Graves' Disease Following SARS-CoV-2 Vaccination: A Systematic Review

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Abstract: (1) Background: Autoimmune diseases, including autoimmune endocrine diseases (AIED), are thought to develop following environmental exposure in patients with genetic predisposition. The vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could represent a new environmental trigger for AIED, including Graves’ disease (GD). (2) Methods: We performed a literature search of MEDLINE/PubMed databases regarding thyroid dysfunction after SARS-CoV-2 vaccination since 1 January 2020 to 31 July 2022, considering only cases of thyrotoxicosis that meet the 2016 American Thyroid Association guidelines criteria for the diagnosis of GD and arising after administration of the anti-SARS-CoV-2 vaccine, regardless of the number of doses. (3) Results: A total of 27 articles were identified, consisting of case reports or case series, of which 24 describe the appearance of 48 new diagnoses of GD and 12 GD recurrences arising after the administration of the anti-SARS-CoV-2 vaccine, and 3 papers that instead report only 3 cases of GD relapse following vaccination. (4) Conclusions: physicians should be aware of the possibility of developing GD and other autoimmune sequelae following SARS-CoV-2 vaccination. Regardless of the underlying pathogenetic mechanisms (autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome), cytokines induction, molecular mimicry, and cross-reactivity), an individual predisposition seems to be decisive for their development.

Keywords: Graves’ disease; SARS-CoV-2; COVID-19; vaccine; hyperthyroidism; ASIA syndrome; autoimmune thyroid diseases

1. Introduction

As of the end of July 2022, the COVID-19 pandemic caused by SARS-CoV-2 has spread around the world with nearly 600 million cases and more than 6 million confirmed deaths, according to the WHO databases [1]. SARS-CoV-2 infection can run asymptomatically or provoke mild upper respiratory tract symptoms such as dry cough, headache, fever, and loss of smell and taste, or it can induce an interstitial pneumonia that can result in ARDS (Acute Respiratory Distress Syndrome) with the need for mechanical ventilation [2]. To date, the most effective weapon to fight SARS-CoV-2 infection is represented by primary prophylaxis with vaccines. In a short time, numerous sera have been released [3], including, for the first time, mRNA-technology-based vaccines (Pfizer-Biontech’s BNT162b2 and Moderna’s mRNA-1273) [4,5]. As with other vaccinations, the anti-SARS-CoV-2 vaccination campaign immediately highlighted the possibility of developing side effects, ranging from mild local reactions (pain at the insertion point) to systemic phenomena (fever, headache, asthenia, muscle aches) [6]. However, beyond these expected events, numerous more severe autoimmune phenomena such as myocarditis [7,8] and other manifestations have
been documented soon thereafter, especially among those subjects already suffering from other forms of autoimmunity or with a familiarity for it [9]. There are several reports of auto-inflammatory and autoimmune reactions also affecting the endocrine system and the thyroid, especially in the form of subacute thyroiditis [10] and GD [11–38]. GD is an autoimmune thyroid disease characterized by the presence of autoantibodies against the TSH receptor (TRAb) expressed on thyrocytes, which cause thyroid gland growth and thyroid hormone synthesis and release with consequent hyperthyroidism [39,40]. Given the remarkable diffusion of anti-SARS-CoV-2 vaccination and its impact on public health, in this review, we report all the postvaccine cases of GD documented in the literature up to 31 July 2022, more than a year after the beginning of the immunization campaign, focusing on their main epidemiological and clinics features. Furthermore, although a causality relationship cannot be proven yet, we summarize the potential pathogenetic mechanisms that could explain the onset of autoimmunity following the anti-SARS-CoV-2 vaccination to provide up-to-date information about this emerging topic.

2. Materials and Methods

We performed a literature search of MEDLINE/PubMed databases regarding thyroid dysfunction after SARS-CoV-2 vaccination from 1 January 2020 to 31 July 2022. We included original articles, reviews, viewpoints, commentaries, case series and case reports, and both published and unpublished articles. The search terms, used both separately and in combination, included: “SARS-CoV-2”, “COVID19”, “thyroid”, “Graves’ disease”, “hyperthyroidism”, “autoimmune thyroid disease”, “vaccine”, “vaccination”, “thyrotoxicosis”, and “thyroiditis”.

In accordance with the 2016 guidelines of the American Thyroid Association [41], only cases of thyrotoxicosis that meet the following criteria for the diagnosis of GD and arising after administration of the anti-SARS-CoV-2 vaccine, regardless of the number of doses, were considered: (a) thyroid function tests consistent with hyperthyroidism; (b) TRAb or TSI positivity; (c) presence of thyroid scan showing high radioactive iodine uptake (RAIU); or (d) thyroid ultrasound picture of the glandular parenchyma with diffuse hypervascularization (“thyroid inferno” pattern). The findings of this review are reported in accordance with PRISMA guidelines [42].

Univariate descriptive statistics were performed. Categorical variables were analyzed using frequencies, and quantitative continuous variables were expressed the median and interquartile range (IQR).

3. Results

3.1. General Characteristics

A total of 27 articles were identified (Figure 1) consisting of case reports or case series, of which 24 describe the appearance of 48 new diagnoses of GD and 12 GD recurrences arising after the administration of the anti-SARS-CoV-2 vaccine, and 3 papers that instead report only 3 cases of GD relapse following vaccination. All these cases have been summarized in Tables 1 and 2 and compared in Table 3.
received Janssen’s Ad26.COV2.S and CoronaVac. In 12 cases, the brand of the vaccine was not specified, but only the type (mRNA based) [38]. All cases who received more than one shot received a homologous vaccination, except for one patient who received the first two doses of Sinovac’s CoronaVac and a third booster dose of ChAdOx1 (24). One patient complained of symptoms after the third dose of mRNA-1273 [35]. Only four patients had a documented previous COVID-19 infection and in all of these patients, a new diagnosis of GD was established.

Figure 1. PRISMA flow diagram of study search and selection.
Table 1. Summary of demographic, clinical, and laboratory characteristics of new Graves’s disease following SARS-CoV-2 vaccination in the literature.

| Gender | Age  | Country | Vaccine | History of COVID | Dose | Personal/Family History of AITD | Medical History | Symptoms | Days until Symptoms | TSH (mIU/L) | FT3 (ng/dL) | FT4 (ng/dL) | TgAb (IU/mL) | TPOAb (IU/mL) | TRAb (IU/L) | Thyroid US | Thyroid Scan | Reference |
|--------|------|---------|---------|------------------|------|-------------------------------|----------------|----------|---------------------|-------------|-------------|-------------|--------------|---------------|-------------|-----------|------------|----------|
| M      | 52   | Italy   | BNT162b2 | No               | 2nd | None                          | Type 2 Diabetes, Vitiligo | Weight loss, asthma, thyroiditis | 20 <0.004 (N: 0.1–0.4) | 15 (N: 2.7–5.7) | 5.96 (N: 0.7–1.7) | 30 (N: 0–30) | 21 (N: 0–1.49) | 6.48 (N: 0–1.49) | Enlargement and hyperthyroidity | N/A |
| F      | 40   | Mexico  | BNT162b2 | Yes             | 1st | None                          | None                        | Nausea, vomiting, fatigue, insomnia, and palpitations | 2 <0.001 (N: 0.27–4.4) | 10.5 (N: 2.4–4.4) | 3.97 (N: 0.95–1.71) | 210 (N: 0–44) | 349 (N: 0–6) | 16.56 (N: 0–1.75) | Enlargement and hyperthyroidity | N/A |
| F      | 28   | Mexico  | BNT162b2 | No              | 1st | None                          | None                        | Anxiety, tachycardia | 3 <0.001 (N: 0.27–4.4) | 9.2 (N: 2.4–4.4) | 1.84 (N: 0.95–1.71) | 33 (N: 0–44) | 823 (N: 0–5.6) | 5.85 (N: 0–1.75) | N/A | Diffuse goiter | V. Lastra [11] |
| M      | 46   | Austria | BNT162b2 | No              | 1st | None                          | None                        | Weight loss | 15 N/A | 5.18 (N: 2.15–4.12) | 1.63 (N: 0.7–1.7) | N/A | N/A | 2.9 (N: 0.1–1.5) | Hypothecogenic panhypopituitarism, large aneuploidic areas with increased vasculatization | N/A |
| F      | 71   | Spain   | BNT162b2 | No              | 2nd | None                          | None                        | N/A | N/A | 7.2 (N: 0.1–1.7) | 8.9 (N: 0.9) | N/A | N/A | 1730 (N: 0–2.9) | Diffuse goiter | Pla Filipi [10] |
| M      | 70   | Thailand| ChA1b1    | No              | 2nd | None                          | None                        | N/A | N/A | 10.9 (N: 0.1–2.9) | 4.9 (N: 0–1.75) | 5.1 (N: 0–1.75) | N/A | N/A | N/A | Diffuse goiter | Pla Filipi [10] |
| F      | 38   | Spain   | BNT162b2 | No              | 1st | None                          | None                        | N/A | N/A | 7.2 (N: 0.1–1.7) | 8.9 (N: 0.9) | N/A | N/A | 1730 (N: 0–2.9) | Diffuse goiter | Pla Filipi [10] |
| F      | 63   | USA     | mRNA-1273 | No              | 1st | None                          | None                        | None | N/A | 4.06 (N: 0.6–1.12) | N/A | N/A | N/A | 3.2 (N: 0–2.9) | N/A | Diffuse goiter | Pla Filipi [10] |
| F      | 71   | USA     | BNT162b2 | No              | 2nd | CMN/None                      | Stage IV breast cancer in remission | N/A | N/A | 7.2 (N: 0.1–1.7) | 8.9 (N: 0.9) | N/A | N/A | 1730 (N: 0–2.9) | Diffuse goiter | Gehin[10] |
| M      | 32   | USA     | BNT162b2 | No              | 1st | None                          | None                        | Palpitations, insomnia, tremors, irritability, sweating, dyspnea | 10 <0.005 (N: 0.25–0.5) | N/A | 3.81 (N: 0.6–1.1) | N/A | N/A | N/A | 1730 (N: 0–2.9) | Diffuse goiter | Pla Filipi [10] |
| M      | 70   | Thailand| ChA1b1    | No              | 2nd | None                          | None                        | Myalgia, palpitations, exertional dyspnea, behavioral disturbances, insomnia, sweating | 4 <0.005 (N: 0.25–4.5) | 7.46 (N: 0.7–1.4) | 2.01 (N: 0–1.75) | 350 (N: 0–6) | 15 (N: 0–1.8) | 8.39 (N: 0–1.75) | Diffuse goiter | Pla Filipi [10] |
| F      | 38   | Spain   | BNT162b2 | No              | 1st | None                          | None                        | Thyroid, tachycardia, palpitations | 5 <0.05 (N: 0.45–4.5) | N/A | 8.50 (N: 0–1.75) | N/A | N/A | N/A | 1730 (N: 0–2.9) | Diffuse goiter | Pla Filipi [10] |
| F      | 63   | USA     | mRNA-1273 | No              | 1st | None                          | N/A (goiter with LES) | Pruritic rash upper chest and neck | 7 0.011 (N: 0.05–4.78) | N/A | 2.4 (N: 0–1.8) | N/A | N/A | N/A | 1730 (N: 0–2.9) | Diffuse goiter | Pla Filipi [10] |
| M      | 30   | USA     | BNT162b2 | No              | 2nd | None                          | None (nontheraputic post-partum GD) | Weight loss, irritability, palpitations, tremors, nausea, sleep | 28 <0.005 (N: 0.45–4.5) | N/A | 1.77 (N: 0.52–1.77) | N/A | N/A | N/A | 1730 (N: 0–2.9) | Diffuse goiter | Pla Filipi [10] |
| F      | 40   | China   | BNT162b2 | No              | 2nd | None                          | None                        | Hypothyroidism/None | 35 <0.02 (N: 0.4–0.46) | 19.8 (N: 2.7–5.7) | 5.17 (N: 0–1.75) | 7.2 (N: 0–9) | 212 (N: 0–6) | 24 (N: 0–4.5) | Diffuse goiter | Vo Lui [22] |
| F      | 35   | Austria | ChAdO1b   | No              | 1st | None                          | None                        | Palpitations, hyperphagia, heat intolerance and tremors | 5 <0.02 (N: 0.6–1) | 19.5 (N: 2.2–3.9) | 4.07 (N: 0.7–1.35) | N/A | N/A | N/A | 1730 (N: 0–2.9) | Diffuse goiter | Raven [20] |
| F      | 46   | South Korea | ChAdO1b | N/A              | 1st | None                          | None                        | Chest pain, dyspnea | 1 0.01 (N: 0.7–0.7) | N/A | 2.25 (N: 0–4.5) | N/A | N/A | N/A | 1730 (N: 0–2.9) | Diffuse goiter | Lee [19] |
| F      | 73   | South Korea | ChAdO1b | N/A              | 2nd | None                          | None                        | Weight loss, dyspnea | 14 <0.005 (N: 0.7–0.7) | N/A | 2.25 (N: 0–4.5) | N/A | N/A | N/A | 1730 (N: 0–2.9) | Diffuse goiter | Lee [19] |
| M      | 20   | India   | ChAdO1b   | N/A              | 1st | None                          | None                        | Weight loss, tremors | 7 0.002 (N: 0.36–5.6) | N/A | N/A | N/A | N/A | 2.6 (N: 0–1.22) | N/A | N/A | Kaushludy [27] |
| F      | 41   | India   | ChAdO1b   | No              | 1st | None/AITD                      | None                        | Weight loss | 10 0.01 (N: 0.36–5.6) | N/A | N/A | N/A | N/A | 410 (N: 0–1.22) | N/A | N/A | Kaushludy [27] |
| F      | 19   | India   | ChAdO1b   | No              | 1st | None/AITD                      | None                        | Weight loss, palpitations, hair loss | 28 0.01 (N: 0.36–5.6) | N/A | N/A | N/A | N/A | 7.3 (N: 0–1.22) | N/A | N/A | Kaushludy [27] |
| Gender | Age | Country | Vaccine | History of AITD | Symptoms during AITD | Days since symptom onset | Thyroid US | Thyroid Scan | Reference |
|--------|-----|---------|---------|-----------------|----------------------|------------------------|-------------|-------------|-----------|
| F      | 37  | India   | ChAdOx1 | None            | None                 | 14                     | N/A         | N/A         | Chaudhary [27] |
| F      | 31  | Japan   | BNT162b2| None            | Type 1 Diabetes     | 7                      | N/A         | N/A         | Sakai [18]  |
| M      | 22  | Belgium | BNT162b2| Yes             | Tumors              | 14                     | N/A         | N/A         | Marta [29]  |
| M      | 54  | Italy   | BNT162b2| 1st             | None                 | 5                      | N/A         | N/A         | Bros [31]   |
| F      | 45  | Singapore| BNT162b2| 1st             | None                 | 4                      | N/A         | N/A         | Chua [31]   |
| F      | 39  | Tunisia | BNT162b2| None            | None                 | 3                      | N/A         | N/A         | Taeib [12]  |
| M      | 57  | Mexico  | ChAdOx1 | None            | Pulmonary edema      | 7                      | N/A         | N/A         | Enlargement and hyperacidity Diffuse uptake Coen [33] |
| M      | 39  | Taiwan  | mKNA-1273| 1st             | Hemorrhage           | 14                     | N/A         | N/A         | N/A        |
| F      | 39  | Taiwan  | ChAdOx1 | 1st             | None                 | 14                     | N/A         | N/A         | N/A        |
| M      | 44  | France  | BNT162b2| 1st             | None                 | 2                      | N/A         | N/A         | Chua [31]   |
| M      | 42  | USA     | mKNA-1273| 2nd             | None                 | 2                      | N/A         | N/A         | Singh [30]  |
| F      | 68  | USA     | Ad26Cov2 | None            | None                 | 30                     | N/A         | N/A         | Singh [30]  |
| M      | 50  | Italy   | BNT162b2| 1st             | None                 | 14                     | 3.8 (N: 0.7-0.1-1)     | N/A         | Enlargement and hyperacidity Diffuse uptake Ruggeri [38] |
| M      | 50  | Italy   | BNT162b2| 1st             | None                 | 14                     | 3.8 (N: 0.7-0.1-1)     | N/A         | Enlargement and hyperacidity Diffuse uptake Ruggeri [38] |
| M      | 47  | Turkey  | BNT162b2| No              | None                 | 5                      | N/A         | N/A         | Bostan [37] |
| M      | 46  | Turkey  | BNT162b2| 2nd             | None                 | 14                     | N/A         | N/A         | Bostan [37] |
| F      | 51  | Turkey  | BNT162b2| 2nd             | None                 | 4                      | N/A         | N/A         | Bostan [37] |
| F      | 53  | Turkey  | BNT162b2| Yes             | None                 | 7                      | N/A         | N/A         | Bostan [37] |
| F      | 33  | China   | N/A     | None            | None                 | 2                      | N/A         | N/A         | Che [39]    |
| F      | 37  | China   | N/A     | None            | None                 | 7                      | N/A         | N/A         | Che [39]    |
| F      | 37  | China   | N/A     | None            | None                 | 21                     | N/A         | N/A         | Che [39]    |
| F      | 34  | China   | N/A     | None            | None                 | 26                     | N/A         | N/A         | Che [39]    |
| F      | 33  | China   | N/A     | None            | None                 | 9                      | N/A         | N/A         | Che [39]    |
| F      | 43  | China   | N/A     | None            | None                 | 13                     | N/A         | N/A         | Che [39]    |

Abbreviations: F: female; M: male; COVID-19: coronavirus disease 2019; AITD: autoimmune thyroid disease; SLE: Systemic lupus erythematosus; GD: Graves’ disease; DM: diabetes mellitus; AITD: anti-thyroid peroxidase antibody; TgAb: anti-thyroglobulin antibody; TRAb: TSH receptor antibody; US: ultrasound.
Table 2. Summary of demographic, clinical, and laboratory characteristics of Graves’s disease relapses following SARS-CoV-2 vaccination in the literature.

| Gender | Age | Country | Vaccine History of COVID | History of AITD | Medical History | Symptoms | Days until Symptoms | Days until Symptoms | TSH (mIU/L) | fT3 (ng/L) | fT4 (ng/dL) | TgAb (IU/mL) | TPOAb (IU/mL) | TRAb (IU/L) | Thyroid US | Thyroid Scan | Reference |
|--------|-----|---------|--------------------------|-----------------|----------------|----------|---------------------|---------------------|-------------|-------------|--------------|--------------|--------------|-------------|------------|-------------|----------|
| F      | 71  | Austria | BNT162b2                | No              | GD/none        | Palpitations and sweating | 30       | N/A                 | 3.56 (N: 0.7–1.7) | N/A         | N/A         | 4.2 (N: 0–1.5) | N/A          | N/A          | Mild increased uptake | Zettining [12] |
| F      | 64  | Japan   | BNT162b2                | No              | Subclinical Hyper-thyroidism/none | Palpitations, dyspnoea, fever, leg edema | 6       | <0.05 (N: 0.4–2.7) | 2.54 (N: 0.79–1.6) | N/A         | N/A         | 33.8 (N: 0–0.55) | N/A          | N/A          | Enlargement and hypervascularity | N/A Yamamoto [26] |
| F      | 34  | Belgium | BNT162b2                | No              | GD/none        | Tumors, sweating, weight loss, swelling of eyelids | 10      | <0.05 (N: 0.4–2.7) | 13.5 (N: 1.95–4.23) | N/A         | N/A         | 80 (N: 0–0.55)   | N/A          | N/A          |  N/A                   | N/A Yamamoto [26] |
| F      | 30  | Thailand | CoronaVac+ ChAdOx1       | No              | GD on MEZ/none | Palpitations, weight loss, increased appetite | 4       | 0.01 (N: 0.15–0.4) | 3.21 (N: 1.86–3.15) | N/A         | N/A         | 13.4 (N: 0–1.25) | N/A          | N/A          | N/A                   | N/A Yaroslavsky [24] |
| M      | 34  | South Korea | Ad26. COV2.S         | 3rd (ChAdOx1) | GD/none        | Tumors, palpitations | 5       | <0.05 (N: 0.7–2.6) | 2.06 (N: 0.81–1.76) | N/A         | N/A         | 4.34 (N: 0–1.25) | N/A          | N/A          | Diffuse hypervascularity | N/A Lee [19] |
| F      | 41  | Singapore | CoronaVac               | No              | GD/none        | Tremors, palpitations | 5       | <0.05 (N: 0.7–2.6) | 3.74 (N: 0.95–1.47) | N/A         | N/A         | 5.35 (N: 0–1.74) | N/A          | N/A          | N/A                   | N/A Chua [31] |
| M      | 44  | Turkey   | CoronaVac               | No              | GD/none        | Sweating, palpitations, asthma | 7       | <0.05 (N: 0.27–4.2) | 2.67 (N: 0.93–1.7) | 119 (N: 1.15) | 284 (N: 0–34) | 12.18 (N: 0–1.5) | N/A          | N/A          | N/A                   | N/A Bostan [17] |
| M      | 49  | Turkey   | BNT162b2                | No              | GD/none        | Sweating, palpitations, tremors, muscle weakness | 30      | <0.05 (N: 0.27–4.2) | 13.50 (N: 2.44–4.4) | N/A         | N/A         | 3.01 (N: 0–1.5)  | N/A          | N/A          | Diffuse hypervascularity | N/A Bostan [17] |
| F      | 31  | Turkey   | BNT162b2                | No              | Breast cancer  | Sweating, asthenia | 21      | <0.05 (N: 0.27–4.2) | 21.7 (N: 3.9–7.7)  | N/A         | N/A         | 3.37 (N: 0–1.5)  | N/A          | N/A          | N/A                   | N/A Bostan [17] |
| M      | 59  | China    | N/A (mRNA)             | No              | GD/AITD       | N/A | N/A | 21.7 (N: 3.9–7.7) | N/A         | N/A         | 12.8 (N: <1)   | N/A          | N/A          | N/A                   | N/A Choi [30] |
| F      | 74  | China    | N/A (mRNA)             | No              | GD/AITD       | N/A | N/A | 11.2 (N: 3.54–6.6) | N/A         | N/A         | 6.2 (N: <1)    | N/A          | N/A          | N/A                   | N/A Choi [30] |
| F      | 25  | China    | N/A (mRNA)             | No              | GD/AITD       | N/A | N/A | 11.2 (N: 3.54–6.6) | N/A         | N/A         | 2.9 (N: <1)    | N/A          | N/A          | N/A                   | N/A Choi [30] |
| F      | 41  | China    | N/A (mRNA)             | No              | GD/none       | N/A | N/A | 11.2 (N: 3.54–6.6) | N/A         | N/A         | 3.9 (N: <1)    | N/A          | N/A          | N/A                   | N/A Choi [30] |
| F      | 24  | China    | N/A (mRNA)             | No              | GD/none       | N/A | N/A | 11.2 (N: 3.54–6.6) | N/A         | N/A         | 2.4 (N: <1)    | N/A          | N/A          | N/A                   | N/A Choi [30] |
| F      | 22  | China    | N/A (mRNA)             | No              | GD/none       | N/A | N/A | 11.2 (N: 3.54–6.6) | N/A         | N/A         | 5.8 (N: <1)    | N/A          | N/A          | N/A                   | N/A Choi [30] |

Abbreviations: F: female; M: male; COVID-19: coronavirus disease 2019; AITD: autoimmune thyroid disease; GD: Graves’ disease; DM: diabetes mellitus; MMI: methimazole; N/A: not available; TSH: thyrotropin; fT3: free triiodothyronin. fT4: free tiroxine; TPOAb: anti-thyroid peroxidase antibody; TgAb: anti-thyroglobuline antibody; TRAb: TSH receptor antibody; US: ultrasound; Ref: reference.
Table 3. Overview of new cases and relapses of Graves’ disease following SARS-CoV-2 vaccination reported in the literature.

| New Onset GD | GD Recurrence |
|--------------|---------------|
| **Number of Cases** | 48 | 15 |
| **Sex** | F (70.8%)—M (29.2%) | F (73.3%)—M (26.7%) |
| **Age (years), median [IQR]** | 43 [IQR 35–50.5] | 41 [IQR 30–59] |
| **Type of SARS-CoV-2 vaccine** | BNT162b2 50% | BNT162b2 33.3% |
| | ChAdOx1 27% | ChAdOx1 + CoronaVac 6.6% |
| | mRNA-1273 8.3% | Ad26.COV2.S 6.6% |
| | Ad26.COV2.S 2.2% | CoronaVac 6.6% |
| | Not specified (mRNA) 12.5% | mRNA-1273 6.6% |
| **Days to symptoms onset, median [IQR]** | 10 [IQR 5–14] | 11 [IQR 6–28] |
| **Major symptoms** | palpitations (61.9%) | palpitations (77.8%) |
| | weight loss (35.7%) | sweating (55.5%) |
| | distal tremor (28.6%) | weight loss (33.3%) |
| | behavioral/sleep disorders (26.1%) | |
| | asthenia (21.4%) | |
| | GI symptoms (14.3%) | |
| **TSH (IU/mL), median [IQR]** | 0.008 [0.004–0.01] | 0.01 [0.008–0.01] |
| **fT3 (ng/L), median [IQR]** | 13.2 [9.83–19.9] | 13.5 [7.97–22.45] |
| **fT4 (ng/dL), median [IQR]** | 3.58 [254–5.34] | 3.32 [1.55–3.86] |
| **TRAb (IU/L), median [IQR]** | 6.45 [4.39–16.56] | 5.8 [3.85–13.4] |

Abbreviations: GD, Graves’ disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IQR, interquartile range; GI, gastrointestinal; TSH, thyrotropin; fT3, free triiodothyronine; fT4, free thyroxine; TRAb, TSH receptor antibody.

Among the new cases of GD, 34 are female (70.8%) and 14 men (29.2%) with a median age of 43 years [IQR 35–50.5]. Eleven women (73.3%) and four men (26.7%) with a median age of 41 [IQR 30–59] had a GD relapse. Data were collected from patients living in Europe, North America, Asia, Africa, and Oceania. Of the patients, 29/63 (46%) received the BNT162b2 vaccine (24/48 (50%) in the newly diagnosed group and 5/15 (33.3%) among relapses); 14/63 (22.2%) (13/48 (27%), and 1/15 (6.7%), respectively) received the AstraZeneca’s ChAdOx1; 5/63 (7.9%) received Moderna’s mRNA-1273; and only 2/63 (3.2%) received Janssen’s Ad26.COV2.S and CoronaVac. In 12 cases, the brand of the vaccine was not specified, but only the type (mRNA based) [38]. All cases who received more than one shot received a homologous vaccination, except for one patient who received the first two doses of Sinovac’s CoronaVac and a third booster dose of ChAdOx1 (24). One patient complained of symptoms after the third dose of mRNA-1273 [35]. Only four patients had a documented previous COVID-19 infection and in all of these patients, a new diagnosis of GD was established.

3.2. Clinical Features

Among those with newly diagnosed GD, only 5 of 48 patients (10.4%) reported a history of thyroid disease: 1 patient was suffering from multinodular goiter [16], 1 from hypothyroidism of unspecified etiology but on hormone replacement therapy [22], and 3 from non-GD AITD [30,34,36]. On the other hand, family history for thyroid autoimmunity was inconsistently specified. A total of 31 out of 48 patients (64.6%) in the new diagnosis group, and 8 out of 15 (53.3%) in the relapse group, developed autoimmune hyperthyroidism after a single dose of vaccine; the median time from immunization to the onset of hyperthyroidism clinical features was 10 days [IQR 5–14] and 11 days [IQR 6–28], respectively.
In patients with new-onset GD following COVID vaccination, when reported (42/48), the most frequent symptoms were palpitations (26/42, 61.9%), weight loss (15/42, 35.7%), distal tremor (12/42, 28.6%), behavioral disturbances and sleep disturbances (11/42, 26.1%), asthenia (9/42, 21.4%), gastrointestinal disturbances (6/42, 14.3%), and finally, with lower frequency, fever, exertional dyspnea, sweating, heat intolerance, and headache. The median value of measured TSH was 0.008 IU/mL (0.4–4.00) [IQR 0.004–0.01], median fT3 13.2 ng/L (2.7–5.7) [IQR 9.83–19.9], and median fT4 3.58 ng/dL (0.7–1.7) [IQR 2.5–5.34], while increased levels of TRAb were reported in 43/48 cases (89.5%) with a median value of 6.45 IU/L (0–1.5) [IQR 4.39–16.56]. A total of 4/48 (8.3%) patients were investigated only for thyroid-stimulating immunoglobulins (TSI), which turned frankly positive in all cases.

Patients affected by GD relapse, when reported (9/15), complained mainly of palpitations (77.8%), sweating (55.5%), and weight loss (33.3%); the thyroid profile showed a median TSH value of 0.01 mIU/L (0.4–4.00) [IQR 0.008–0.01], median fT3 of 13.5 ng/L (2.7–5.7) [IQR 7.97–22.45], median fT4 of 3.32 ng/dL (0.7–1.7) [IQR 1.55–3.86], and TRAb level above the normal range in all cases (100%).

In both groups, antibodies directed against thyroid antigens (thyroglobulin antibodies (TgAb) and thyroperoxidase antibodies (TPOAb)) were occasionally measured, just as an imaging examination (thyroid ultrasound or RAIU) was not always performed (Tables 1 and 2). When available, the neck ultrasonography showed a picture of a widespread increase in gland size and vascularity, while the RAIU was high.

Given the short period of observation of these patients, all the authors reported the administration of antithyroid drugs (Thionamides) and beta-blockers as an initial therapy and symptom-control strategy for hyperthyroidism.

4. Discussion

Previous studies have already reported that vaccines, including those against human papillomavirus (HPV), hepatitis B (HBV), and influenza, can trigger the development or recurrence of autoimmune diseases, including chronic lymphocytic thyroiditis [43–45]. To respond quickly and efficaciously to the global health emergency represented by the SARS-CoV-2 pandemic, several vaccines have been approved in a short time: some of them use existing technologies, such as viral vectors (ChAdOx1, Ad26.COV2.S) [46,47] or inactivated viruses (CoronaVac) [48], but others have been based on platforms never used before, such as those based on mRNA: BNT162b2 and mRNA-1273. The latter uses a carrier system for the nucleic acid consisting of lipid nanoparticles that transfer the mRNA encoding for the antigen (SARS-CoV-2 spike protein) inside the host cells, where it is translated by the ribosomes and stimulates a robust immune response mediated by CD4 + and CD8 + T-cells [49].

The GD cases are largely collected following the administration of mRNA-based vaccines (46/63, 73%). However, it must be mentioned that these types of vaccine are the most widely administered globally. In fact, as of 11 August 2022, in the European Union, more than 1 billion shots out of approximately 1.2 billion doses administered were produced by Pfizer-Biontech and Moderna [50].

Several pathogenetic mechanisms have been considered to explain the development of thyroid autoimmune reactions after SARS-CoV-2 vaccination (Figure 2).
Many authors agree that these manifestations are the result of the “autoimmune/inflammatory syndrome induced by adjuvants” (ASIA), defined by Shoenfeld in 2011 [51]. According to this theory, the adjuvants contained in the vaccine with the aim of increasing their immunogenicity can activate an immunological cascade capable, in predisposed subjects, of breaking the immunological tolerance towards self-antigens. In adenovirus-based vaccines (ChAdOx1), this role could be played by buffer/oxidation inhibitor molecules (histidine) and non-ionic surfactant (polysorbate 80), while in inactivated virus vaccines (CoronaVac), this role is played by aluminum salts [52]. Of mRNA-based vaccines (BNT162b2 and mRNA-1273), both the nucleic acid molecule itself, capable of inducing the so-called self-adjuvant effect [53], and the lipid conjugates of polyethylene glycole (PEG) [54], which stabilize the transport nanoparticles, are believed to be responsible. Moreover, PEGs have also been considered to be the culprit of hypersensitivity and anaphylaxis reactions [55].

Regarding the ASIA syndrome hypothesis, in animal models, inflammatory responses induced by the lipid nanoparticles have been described, and they were characterized by a significant neutrophil infiltrate and by the production of numerous cytokines and chemokines, including IL-1beta/IL-6 and the macrophage inflammatory protein-α and macrophage inflammatory protein-β, which in turn could trigger a sustained inflammatory response [56].

According to Sprent and King [57], the adverse effects of anti-COVID-19 vaccines are nothing more than the epiphenomenon of an important production of interferon (IFN) type 1 and thus of a concomitant activation of the immune response. Precisely these cytokines, such as IFN-alpha, IFN-gamma, and CXCL10/IP10, peculiar of Th1-type immune response, play a crucial role in the pathogenesis of autoimmune thyroid diseases, including GD and Graves’ ophthalmopathy (GO) [58–62].

In addition, Poma et al. recently demonstrated that thyrocytes with direct evidence of SARS-CoV-2 genome and antigens taken from patients who died of COVID-19 carry transcriptional variations of the immunity genes, resulting in an important activation of IFN type 1 (IFN alpha) and type 2 (IFN gamma) pathways, which in turn are able to induce or reactivate thyroid autoimmunity [63]. Therefore, although the above data were obtained following natural infection, it could be speculated that the initial burst in IFN-1 release induced by vaccination could also contribute to triggering autoimmune reactions in predisposed subjects, similarly to what seems to be possible after the virus entry into the cells.

A further mechanism considered plausible for the development of autoimmune reactions from the anti-SARS-CoV-2 vaccine is represented by the “molecular mimicry” and by the cross-reactivity between some SARS-CoV-2 proteins and a variety of host antigens. In fact, it has been shown that the spike protein, the nucleoprotein, and the membrane

Figure 2. Potential pathogenetic mechanisms underlying the development of GD following SARS-CoV-2 vaccination.
protein of SARS-CoV-2 all cross-react with thyroid peroxidase (TPO) due to the similarity and homology of peptide sequences between this thyroid enzyme and the viral proteins [64,65]. Therefore, the SARS-CoV-2 spike protein produced within the host cells to stimulate the immune response against it could induce autoimmune reactions through the molecular mimicry mechanism. However, as observed for other vaccines (HPV, influenza and HBV) [43–45], the development of cross reactivity between exogenous and endogenous antigens seems limited to a minority of vaccinated subjects, demonstrating that even “molecular mimicry”, such as ASIA syndrome, requires an individual predisposition, probably of genetic nature. Nevertheless, to date, no data capable of explaining or predicting this susceptibility are available.

5. Conclusions

The risk of developing autoimmune sequelae after vaccination remains to be defined and there are no universally accepted criteria for their diagnosis yet. In addition, the management of these phenomena is not well defined, and the standard therapies for the “sporadic” counterparts are generally adopted. Moreover, it is becoming challenging for healthcare workers to establish the pertinence to inject the next scheduled shot in patients who have suffered from debilitating autoimmune sequelae such as in some cases of severe hyperthyroidism.

After all, we support and encourage the COVID-19 vaccination campaign as a major weapon in the fight against the pandemic, but at the same time, we want to underline the importance of being vigilant for the development of any autoimmune adverse events, including GD and hyperthyroidism, in order to have a rapid diagnosis along with the proper management of affected patients.

The small number of available papers and cases does not allow a statistical interpretation of the results, and the proposed pathogenetic mechanisms are only attempts to describe the development of this immune event without proving a causal relationship. Despite these limitations, our paper provides the most updated insight into the topic.

More than a year after the beginning of the immunization campaign, in this paper, we review the new cases and relapses of GD arising after the anti-SASR-CoV-2 vaccination, and we discuss the main features of the affected patients and the most plausible pathogenetic mechanisms (ASIA syndrome, cytokines induction, molecular mimicry, and cross-reactivity): considering the small number of cases compared to millions of vaccinated, an individual predisposition seems required; furthermore, the entire literature considered here consisted of case reports or series, proving only a temporal association.

The aim of this review is to raise awareness of healthcare workers about the possibility of developing GD and other autoimmune sequelae after SARS-CoV-2 vaccination, with the hope that future studies will allow us to identify the exact underlying pathogenetic mechanisms and subjects at highest risk.

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