/vaccines10060941
7. Sears CM, Wang Y, Bailey LA, Turbin R, Subramanian PS, Douglas R, Cockerham K, Kossler AL (2021) Early efficacy of teprotumumab for the treatment of dysthyroid optic neuropathy: A multicenter study. Am J Ophthalmol Case Rep 23:101111. https://doi.org/10.1016/j.ajoc.2021.101111
8. Rubinstein TJ (2021) Thyroid eye disease following COVID-19 vaccine in a patient with a history Graves' disease: a case report. Ophthalmic Plast Reconstr Surg 37(6):e221–e223. https://doi.org/10.1097/IOP.0000000000002059
9. Pierman G, Delgrange E, Jonas C (2021) Recurrence of Graves' disease (a Th1-type Cytokine Disease) following SARS-CoV-2 mRNA vaccine administration: a simple coincidence? Eur J Case Rep Intern Med https://doi.org/10.12890/2021_002807
10. Goblirsch TJ, Paulson AE, Tashko G, Mekonnen AJ (2021) Graves' disease following administration of second dose of SARS-CoV-2 vaccine. BMJ Case Rep 14:e246432. https://doi.org/10.1136/bcr-2021-246432
11. Bostan H, Ucan B, Kizilgul M, Calapkulu M, Hepsen S, Gul U, Ozturk Unsal I, Cakal E (2022) Relapsed and newly diagnosed Graves' disease due to immunization against COVID-19: A case series and review of the literature. J Autoimmun 128:102809. https://doi.org/10.1016/j.jaut.2022.102809
12. Patrizio A, Ferrari SM, Antonelli A, Fallahi P (2022) Worsening of Graves' ophthalmopathy after SARS-CoV-2 mRNA vaccination. Autoimmun Rev 21(7):103096. https://doi.org/10.1016/j.autrev.2022.103096
13. Park KS, Fung SE, Ting M, Ozzello DJ, Yoon JS, Liu CY, Korn BS, Kikkawa DO (2022) Thyroid eye disease reactivation associated with COVID-19 vaccination. Taiwan J Ophthalmol 12(1):93–96. https://doi.org/10.4103/tjo.tjo_61_21
14. Chee YJ, Liew H, Hoi WH, Lee Y, Lim B, Chin HX, Lai RTR, Koh Y, Tham M, Seow CJ, Quek ZH, Chen AW, Quek TPL, Tan AWK, Dalan R (2022) SARS-CoV-2 mRNA vaccination and Graves' disease: A report of 12 cases and review of the literature. J Clin Endocrinol Metab 107(6):e2324–e2330. https://doi.org/10.1210/clinem/dgac119
15. Chen RT, Pless R, Destefano F (2001) Epidemiology of autoimmune reactions induced by vaccination. J Autoimmun 16(3):309–318. https://doi.org/10.1006/jaut.2000.0491
16. Sturkenboom MC, Heinzlef O, Roullet E, Rozenberg S, Begaud B, Fautrel B (2000) Vaccination against Hepatitis B and Graves' Disease. Pharmacoepidemiol Drug Safe 9:S70
17. Liu EY, Smith LM, Ellis AK, Whitaker H, Law B, Kwong JC, Farrington P, Lévesque LE (2018) Quadrivalent human papillomavirus vaccination in girls and the risk of autoimmune disorders: the Ontario Grade 8 HPV Vaccine Cohort Study. CMAJ 190(21):E648–E655. https://doi.org/10.1503/cmaj.170871
18. Leiva S, Madrazo J, Podesta C (2018) Narcolepsy with cataplexy and hyperthyroidism sudden appeared after H1N1 vaccination. Sleep Sci. 11(1):34–36. https://doi.org/10.5935/1984-0063.20180008
19. Yu O, Bohlke K, Hanson CA, Gatto NM, Caffrey AR (2007) Hepatitis B vaccine and risk of autoimmune thyroid disease: a Vaccine Safety Datalink study. Pharmacoepidemiol Drug Saf 16:736–745. https://doi.org/10.1002/pds.1354
20. Vojdani A, Vojdani E, Kharrazian D (2021) Reaction of human monoclonal antibodies to SARS-CoV-2 proteins with tissue antigens: implications for autoimmune diseases. Front Immunol 11:617089. https://doi.org/10.3389/fimmu.2020.617089
21. Bragazzi NL, Hejly A, Watad A, Adawi M, Amital H, Shoenfeld Y (2020) ASIA syndrome and endocrine autoimmune disorders. Best Pract Res Clin Endocrinol Metab 34:101412. https://doi.org/10.1016/j.beem.2020.101412
22. Passah A, Arora S, Damle NA, Reddy KS, Khandelwal D, Aggarwal S (2018) Occurrence of subacute thyroiditis following influenza vaccination. Indian J Endocrinol Metab 22:713–714. https://doi.org/10.4103/ijem.IJEM_237_18
23. Hsiao JY, Hsin SC, Hsieh MC, Hsia PJ, Shin SJ (2006) Subacute thyroiditis following influenza vaccine (Vaxigrip) in a young female. Kaohsiung J Med Sci 22:297–300. https://doi.org/10.1016/s1607-551x(09)70315-8
24. Girgis CM, Russo RR, Benson K (2010) Subacute thyroiditis following the H1N1 vaccine. J Endocrinol Invest 33:506. https://doi.org/10.1007/BF03346633
25. Toft J, Larsen S, Toft H (1998) Subacute thyroiditis after hepatitis B vaccination. Endocr J 45:135
26. Pellegrino P, Perrone V, Pozzi M, Carnovale C, Perrotta C, Clementi E, Radice S (2015) The epidemiological profile of ASIA syndrome after HPV vaccination: an evaluation based on the Vaccine Adverse Event Reporting Systems. Immunol Res 61:90–96. https://doi.org/10.1007/s12026-014-8567-3
27. Pujol A, Gómez LA, Gallegos C, Nicolau J, Sanchís P, González-Freire M, López-González ÁA, Dotres K, Masmiquel L (2022)

Thyroid as a target of adjuvant autoimmunity/inflammatory syndrome due to mRNA-based SARS-CoV2 vaccination: from Graves' disease to silent thyroiditis. J Endocrinol Invest 45(4):875–882. https://doi.org/10.1007/s40618-021-01707-0
28. Taieb A, Sawsen N, Asma BA, Ghada S, Hamza E, Yosra H, Amel M, Molka C, Maha K, Koussay A (2022) A rare case of Grave's disease after SARS-CoV-2 vaccine: is it an adjuvant effect? Eur Rev Med Pharmacol Sci 26(7):2627–2630. https://doi.org/10.26355/eurrev_202204_28500
29. Taşkaldıran I, Altay FP, Bozkuş Y, İyidir ÖT, Nar A, Tütüncü NB (2022) A case report of concurrent Graves' disease and subacute thyroiditis following SARS-CoV-2 vaccination: an Autoimmune/Inflammatory Syndrome (ASIA). Endocr Metab Immune Disord Drug Targets. https://doi.org/10.2174/1871530322666220621101209
30. Li Q, Wang B, Mu K, Zhang JA (2019) The pathogenesis of thyroid autoimmune diseases: New T lymphocytes - Cytokines circuits beyond the Th1-Th2 paradigm. J Cell Physiol 234:2204–2216. https://doi.org/10.1002/jcp.27180
31. Smith TJ, Hegedüs L (2016) Graves' disease. N Engl J Med 375:1552–1565
32. Davies TF, Andersen S, Latif R, Nagayama Y, Barbesino G, Brito M, Eckstein AK, Stagnaro-Green A, Kahaly GJ (2020) Graves' disease. Nat Rev Dis Primers 6:52. https://doi.org/10.1038/s41572-020-0184-y
33. Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, Marinò M, Vaidya B, Wiersinga WM (2021) The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. Eur J Endocrinol 185:G43–G67. https://doi.org/10.1530/EJE-21-0479
34. Dalan R, Boehm BO (2022) Micronutrient supplementation before COVID-19 vaccination can protect against adverse effects. Clin Nutr ESPEN 47:433–434. https://doi.org/10.1016/j.clnesp.2021.11.008