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SARS-CoV-2 and thyroid diseases

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ABSTRACT

SARS-CoV-2 virus responsible for acute respiratory disease affected other organs leading to co-existence symptoms or complications. Thyroid gland was one of them due to expression of angiotensin-converting enzyme 2 (ACE2), the protein facilitating viral binding to the host cells. Moreover, thyroid gland, important for regulation of hormonal network, is extremely sensitive to any changes in homeostasis and metabolism. It was shown, that COVID-19 was associated with induction of thyroid disease or increasing existing functional disturbances or autoimmune process. Thyroid diseases are mainly based on immunological pathomechanism although the relation between immune system and thyroid function is bidirectional e.g. thyroid hormones modulate specific immune responses, including cell-mediated immunity, NK cell activity, the production of antiviral interferon (IFN) and proliferation of T- and B-lymphocytes. The effects of COVID-19 and mRNA vaccine on thyroid function and diseases are discussed.

1. Introduction

SARS-CoV-2 virus is currently considered as pathogen leading to systemic infection involving mainly respiratory system and frequently associated with chronic complications. Besides respiratory system, the profound fatigue, dyspnea, reduced lung capacity, sleep difficulties (hyposmia/anosmia), anxiety or depression, memory/cognitive impairment are noted as the symptoms of COVID-19 and its following complications. There are risk factors of such late complications established based on observations on reasonable number of patients. The severity of clinical course, more than five symptoms in the first week of the disease, female gender, older age, the presence of comorbidities, and the weak anti- SARS-CoV-2 antibodies response were noted as such risk factors. The ACE2 receptors are believed to be the way of virus entry into the cell, so all cells expressing this receptor are susceptible for this infection. Due to high ACE2 expression on thyroid cell, the thyroid may be a target for this infection. The occurrence and type of thyroid dysfunction are the combination of different factors and mechanisms, not yet fully described. The proposed mechanisms included the direct effect of COVID-19 on target cells, the indirect effect of systemic inflammatory or autoimmune response and dysfunction of the hypothalamic-pituitary-thyroid (HPT) axis leading to decreased thyroid stimulating hormone (TSH) level in the serum [1]. Autoimmune thyroid diseases (ATD) are the most common autoimmune dysfunction, affecting approximately 2 % of the female population and 0.2 % of the male population in adulthood. In children, autoimmune mechanism is the most common etiology of acquired thyroid disease [2]. ATD including Graves' disease (hyperthyroidism) and Hashimoto disease (hypothyroidism) are the effect of specific autoantibodies reacting with autoantigen – receptor for TSH. The antibodies stimulating production of thyroid hormone resulting in Graves' disease (GD) are present in serum in 60–80 % of patients [2]. In Hashimoto disease (HD), the antibodies are antagonistic, blocking the receptor, what results in hypothyroidism characterized with lymphocyte/plasmocyte infiltration of thyroid. The clinical symptoms of Hashimoto thyroiditis occurred very often after different time of ongoing autoimmune process of thyroiditis [3]. Viral infections are one of the environmental factors inducing or intensify of ongoing subacute thyroiditis and autoimmune thyroid diseases. Direct evidence of the presence of viruses or their components in the thyroid were shown for mumps in subacute thyroiditis and for retroviruses (HTLV-1, HFV, HIV and SV40) in Graves' disease, for HTLV-1, enterovirus, rubella, mumps virus, HSV, EBV and parvovirus in Hashimoto's thyroiditis [4]. Moreover, the hepatitis C virus and human parvovirus B19 are candidates for the role of possible inductors due to detection of viral components in thyroid tissues and sera of patients with

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Abbreviations

ACE2	angiotensin-converting enzyme 2
ATD	autoimmune thyroid disease
ATG	antibodies to thyreoglobuline
ATPO	antibodies to thyroid peroxidase
ASIA	autoimmune/inflammatory syndrome induced by adjuvants
COVID-19	Corona virus disease caused by the SARS-CoV-2 virus
HD	Hashimoto disease
HPT	hypothalamic-pituitary-thyroid axis
GD	Graves' disease
GTT	gestational transient thyrotoxicosis
OR	odds ratio
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TFT	thyroid function tests
Treg	T regulatory lymphocytes
TSHR	receptor for TSH
TSHR-Abs	autoantibodies to TSHR

Hashimoto's thyroiditis [5]. COVID-19 are concentrated in respiratory system, mainly in the lungs, especially in the lung parenchyma through the respiratory system as way of entry. The virus spike S proteins react with angiotensin-converting enzyme 2 (ACE2) present on the surface of pneumocytes, what mediates the entry of the virus to the host cells. This mechanism is also used for infection of other cell types in the different organs. In endocrine system, the pancreas, testis, ovary, adrenal gland, pituitary gland and thyroid gland cells are ACE2-expressing. The highest expression of ACE2 is noticed in testes followed by thyroid and with the lowest expression on the hypothalamus cells. The pituitary–thyroid axis is considered as a vulnerable target for COVID-19. The direct or indirect damage of pituitary gland, was recognized as the determining factor for secondary hypothyroidism (functional or organic) [6]. Moreover, it was shown, that thyroid follicular cells encode the messenger RNA for ACE2 receptors, being a potential target for SARS-CoV-2. The relations between ACE2 expression and thyroid hormones was shown as positive correlation of 3,5,3′-triiodothyronine (T3) and thyroxine (T4) level and level of circulating ACE2 receptor in serum [7–9]. The data from recent SARS-CoV-2 pandemic (including COVID-19 severe course) and from previous coronaviruses epidemy showed the thyroid abnormalities in reasonable number of SARS-CoV-2 infected patients. In the study of SARS-CoV-2 infection survivors, approximately 7 % of them demonstrated symptoms of hypothyroidism. Moreover, there were suggestions of disturbances in pituitary gland function followed by the whole axis hypothalamic-pituitary-adrenal dysfunction. The laboratory data of thyroid parameters in the limited number of SARS-CoV-2 patients showed decreased serum T3, T4 and TSH levels. Subacute thyroiditis, autoimmune thyroiditis and an atypical form of thyroiditis were noted as complications of COVID-19. Thyroid dysfunction is an additional factor associated with increased mortality in critical course of acute respiratory distress syndrome in COVID-19. Based on the available results obtained in the pandemic, the monitoring of the thyroid function during COVID19 and thereafter is suggested [6]. The interesting observation noted association between IL-10 and fT4 levels and organs failure in severe course of disease. The systematic review, meta-analysis and the pooled analysis showed thyroid dysfunction in 15 % of 9707 studied COVID-19 patients. There were association between percentage of patients demonstrating the thyroid dysfunction and severity of COVID-19 clinical course (abnormal thyroid function tests - TFT) in 6.2 % in mild disease vs. 20.8 % in severe form) [10]. The pooled overall rate for abnormal TFT and the severity of COVID-19 obtained from 3865 COVID-19 patients was 3.77 [11]. Moreover, the recent studies suggest higher risk of hyperthyroidism (Graves's disease) within patients with COVID-19 [12]. The impact of COVID-19 on TSH secreting cells is significant, leading to decreased level of TSH in majority of patients and, in consequence, the disturbance of the pituitary axis feedback loops. The disturbances of TSH secreting cells function occurs based on mechanisms: direct damage to the pituitary gland by COVID-19, or an indirect – the effect of pro-inflammatory cytokines: IL-14, IL-16, IL-17, IL-18, IL-21, IL-22 leading to "cytokine storm", chronic stress caused by hypoxia and the additional effect of drugs used in therapy e.g. glucocorticoids (methylprednisolone), often in high dose [13].

2. Autoantibodies in thyroid diseases

Thyroid peroxidase (TPO) is one of the thyroid cell autoantigens. The most common antibodies circulating in serum patients with thyroid disease are directed to peroxidase, thyreoglobulin and TSH receptor. The last type is important due to stimulating or blocking of the receptor after reaction with autoantibodies. The detection of anti-thyroid autoantibodies, anti-TPO, anti-thyreoglobulin and anti-TSH receptor autoantibodies are used as diagnostic tests for autoimmune thyroid diseases and as a marker for treatment efficacy. To diagnose of chronic thyroiditis, detection of autoantibodies to TPO (ATPO) is the most sensitive test, among the other anti-thyroid autoantibodies. Eighty-five to 90 % of patients with chronic thyroiditis have ATPO autoantibodies [14]. The different types of the anti-thyroid antibodies activity corresponding to different cellular location of the antigens, titers of the circulating antibodies in the serum are associated with different type of thyroid dysfunction e.g. Graves' hyperthyroidism or Hashimoto hypothyroidism [15]. The summary of anti-thyroid antibodies are shown in Table 1.

2.1. Antibodies to TSH receptor

The receptor of thyroid stimulating hormone (thyrotropin receptor - TSHR) belongs to the large family of G-protein coupled receptors with seven transmembrane spanning domains (class 5 or E, the cAMP generators). Expression of the TSHR is not confined to the thyroid gland only. The presence of biologically active TSHRs has been confirmed on the variety cells including adipocytes and fibroblasts, osteoblasts and osteoclasts, bone marrow cells, cardiomyocytes and others. Moreover, the TSHR is expressed early in development of the embryonic stem cells (ES-cells). The widespread and early expression profile of the receptor indicates that TSHR plays different additional roles rather than solely regulating thyroid metabolism. The thyroid stimulating hormone (TSH) is secreted by the anterior pituitary gland and acts as the main regulator of thyroid cell, stimulating the growth of thyroid gland, the synthesis and secretion of thyroid hormones. The present classification divides antibodies to TSHR according to their stimulating, blocking (competing with TSH binding) and neutral (no signaling) effects. The stimulating TSHR-Abs are found in the most patients with Graves' disease correlating with severity of the disease and degree of extrathyroid symptoms including ophthalmic involvement, cardiac arrythmias, and diarrheas [16].

2.2. Autoantibodies to thyroid peroxidase

The autoantibodies to thyroid peroxidase (ATPO) are the most common antibodies circulating in autoimmune thyroid disease patients' sera both – in Hashimoto's thyroiditis (HD) and in Graves' disease (GD). The activity of ATPO antibodies in healthy people (detected in low level) is not destructive to thyrocytes in contrary to their activity in patients with thyroid autoimmune process. The ATPO are mainly immunoglobulin class IgG4 besides IgG1, what is interesting because IgG4 is not activating complement system. The another property of ATPO is the induction of oxidative stress showed by decreased antioxidant potential, advanced glycosylation products and oxygen metabolites in blood [15, 17]. The destruction of thyroid cells (observed mainly in Hashimoto

Table 1
The characteristics of anti-thyroid antibodies circulating in serum (acc. 15).

Parameter	Antibodies to		
	aTSHR	aTPO	aTG
Antigen localisation	Surface of the cell	intracellular	intracellular
Access of immune cells to antigen	Without cell destruction	After the cell destruction	After the cell destruction
Duration of antigen exposure	Short, usually normalisation upon treatment	Prolonged time, even during therapy	Prolonged time, even during therapy
Type of antibody	oligoclonal	Polyclonal one domain	Polyclonal different epitopes, oliclonal mainly in patients
Class of antibody	Mainly IgG1	IgG1, IgG4>IgG2, IgG3, low level of IgA	IgG1, IgG4>IgG2, IgG3, low level of IgA, IgM in healthy
Prevalence in thyroid disease	90 % Graves' 10 % Hashimoto	>80 % in both – Graves and Hashimoto	>50 % in both
Action of antibodies	Stimulating, blocking, neutral	Little action by themself	No defined action
Presence in other autoimmune diseases	Low (18 %) in type1 diabetes mellitus (T1DM)	Rheumatoid arthritis (16–37 %), T1DM (40 %), celiac disease (12–20 %)	Rheumatoid arthritis (12–23 %), T1DM (30 %), celiac disease (12–32 %)
Other associations		Potential protective effect in breast cancer progression Infertility, miscarriages	Potential protective effect in breast cancer progression Infertility, miscarriages (with anti-TPO)
Significance of antibody detection	Marker of autoimmune process in thyroid Low level in serum	Marker of autoimmune process in thyroid Commonly used, often high level in serum	Marker of autoimmune process in thyroid Less significant due to presence in healthy people
Methods of detection	RIA (radioimmuno assay	ELISA enzyme-linked immunosorbent assay	ELISA

disease) are effect of cytotoxicity mediated by ATPO (antibody-dependent cytotoxicity) with complement system activation. Moreover, it has been suggested that thyroid infiltrating B lymphocytes acting as antigen presenting cells through membrane-bound ATPO antibodies are modulating antigen processing [18]. The reactivity of sera from 45 HD and 48 GD against native thyroid microsomes showed two specific regions of ATPO binding, what is associated with the differences in the autoantibody response to TPO in Hashimoto's and Graves' diseases [18,19].

2.3. Antibodies to thyreoglobuline

Thyroglobulin (TG) is a large (600 kDa) dimeric glycoprotein containing in average, 2–3 molecules of T4 and 0.3 molecules T3. This molecule is heterogeneous regarding hormone content, glycosylation and size. The production of antibodies against TG (ATG) may be induced by massive destruction of the thyroid gland, however, high TG levels in blood do not initiate antibody production. ATG differ between healthy subjects and thyroid disease patients - the polyclonal antibodies are seen in healthy subjects, in contrast to oligoclonal antibodies in patients. Antibodies in healthy subjects and in patients differentially recognize two conformational epitopes of the thyroglobulin molecule. The main difference between healthy people and patients with thyroiditis is in high production, release and level of ATG in patients' sera. It has been hypothesized, that normal levels of TG induce self-tolerance of T cells but not of B cells., The B cells subpopulation recognizing TG do not interact with CD4 helper T lymphocytes. The lack of this interaction prevents the B cells from migrating out of the T cell zones into the follicles and undergoes apoptosis. Because of B cell activity, healthy individuals have very low level of ATG antibodies, usually below detection. ATG antibodies are not complement fixing due to belonging to IgG4 class and due to wide space between epitopes, what prevent cross-linking. Consequently, ATG antibodies are not destructive for thyroid cells. The proposed mechanisms inducing production of ATG are either antibody formation due to massive release of antigens following thyrocyte destruction or generation of new epitopes by changed and more immunogenic conformation of the TG molecule. The each of or both mechanisms are supporting production of ATG leading to high titer in thyroiditis [15].

3. Thyroid disease with autoimmune background

Autoimmunity is a process involving autoreactive T and B cells resulting in production of autoantibodies, prolonged inflammation and destruction of target cells and tissues. Between many different diseases with autoimmune process, the thyroid diseases are most common and typical for these pathological mechanisms. The hall marks of autoimmunity process are circulating autoantibodies against cell-derived autoantigens e.g. receptors, organelles, enzymes, nuclear and nucleolar proteins. In thyroid disease the most common are autoantibodies to thyroid peroxidase (ATPO), thyroglobulin (ATG) and thyroid-stimulating hormone receptor (TSHR-Abs). As a result of autoimmune process, the clinical symptoms of hypothyroidism (Hashimoto's disease - HT) or hyperthyroidism (Graves' disease - GD) occurred in different period of time [15,20]. TSHR-Abs are found in majority of GD patients (more than 90 %) and small number of HT patients (0–20 %). Prolong stimulating activity of TSHR-Abs leads to hyperactive thyroid and clinical symptoms of GD. In both types of thyroiditis, the autoantibodies - ATPO and ATG are detected usually in high titer. Besides the production of autoantibodies representing humoral response of immune system, the cellular mechanisms are also involved from the beginning of the process. Reduction of immune tolerance and changes in thyroid microenvironment are contributing factors for development thyroid autoimmune diseases. However, the immune system deregulation is different in hyperthyroidisms than hypothyroidisms. The precise and exact mechanism leading to hypothyroidisms is not fully known. Proposed mechanisms include decreased function of regulatory T lymphocytes, increased activity of T helper cells present in thyroid follicle and apoptosis with DNA fragments release. This last described mechanism is associated with alteration in miRNA profile as initiation and support of prolonged thyroiditis and lymphocytic infiltrations. The role of regulatory T cells (Treg) is important in controlling autoimmunity, so decrease of number or decreased function of this subpopulation of T lymphocytes are promoting autoimmune process. Supplementation of hormones are decreasing the glandular cells activity and increasing the number of T regulatory cells [15,20]. Hyperactivity of thyroid cells with high level of produced and released hormones are leading to clinical symptoms of GD. The therapy of hyperthyroidisms is based on inhibition of hormones production with pharmacological therapy, surgical thyroidectomy partial or total (when conservative therapy is not effective) or radioiodination. The therapy of Hashimoto's disease, despite of variants (fibrous, atrophic, goitrous form) is based on regular supplementation of thyroid hormones in dose adjusted to hormones level, age and weight of patient, even seasons of weather. Despite of immunological mechanisms, the autoimmune thyroid diseases are treated according to disturbances of hormones production and thyroid function than due to immunological mechanisms [15,20].

4. Infection and autoimmune diseases

Two main theories have been proposed for the explanation of

autoimmunity induction by infectious pathogens: the molecular mimicry theory suggesting that sequence similarities between viral or bacterial proteins and self-proteins are inducing a cross-over immune response to self-antigens and the bystander activation proposing reaction between viral infection of a certain tissue is inducing local inflammation and cytokine release. It may activate the autoreactive T cells, what in case of not effective Treg cells suppression is leading to autoimmunity [21]. However, the finding of cross-reactive autoantibodies or sequence homology between pathogens and autoantigens does not necessarily induce biologically meaningful of molecular mimicry and the importance for disease pathogenesis. These antibodies need to be directed against biologically important domains of host cell proteins to mediate autoimmune disease. Despite extensive homology between two sequences, a cross-reactive immune response may not be generated [21]. The association of viral or non-viral infection and autoimmune thyroid diseases had often been suggested, e.g., serological evidence of infection with human herpesvirus-6 (HHV-6), Toxoplasma gondii, HCV were shown in patients with thyroiditis at the time of diagnosis of thyroiditis [22]. The strongest association of autoimmune thyroid diseases (ATD) with an infectious agent was shown for hepatitis C virus (HCV). In studies examining the frequency of thyroid disorders in HCV patients, in sera of approximately 10 % of them, the circulating autoantibodies were detected before the introduction of interferon therapy. The cumulating data from studies on HCV infection and thyroid autoimmunity indicated the significantly higher risk of thyroiditis within HCV infected patients [2].

4.1. Molecular mimicry

Molecular mimicry is one of the mechanisms leading to induce autoimmune process following presence and activity of infectious or chemical agents. It occurs when similarities between foreign peptides and self-peptides stimulate the activation of autoreactive T or B cells by the foreign-derived antigen in a susceptible individual. However, molecular mimicry is unlikely to be the only underlying mechanism for autoimmune responses; other factors such as disorders in central tolerance, non-specific bystander activation, or persistent antigenic stimuli (amongst others) may also contribute to the development of autoimmune diseases [23]. Molecular mimicry is defined as similar structures shared by products of dissimilar genes. Antibodies reacting with products of bacterial and viral genes sometime cross-react with normal cellular proteins. Sera from patients with systemic autoimmune diseases show cross-reactivity with some bacterial and/or viral gene products in the significant number. The presence of amino acid sequences shared between microbial proteins and autoantigens and the detection of antibodies in patients' sera binding to the cross-reactive epitopes, suggest the initiation of the production of autoantibodies following the immune responses to bacterial and viral infections [24].

5. COVID-19 infection and autoimmune diseases

The immunological mechanisms of response to viral infection and induction of inflammation are involving cellular mechanisms of recognition, signal transmission, activation and proliferation lymphocytes T and NK cells. Production of specific antibodies is a result of B cell activation. Despite of specific antibodies to COVID-19 antigens produced during the symptomatic disease or asymptomatic infection, the different types of autoantibodies were described. The hypothesis of theses autoantibodies production indicated possible cross-reactivity of virus epitopes and autoantigens. The mechanism of molecular mimicry was suggested as an inductor of the autoantibodies production during SARS-CoV-2 infection. Viral amino acids sequence showing similarity with human heat shock proteins 90 and 60 are associated with Guillain-Barre syndrome occurred after infection [25]. Infection with SARS-CoV-2 showed bi-directional effect – production of autoantibodies during clinical disease without co-existing autoimmune disease and worsening clinical course of autoimmune diseases due to this viral infection [25]. The thyroid gland is on the list of organs with high expression of ACE2 receptor on cells. During COVID-19 the injury of thyroid gland may be direct or indirect through immune-mediated mechanism. The immune reaction to SARS-CoV-2 infection in severe clinical form is associated with immune system imbalance due to proinflammatory cytokines overproduction [1,26,27]. Moreover, there are clinical observations of exacerbation of previous thyroid disease or onset of new immune-mediated thyroiditis mainly with hyperthyroid phenotype during COVID-19 [26,27].

The expression of ACE2 receptor on thyroid cells, facilitates infection and internalization of SARS-CoV-2 virus into these cells. There are clinical observations that COVID-19 is associated with thyroid dysfunction, frequently noted as subacute thyroiditis occurring within first two weeks [26,28]. Moreover, the stable autoimmune process in thyroid during COVID-19 may be activated with clinical symptoms of exacerbation. Within cohort of 191 mild to moderate clinical course of COVID-19, thyroid dysfunction was demonstrated in about 15 % patients, however, in other study it was almost half of 50 % patients. The low level of TSH was associated with poorer prognosis, what indicates the role of hormone axis in the course of COVID-19. However, the precise role of this type of thyroid dysfunction is not fully clarified [11]. In opposite to hypothyroidism, hyperthyroidism is more important due to clinical significance. In severe course of COVID-19, thyrotoxicosis was noted in about 20 % of patients. It seems, that high level of IL-6 in the cytokine net disturbances, is an inducting factor for low level of TSH, high activity of thyroid cells and thyrotoxicosis symptoms. Another point of view suggests secretion of thyrotropin from pituitary gland as results of direct or indirect injury related to COVID-19. Low levels of TSH and fT4 during acute stage of COVID-19 normalized during convalescence [26,28]. The opposite relation between COVID-19 and thyroid was observed comparing the clinical course in patients with diagnosed and treated thyroid autoimmune disease. The study of 3703 COVID-19 positive patients, showed some patients (6.8 %) with hypothyroidism treated with levothyroxine. There were no differences in COVID-19 course between patients with hypothyroidism treated with hormone supplementation and otherwise healthy population [26].

6. COVID-19 vaccines (mRNA) and immune system response

The vaccines against COVID-19 were produced in a short time to prevent spreading of pandemic with high rate of death and long-lasting complications. The vaccines were constructed based on different models from whole viral molecule (live attenuated viral vaccines) to very small nucleic acid vaccines (mRNA, saRNA, DNA). The immune system response is different depending on structure of vaccine and present adjuvants. The mechanism of immune system response to mRNA vaccine is based on transport of RNA package in nanoparticles into the cytoplasm of host target cell to produce encoded protein. In mRNA vaccine the mRNA molecule was covered with lipid nanoparticles formulated in way facilitating release of mRNA into cell from endosomes [29–32]. The non-replicated mRNA is encoding the gene inducing production of coded viral protein being the antigen for immune response in target cells [31]. Vaccine mRNA molecules freed from lipid capsule are recognized by Toll-Like Receptors type 3, type 7 and type 8 (TLR3, TLR7, TLR8) or retinoid acid-inducible gene (RIG-I). It activates IFN type I production with stimulation Th1 cellular response of immune system. The ribosome translation is followed by proteasome degradation with small peptides presented by the major histocompatibility complex class I (MHC-I). Another way is an effect of antigen uptake by APC and presentation with MHC class II determinants. In lymph nodes antigen presentation is initiating T and B lymphocytes response on normal, routine way as for other antigens. The effective response is leading to activation of cytotoxic T lymphocytes, production of specific antibodies, induction of specific memory T and B cells [29–32]. The level of specific antibodies against S spike protein of SARS-CoV-2 is easy for monitoring of time

lasting humoral response. The antibodies level is believed to be a marker for activity of the immune system.

6.1. COVID-19 vaccines and autoimmune diseases

There are only few studies concerning efficacy of vaccination against SARS-CoV-2 virus in patients with autoimmune diseases, due to exclusion of patients on immunosuppressive therapy from vaccination protocols. The only one clinical trial with BNT162b2 vaccine included group of 118 patients with wide spectrum of rheumatoid diseases on therapy. The exclusion of patients with autoimmune disease from such protocols was based on possible effect of mRNA vaccine triggering IFN pathway after vaccination, what may modify the disease symptoms due to hyperactivation of IFNs. However, the reduced effect of mRNA COVID-19 vaccine is expected in patients on immunosuppressive therapy with high dose of steroids and rituximab. For the patients on rituximab therapy, the period about 6 months after last injection of monoclonal antibodies to vaccination is suggested. Although, the immune response during immunosuppressive therapy may be reduced, the vaccines are not contraindicated due to risk of more severe course of COVID-19 in immunocompromised patients [33].

6.2. SARS-CoV-2 vaccines and thyroid

The observations after first year of vaccination in worldwide scale, showed different adverse effects of vaccines. Some of these post vaccine symptoms are associated with specific type of vaccines including singular numbers of the symptoms involving the thyroid often published as case reports. The seven cases of Graves' disease occurred after mRNA COVID-19 vaccinations and nine cases of subacute thyroiditis after different type of vaccines were described [34–37]. One of hypothesis explaining stimulating effect of mRNA COVID-19 vaccine on thyroid function is based on molecular mimicry between viral S1 protein and thyroid target protein. This reaction is inducing autoimmune process leading to Graves' disease. The period between vaccination and overt symptoms of Graves' disease lasted from few days to months after second vaccine dose. The association between hyperthyroid and mRNA vaccine especially in such short time period was not clear [34,38]. The hyperthyroid symptoms were noted in association with mRNA vaccine in contrast to hypothyroiditis noted more often and after different types of COVID-19 vaccines. There are several hypotheses concerning mechanism of subacute thyroiditis after vaccinations. One on them suggested adjuvants as inducing factor. This phenomenon is known as ASIA – autoimmune/inflammatory syndrome induced by adjuvants. ASIA is believed to be a mechanism of 50 cases of subacute thyroiditis after other anti-viral vaccines e.g., against influenza, HPV, HBV. In these vaccines the adjuvants are used as support of immunogenicity stimulation [34,35,38,39].

6.3. Hypothyroid and SARS-CoV-2 mRNA vaccine - our observations

The studied group of health care workers included 5 women diagnosed with Hashimoto disease and 2 diagnosed with hypothyroid other than Hashimoto disease. All of them were vaccinated according to mRNA vaccination protocol with antibody response assayed in check points. There were no clinical symptoms of vaccine adverse effects involving thyroid gland. The levels of hormones were stable during whole time of observation. The response to vaccine measured as IgG antibodies level was high with typical tendency to decrease with time (Table 2). Parallel checking of anti NP antibodies as indication for infection with COVID-19 showed the weak positivity in IgM class only in one person (ID 79) not presenting clinical symptoms of disease [40].

Table 2
The mRNA SARS-CoV-2 vaccine in patients diagnosed and treated for hypothyroidism and Hashimoto disease. The antibodies level (ATPO and anti S1) in IgG class after following vaccination's doses, are shown.

Patient ID	Check point	ATPO (IU/ml)	NP IgG (U/ml)	S1 IgG (BAU/ml)	Comments Clinical state, therapy
10	0	6,4	1,0	0,0	Hashimoto's disease
	2	7,5	3,0	8977	Regular thyroid hormone
	4	10,0	1,0	336	supplemention
16	0	<5,0	0,0	0,0	Antinuclear antibodies
	2	<5,0	0,0	4539	(ANA) positive
	3	<5,0	0,0	280	Mainly non-specific
	4	<5,0	0,0	958,4	(DFS70) Subclinical hypothyreoidism Without hormon supplemention
18	1	35,1	1,0	81	Hashimoto's disease
	2	35.8	1,0	436	Regular thyroid hormone
	3	33,0	1,0	155	supplemention
	4	ND	2,0	2752	
79	2	53,4	7,0	342	Hashimoto's disease
	3	12,3	6,0	167	Euthyreosis, no hormone supplemention
211	2	11,7	0,0	4488	Hashimoto's disease,
	3	8.3	0,0	386	Diabetes mellitus type 1
	4	7,9	0,0	ND	(T1DM) Thyroid hormone and insuline supplemention
623	2	<5,0	2,0	378	Celiac disease, Adisone-
	3	<5,0	3,0	58	Biermer anemia,
	4	<5,0	3,0	248	Hashimoto's disease Euthyreosis, no hormone supplemention
475	2	15,3	0,0	728	Breast cancer after
	3	9,5	1,0	188	surgery (remission)
	4	8,5	1,0	3092	Observation for Hashimoto's disease Euthyreosis, no hormone supplemention

Check points: 0 - before vaccination, 1 – after first vaccination, 2- after second dose (1–2 months), 3–6 months after 2nd dose of vaccine, 4 – after 3rd vaccination.
Interpretation of antibodies level: ATPO (IU/ml) NP (IgG U/ml) S1 (IgG BAU/ml).
Normal/negative <40 < 8,0 < 16,0.
Equivocal 40–60 8,0–12,0 16,0–24,0.
Positive >60,0 > 12,0 > 24,0.

7. Autoimmune thyroiditis in childhood

Autoimmune thyroiditis (AIT) is the most common thyroid disorder within the pediatric population. Both a goitrous (Hashimoto's thyroiditis) and a nongoitrous (atrophic thyroiditis, also called primary myxedema) variant of AIT are noted. The most common age for the autoimmune thyroiditis is adolescence, however, the disease may occur at any time, very rarely in infants below one year of age. In majority of patients (about 70 %) the familiar predisposition associated with higher risk of development of disease is noted. The incidence ratio of chronic autoimmune thyroiditis for girls and boys is about 2:1. The environmental factors are often playing the role in triggering of thyroid disease probable with epigenetic mechanism [2]. The precise triggering factors are not known, however, the infections, some drugs (e.g. lithium, amiodarone, interferon-alpha), hormones (estrogen), dietary substances (iodine, selenium), stress, smoking, and most recently, environmental toxins, have been recognized. Like thyroid diseases diagnosed in adults, the thyroid peroxidase antibodies (ATPO) and thyroglobulin antibodies (ATG), present in majority of children (about 80 %), are valuable for diagnosis being the markers for underlying autoimmune thyroid process. Blocking TSHR-Abs are found in about 18 % of children and adolescents with severe hypothyroidism. Autoimune thyroid disease may coexist with other organ-specific autoimmune diseases e.g. diabetes type 1. The ultrasound (USG) examination of thyroid gland showed

heterogeneous echogenicity before occurrence of antibodies in serum, however, the typical picture of spotty uptake of radioactive iodine that is seen in adults is rare in children [41].

7.1. Clinical symptoms of hyperthyroidism (GD) in children

Hyperthyroidism with clinical phenotype of GD is relatively rare in children (8 per 1,000,000/year in children <15 y.o. and 1 per 1,000,000/year in children <4 y.o.). Girls are affected four to five times more frequently than boys, although there is gender difference within patients younger than 4 years of age. The presentation of GD in childhood may be insidious and a careful history often reveals a several months of progressing symptoms. Children may have the same signs and symptoms of hyperthyroidism as do adults, but most often they present with behavioral disturbances: decreased attention span, difficulty concentrating (which may lead to deteriorating performance in school), emotional lability, hyperactivity, difficulty sleeping, and nervousness. Typical cardiovascular findings include tachycardia, palpitations, widened pulse pressure, and an overactive precordium. Any child who has persistent tachycardia should be evaluated for hyperthyroidism. Tremors, a shortened deep tendon reflex relaxation phase, fatigue, and proximal muscle weakness are possible neuromuscular manifestations of thyrotoxicosis. Despite an increase in appetite, affected children often lose weight and sometimes have diarrhea, but usually have frequent bowel movements associated with intestinal motility. Increased perspiration, warmth, and heat intolerance tend to be late findings. Post pubertal girls often have menstrual irregularities. A goiter is palpable in the majority of cases, characterized by diffuse enlargement, which is smooth, firm, and nontender. The pretibial myxedema common and typical feature of GD in adults are rare in children. Extrathyroidal manifestations such as ophthalmopathy and dermopathy are rarer in children and less severe than in adults. The ocular manifestations have been estimated to 25–60 % of GD children patients. The ocular symptoms are usually mild and limited to lid retraction, the slight proptosis associated with the inflammation and muscle swelling rather than to infiltrative disease of the orbital structures. These symptoms improved in most patients in the euthyroid state during therapy. Unique to pediatric GD is the acceleration of linear growth and bone maturation associated with prolonged hyperthyroidism [2].

7.2. COVID-19 and autoimmune thyroid diseases in children

The SARS-CoV-2 infection in children was in majority subclinical or asymptomatic in majority infected children. The clinical onset and course of disease was usually mild with gastrointestinal involvement due to ACE2 receptor expression. However, in pediatric population the late complications, multiorgan inflammatory syndrome (PIMS or MIS-C) were observed. Similar to adults, after SARS-CoV-2 infection, the endocrine disorders are noted in small population of children [42]. Although studies suggest a potential link between COVID-19 and thyroid dysfunction in adults, there are insufficient data to confirm that association in children. There are very limited studies of the effects of the pandemic on the thyroid function, disorders and overt diseases in children and young people. One study from an outpatient pediatric practice in New York reported increased number of thyroid screening tests in children 6–18 y did not show the differences in TSH concentrations pre- and post-pandemic. The association between COVID-19 and significant thyroid dysfunction including thyroid storm, with severe course was reported in few children only [43]. The asymptomatic course of COVID-19 infection in children forced the testing of antibodies to S1 in wide scale, to prove contact with virus and allowed to estimate association of observed symptoms with infection. The probability of SARS-CoV-2 infection was higher after contact with infected family member [44]. The retrospective observation from the tertiary pediatric endocrine center did not show the significant changes of the thyroid function in children in pre- and post-pandemic study. This observation contrasts with adult studies showing increase of autoimmune mediated dysfunction after the pandemic. Such data have not yet been reported in children due to low number of patients with clinical symptoms of COVID-19 infection [43]. The effect of COVID-19 on the endocrine system observed in adults is an indication for careful observations of children in pandemic and post-pandemic period considering asymptomatic SARS-CoV-2 infection in this population. Evidence emerging from pediatric studies provides some guidance but highlights the need for more research in this area. Currently, there are no data indicating increased risk of COVID-19 or altered disease course in children and adolescents with underlying thyroid disorders [42,45].

8. Autoimmune thyroid disease in pregnancy

The physiology of pregnancy includes substantial changes in function of endocrine system, involving suprarenal and thyroid glands. The thyroid hormones play the vital role from the first moment of implantation of fertilized ovary during the development of fetus and placenta. Thyroid gland volume usually enlarges during pregnancy, and thyroid hormones (TH) synthesis increases about 50 % above the preconception level [46]. Complications with pregnancy occur when autoimmune process affects thyroid function and over produced antibodies are circulating and localized in tissues. The observations suggesting the association between autoimmune thyroid diseases and problems with fertility, pregnancy loss or other complications like preterm delivery, are relatively new. Moreover, this association exists even in the absence of a significant changes in TSH level, what reflects subtle thyroid dysfunction, despite of presence of antibodies (ATPO, ATG) in serum even in high level [46].

8.1. Thyroid autoimmunity and infertility

Infertility is the failure to achieve a successful pregnancy after 12 months of regular unprotected intercourse or therapeutic donor insemination. Infertility could be due to both known male and female factors, although it could be due to multiple causes or be unexplained [49]. The relations between the fertility and endocrinopathies is bi-directional - gestation is influencing the clinical course of these endocrinopathies in patients who were diagnosed before conception and endocrinopathies (mainly thyroid diseases) are modifying fertility. Multiple particles, like TSHR-Abs stimulating function of thyroid hormones, glucocorticoids, and anti-thyroid drugs, are crossing the placental barrier and evoke biological action in fetal tissues. Thyroid pathology in the form of postpartum thyroiditis is particularly prevalent in patients with circulating ATPO and ATG. Thyroid dysfunction is associated with high risk of spontaneous abortion, premature delivery, pre-eclampsia, or gestational diabetes mellitus. The pathogenesis of autoimmune thyroid disorders is based on the activation of $CD4^{+}$ lymphocytes, what co-stimulates B lymphocytes to antibody production. The circulating ATPO and/or ATG in pregnant women are detected in up to 5–14 % and 3–18 % (respectively), what should be carefully monitored during pregnancy up to delivery time. There are data suggesting that even euthyroid patients with circulating anti-thyroid antibodies are at higher risk of spontaneous abortion, premature birth, progression to hypothyroidism, and development of postpartum thyroiditis [46]. Subclinical hypothyroidism (elevated TSH and free thyroxine [fT4] within the normal limits) is the most common form of thyroid pathology during gestation and occurs in 2.5 % of pregnant women. Up to 60 % of women with subclinical hypothyroidism present circulating antibodies. Overt hypothyroidism with clinical symptoms (Hashimoto's disease) is significantly less common and is observed in 0.2–0.5 % of pregnant women. Hypothyroidism is undoubtedly connected with numerous complications both in the mother and in the fetus: spontaneous abortion, premature birth, gestational hypertension, preeclampsia, low birth weight, placental abruption, and postpartum hemorrhage [47].

8.2. Thyroid autoimmunity and miscarriages and preterm delivery

Miscarriage is defined as spontaneous pregnancy loss occurring before 20 weeks of gestation with most of them lost as early as 10 weeks of gestation. This time range is important because in many studies the thyroid autoimmunity status is assayed after the first 10 weeks of gestation, what means possible underestimated the risk of early miscarriage. Miscarriage affects 15–25 % of pregnancies. Preterm delivery is defined as birth occurring before 37 weeks of gestation, whereas very premature delivery is defined as birth occurring before 34 weeks. Preterm births are the leading cause of perinatal mortality and long-term morbidity [47].

8.3. Hyperthyroidism and pregnancy

Hyperthyroidism during pregnancy is relatively uncommon with the overall prevalence rate about 0.1%–0.4 % of pregnant women, with Graves' disease (GD) phenotype accounting for 85%–90 % of all cases. Gestational transient thyrotoxicosis (GTT) occurs much more often (2%–3% of women), but it cannot be considered as a disease [46]. Graves' disease is the most common cause of autoimmune hyperthyroidism in pregnant women, however, the therapy of GD controls symptoms of hyperthyroidism, so, majority of women decided for pregnancy are in euthyreosis [47]. Hyperthyroidism in pregnancy demonstrates similar symptoms to hyperthyroidism in women without pregnancy with additional symptoms associated with pregnancy. The list of such symptoms typical for pregnancy includes - premature labor, pre-eclampsia and hypermetabolic crisis within the perinatal period. Hyperthyroidism in mothers can bring serious complications to fetuses. Besides the low birth weight, the most common unfavorable outcomes include higher chance of congenital defects, increased perinatal mortality, and fetal hyperthyroidism noted in 0.6 % in infants of mothers with GD [48]. The excess of thyroid hormones crossing the placenta to fetus are associated with increased risk of fetal death and may lead to accelerated bone maturation and early epiphyseal fusion and growth cessation. Long-term exposure may lead to osteopenia in adolescence and adulthood. The monitoring of pregnancy in GD diagnosed women include fetal heart rate and intrauterine growth. The measurement of TSHR-Abs during at-risk pregnancies has been recommended as a predictor for the development of fetal/neonatal GD. The presence of fetal goiter, tachycardia, and intrauterine growth retardation suggests fetal hyperthyroidism. Maternal immunoglobulins in IgG class are circulating in newborn approximately up to 4 months, so most symptoms of neonatal Graves disease resolves within first 2–3 months of infant life. The maternal medical history and estimation of her status at the beginning of pregnancy are critical [2].

9. COVID-19 and autoimmune thyroid diseases in pregnant women

There are many studies investigating the association between thyroid functions and COVID - 19, but similar studies on pregnant women are limited and restricted to comparison between the preand post-pandemic periods. The COVID-19 seems to have an impact on the thyroid function of pregnant women, and particularly FT3 level seems to be correlated with disease severity. No comparison studies of the thyroid function in pregnant women after COVID-19 with population without COVID-19 were published [49]. COVID-19 is associated with disarrangement of thyroid hormones in pregnant women directly through thyroid gland damage or indirectly through inflammation-induced suppression in diverse links of hypothalamic–pituitary–thyroid axis [50]. However, there are no data about increased ratio of pregnancy loss during SARS-CoV-2 pandemic, or more severe COVID-19 in pregnant women. It suggest that the impact of SARS-CoV-2 infection on pregnancy was not so strong as it might be expected.

10. Comments

The high expression of ACE2 receptor on thyroid cells is possible trigger leading to bi-directional effects of thyroid function and COVID-19 infection. Stimulation of COVID-19 protein synthesis after vaccine initiates similar mechanisms of interaction between the viral S1 protein and thyroid gland being the target. Another mechanism of thyroid dysfunction is associated with presence of adjuvants in vaccines. The mechanism may explain different types of thyroid dysfunction after COVID-19 vaccines. The associations between viral infection and thyroid autoimmunity process, disease in adults and children including special group as pregnant women are supported by convincing evidence, but the mechanisms of these associations are unknown. The COVID-19 vaccines are noted as inducers of thyroid function disturbances, in few cases with clinical symptoms of thyroid autoimmune disease. These observations are suggesting precise monitoring of anti-thyroid antibodies and thyroid function in all individuals with potential risk of autoimmune thyroid disease.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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