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Review Article

REVIEW OF SARS-CORONAVIRUS-2 REPERCUSSIONS ON THYROID GLAND IN THE CONTEXT OF HYPERTHYROIDISM

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ABSTRACT

The thyroid gland may generate, store, and release hormones (such as Triiodothyronine and Thyroxin also called T3 and T4 hormones respectively) into the bloodstream and let them go to the body's cells. Every enzymatic process in the production and secretion of thyroid hormones is controlled by Thyroid stimulating hormone (TSH). All people worldwide are susceptible to thyroid disease, which is often accompanied by hyperthyroidism and hypothyroidism. The thyroid's structural proximity to the upper airways, a main route for coronavirus entry, holds up the idea that the thyroid gland might be a target for Covid-19 or SARS-CoronaVirus-2. When the thyroid gland makes and secretes too much thyroid hormone, it is referred to as hyperthyroidism and if the patients do not take any precautions, hyperthyroidism may lead to cardiac hypertrophy. The Covid-19 epidemic had a substantial influence on our daily lives and has unexpectedly changed the way of medical research. This review aimed to discuss the effects of SARS-CoronaVirus-2 on the Thyroid Gland in the Context of Hyperthyroidism and related causing diseases, highlighting the common causing diseases of hyperthyroidism along with their treatments. We also highlight the impact of SARS-CoronaVirus-2 and its mRNA immunization. So that future studies should focus on the number of important advances and improved drug management in the treatment of Thyroid relating diseases, which may or may not be triggered by the coronavirus and its immunization.

Keywords: Hyperthyroidism, SARS-corona virus-2, Thyroid gland, Graves disease, Covid-19

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INTRODUCTION

The thyroid is a pivotal endocrine organ of the human body, it is situated in the anterior neck's lower region [1] inferior to the larynx or between the 2nd and 3rd tracheal rings. The thyroid cartilage of the trachea (also called windpipe), which was characterized as having a "shield-like" shape (the Greek word for the shield is "thyreos"), inspired the name of this shield-shaped organ. It has two sections called lobes that park yourself on the left and the right sides of the tracheal wall, respectively. The isthmus, a thin band of thyroid tissue that crosses the front surface of the trachea, serves as the connection between both lobes. Each lobe is typically a few mm thick and measures around 3–4 cm in length by 2 cm wide. The isthmus often has a height of up to 15 mm and a thickness of only a few mm [2].

For the hormones (such as T3 and T4) to reach the body cells, the thyroid gland may generate, store, and release them into the bloodstream. The thyroid gland produces the thyroid hormones T3 and T4 in about a 1:7 molar ratio, respectively. TSH controls every enzymatic phase in the synthesis and secretion of T3 and T4. T4 is largely a prohormone and has direct effects on specific brain tissues. T4 is largely transformed into T3 in the kidney, liver, pituitary gland, and skeletal muscle by a process known as 50-monodeiodenation. T3 is the biologically active form of thyroid hormone. Both T3 and T4 circulate in blood just about completely (>95%) bound to thyroxine-binding globulin and a family of other hormone-binding proteins. It has recently been demonstrated that 50-mono-deiodinase, which catalyzes the conversion of T4 to T3 in both the liver and pituitary, can be altered in some cardiac disease conditions in addition to the traditional TSH regulation of thyroid hormone metabolism [3].

All people worldwide are susceptible to thyroid disease, which is often accompanied by hyperthyroidism and hypothyroidism, especially in pregnancy and childhood [4]. A clinical ailment known as hyperthyroidism (fig. 1) is characterized by a hypermetabolic state carried on by an increase either in free triiodothyronine (FT3) or free thyroxine (FT4) and in both FT3 and FT4 in the blood [5].

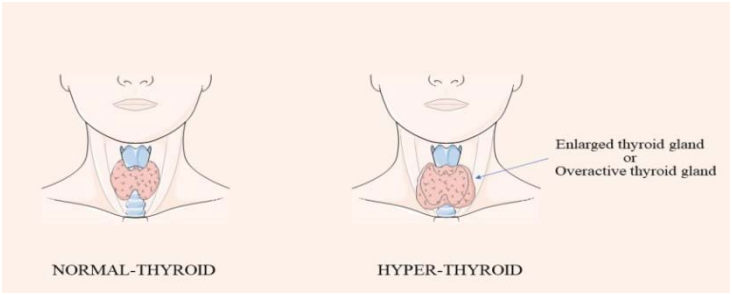

Fig. 1: The diagram shows the divergence of the normal and hyperthyroid glands [5]

Hyperthyroidism frequently manifests as decreased cerebral performance, depression, weight loss, anxiety, and irritability. According to studies, those with sub-clinical hyperthyroidism have an advanced risk of dementia at a two-year continuation as well as angina or myocardial infarction. Toxic multi-nodular goiter, painless thyroiditis, toxic adenoma, and graves disease are typical endogenous causes of hyperthyroidism [6] as shown in table 1.

Table 1: Common reasons or causing diseases of hyperthyroidism along with their Mechanism

Causes	Mechanism	References
Graves disease	Antibodies that activate the TSH receptor during an autoimmune process cause thyroid hormone to be produced excessively.	[7]
Transient or Painless thyroiditis	The immune system attacks thyroid tissue, releasing already-made thyroid hormones as a result.	[8]
Toxic adenoma (Plummer disease)	thyroid nodule with Gs alpha gene mutation or somatic TSH receptor	[9]
Toxic multi-nodular goitre	development of clonogenic cells with a mutation that stimulates the TSH receptor	[10]

It is widely known that the thyroid and viral infection interrelate complicatedly through hormones and immunomodulatory signaling molecules. In clinical and physiological circumstances, these connections have been demonstrated [11]. Biological concentrations of 3,3',5-triiodo-L-thyroxine (T3), and L-thyroxine (T4) upsurges the generation and release of cytokines, which are also a part of the "cytokine storm" that may characterize systemic viral infections [11].

Widespread in humans and other mammals, coronavirus is a non-segmented, enveloped positive sense RNA virus that belongs to the family Coronaviridae and the order Nidovirales [12]. The thyroid's structural proximity to the upper airways, a main route for coronavirus entry, holds up the idea that the thyroid gland might be a target for Covid 19 or SARS-CoronaVirus-2 (here, SARS is referred to as severe acute respiratory syndrome) [13] as shown in fig. 2. It has been previously documented that deviations in thyroid function and interruption of the follicular architecture were present in a significant proportion of SARS-CoronaVirus-2 patients [13].

Complications seen in hyperthyroidism resulting in cardiovascular, adrenergic, and cutaneous symptoms are mentioned in table 2.

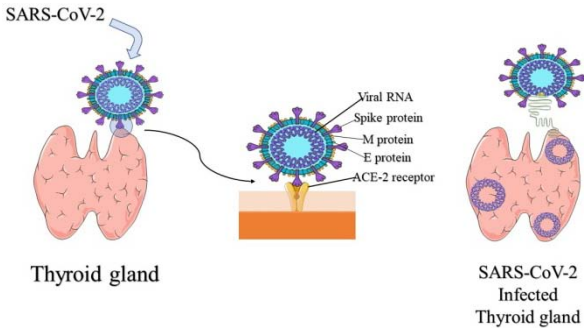

Fig. 2: Thyroid follicular cells' ACE-2 receptors and SARS-CoronaVirus-2 entrance [13]

Table 2: Symptoms and indications of hyperthyroidism

Cardiovascular	Atrial fibrillation, tachycardia, an irregular heartbeat, peripheral edema (in heart failure), dyspnea, and orthopnea	[5]
Adrenergic	Trembling, palpitations, jitteriness, anxiety, diaphoresis, tachycardia, heat intolerance, lid lag, staring, and hyper defecation are some of the symptoms (not diarrhea)	[5]
Cutaneous	Onycholysis (Plummer nails), hyperpigmentation that is patchy or all-over pathognomonic signs (especially on neck and face) of Graves disease include: thyroid acropachy and pretibial myxedema (thyroid dermopathy) Graves ailment can also cause patchy vitiligo.	[6]
Hypermetabolism	Despite increased appetite and fever, there is weight loss (in thyroid storm)	[14]
Neuromuscular	Activation of proximal muscles is feeble and peripheral reflexes are rapid with an accelerated relaxation phase.	[6]
Neuropsychiatric	Anxiety, hurried speech, psychosis, and sleeplessness	[14]
Ocular	Incomplete eye closure while sleeping as conveyed by the patient's partner, increased tearing, photophobia, increased susceptibility to smoke or wind, gritty feeling in the eyes or the sand. Exophthalmos, periorbital edema, decreased color perception, impaired vision, and diplopia are pathognomonic symptoms of Graves disease.	[15]

We searched the studies in three databases, including Google Scholar, PubMed, and Elsevier websites, for the last ten years to find all related articles on hyperthyroidism and Covid-19. Papers with any language having an English abstract were included in the first step of the search. We used the following words and terms, including: “COVID-19”, “Hyperthyroidism”, “Thyroid gland”, and “Vaccination”. Inclusion criteria in the present study were the studies assessing the epidemiology, etiology, pathophysiology, prevention, and treatment of hyperthyroidism, but the papers with insufficient data, the abstract without full text, in conformity between methods and results, the inappropriate explanation of the findings were excluded from this review.

Hyperthyroidism's pathogenesis and etiology

When the thyroid gland makes and secretes too much thyroid hormone, it is referred to as hyperthyroidism, normal or high thyroid radioactive iodine uptake is a defining feature [15]. The most recurrent cause of hyperthyroidism in those who live in iodine-rich zones is Graves disease. Other frequent causes include autonomously operating thyroid adenoma and toxic multinodular goiter. Younger individuals, who have greater thyroid hormone (i.e., T3 and T4) levels and are more probable to exist with overt hyperthyroidism than subclinical hyperthyroidism, are more likely to have less frequent causes [14].

Graves disease (GD)

The utmost common reason for hyperthyroidism and the most spectacular semiology is Graves disease [16]. GD, commonly referred to as von Basedow disease, is an illness marked by ocular abnormalities (Graves' orbitopathy; GO), an overactive and enlarged thyroid gland (Graves' hyperthyroidism), and localized dermopathy (pretibial myxoedema; PTM) [17]. It is evident that thyroid-stimulating antibodies (i.e., TSA), bind to and activate the thyrotropin receptor on thyroid cells, which are induced Graves' hyperthyroidism

[18]. Weight loss despite regular eating habits, tremors, anxiety, heat sensitivity, irritability, erectile dysfunction or diminished libido, changes in menstrual cycles, weariness, palpitations, frequent bowel movements, and others are typical symptoms [19].

Treatments

Management of graves disease, along with their doses and adverse properties/effects mention below in table 3.

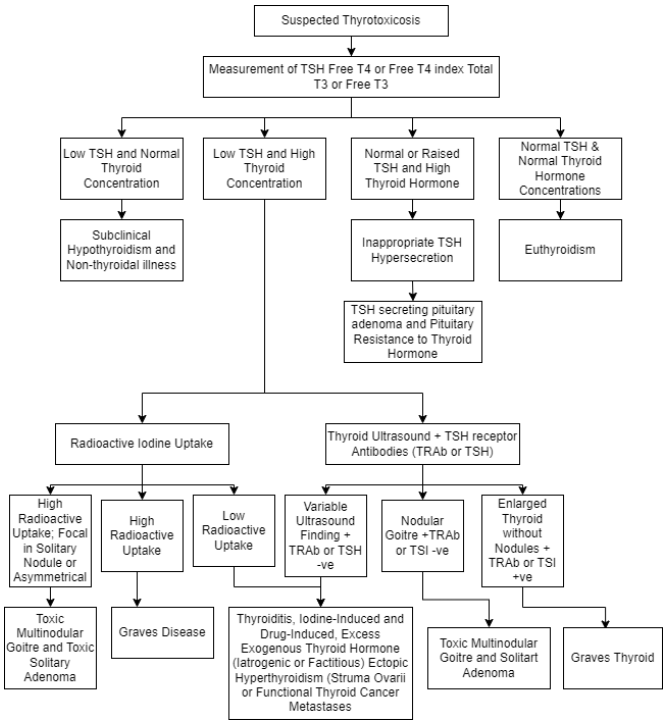

Fig. 3: The flow chart shows the algorithm for the assessment of thyrotoxicosis/hyperthyroidism [14–30]

Table 3: Management of graves' hyperthyroidism

Treatments	Doses	Adverse properties or effects	References
Iodine ^{131} radioactive	typically based on clinical evaluation, however other facilities base dose calculations on absorption and turnover studies	Temporary exacerbation of ophthalmopathy, transitory hypothyroidism (temporary or permanent), thyroiditis brought on by radiation, hypoparathyroidism, radiation overexposure in children, and thyrotoxic crises	[20]
Subtotal thyroidectomy or near-total thyroidectomy	The surgical removal of both thyroid lobes, save for a small portion of thyroid tissue, is known as a "near-total thyroidectomy" (on one or both sides less than 1.0 ml). 3 to 5 g of the thyroid glands less-affected side are left after subtotal thyroidectomy.	Problems from anesthesia, hypoparathyroidism, laryngeal edema, hemorrhage, and recurrent laryngeal nerve injury	[21]
Antithyroid medications (carbimazole or its metabolite MMI, or PTU)	a single, fixed high dose (e. g., 5-30 mg of MMI per day or 5-40 mg of carbimazole per day) is administered along with thyroxine to prevent hypothyroidism or dose reduced until euthyroidism is reached (titration regimen).	Major Vasculitis, lupus-like syndrome, acute hepatic necrosis, thrombocytopenia, agranulocytosis, acute hepatitis, cholestatic hepatitis, and insulin-autoimmune syndrome Minor Nausea, rash, fever, urticaria, anorexia, arthralgia, strange flavors, and odors	[22]

Toxic nodular disease

The common root of thyrotoxicosis in elderly people, particularly those living in iodine-scarce regions, is toxic nodular goiter or toxic nodular disease [14]. An enlarged gland has several nodules of various sizes, as the name suggests. Although lymphocytic stromal infiltration may be present both within the non-nodular thyroid and in the nodules or nodular thyroid, the nodules typically exhibit papillary and follicular hyperplasia [5]. Toxic multinodular goiter, in which numerous independently functioning thyroid nodules emit too much thyroid hormone, and toxic adenoma, in which a single thyroid nodule is hyperactive, are other prevalent causes of hyperthyroidism [23].

Treatment

Radioactive iodine ablation or surgery can be used to treat toxic nodular goiter. Antithyroid medications are a possibility, but they must be taken continuously for the rest of one's life because it is doubtful that hyperthyroidism will go away [24].

Subacute thyroiditis (SAT)

(Chronic thyroiditis) for many years, the pathophysiology and factors that determine the clinical passage of SAT, also known as de Quervain's thyroiditis or granulomatous thyroiditis, remained unknown [25]. This illness, which is frequently a painful cause of hyperthyroidism, is thought to be related to systemic and/or thyroid infection that is typically viral in nature. Patients with this illness frequently complain of neck pain, which may relate to the chest or the jaw. Clinical evidence of hyperthyroidism symptoms is frequently seen in the early stages of this illness. The follicular epithelium is destroyed when the gland is replaced by an inflammatory granulomatous process, and thyroid hormone that has

been held in ruptured follicles within the colloid is released into the bloodstream [5].

Treatment

Self-limiting illnesses like subacute thyroiditis typically go away on their own within six months. Antithyroid drugs and radioactive iodine ablation have no place in the management of thyroiditis. If necessary, β blockers can be administered to manage adrenergic symptoms. A nonsteroidal anti-inflammatory medicine (NSAID) may be used to treat the pain brought on by subacute thyroiditis [26].

Drug-induced hyperthyroidism

Hyperthyroidism brought on by drugs. Since the 1960s, the iodine-abundant compound i.e., amiodarone, has been used in medical settings and is still often given as an anti-arrhythmic medication. With a female: male ratio of up to 1:3, amiodarone-induced thyrotoxicosis seems to be more common in males and is more prevalent in iodine-abundant areas [14]. IFN (Interferon)-α/β, lithium, immunological checkpoint mediators, highly active antiretroviral treatments, tyrosine kinase inhibitors, and humanized monoclonal antibodies used to treat various sclerosis are additional medications that can result in thyrotoxicosis [27]. While immune-modifying medications like IFN-α/β, highly active antiretroviral actions, and alemtuzumab can temporarily produce thyrotoxicosis through destructive thyroiditis, they can also cause graves disease through less obviously understood immunological reactivation pathways [28].

Sub-clinical hyperthyroidism

Subclinical thyroid hypertrophy. Thyrotropin levels are repressed, thyroid hormone (i.e., T3 and T4) levels are naturally in the upper to middle range of normal, and FT3 and FT4 levels are normal in subclinical hyperthyroidism [29]. Exogenous subclinical hyperthyroidism brought on by excessive use of levothyroxine, liothyronine, or desiccated thyroid may be the result of unintentional overtreatment, deliberate usage (typically done covertly) by the patient, or deliberate use to inhibit thyrotropin production. Compared to endogenous subclinical hyperthyroidism, exogenous subclinical hyperthyroidism is much more prevalent. Serum T3 levels in endogenous instances are often normal or at the higher end of the reference range, but T3 levels in levothyroxine-treated patients are frequently in the middle or lower portion of the reference range [30].

Treatment

Subclinical hyperthyroidism's underlying cause should determine the course of treatment. Because spontaneous remission is unlikely to occur, radioactive iodine ablation is a preferred therapy choice for individuals with toxic multinodular goiter or a solitary autonomous nodule. Effective therapies for graves disease patients include radioactive iodine ablation therapies and antithyroid drugs [31].

Iodine-induced hyperthyroidism (hyperthyroidism brought on by iodine)

The Jod-Basedow phenomenon, also known as iodine-induced hyperthyroidism, is more prevalent in elderly people with nodules or nodular goiter and in areas with chronic iodine deficit where the population is getting iodine supplementation [14]. A crucial micronutrient in the coalescence of thyroid hormones (i.e., T3 and T4) is iodine. The WHO referred to as World Health Organization has set a suggested daily allowance for it of 150 g for individuals other than pregnant patients; of this amount, roughly 80 g is required to maintain optimal thyroid hormone synthesis, while the remaining grams account for fecal and urinary losses [32]. Radiographic divergence agents can also result in iodine-induced hyperthyroidism in addition to iodine supplementation. The likelihood of developing iodine-induced hyperthyroidism after receiving a radiographic contrast agent is greatest in people with precedent multinodular goiter or people from iodine-scarce regions [33].

Hyperthyroidism in pregnancy (Pregnancy-related hyperthyroidism)

An estimated 2.5% of cases of subclinical thyrotoxicosis and 0.2% of cases of overt thyrotoxicosis occur during pregnancy. The frequent reason for thyrotoxicosis during pregnancy is graves' disease [34]. GD, which is brought on by thyroid activation by gestational transient thyrotoxicosis (GTT) and TSH receptor antibodies (TRAbs) are the two utmost frequent sources of hyperthyroidism in pregnant women [35]. Anti-TSH-receptor antibodies should be examined for the following, as they frequently confirm the diagnosis: Absence indicates transient gestational hyperthyroidism, but presence indicates Graves' disease. The mother and fetus may occasionally experience significant difficulties as a result of hyperthyroidism during pregnancy. Studies have shown an increased menace of pre-eclampsia and heart failure [36].

Treatment (Therapy)

In maximum cases, women with gestational thyrotoxicosis don't need to be treated. Because of the temporary nature of the anomalies, the danger of maternal and fetal hypothyroidism, and the potential for teratogenicity, Antithyroid drugs (ATDs) are not advised [37]. Early research revealed that Propylthiouracil (PTU) was less permeable to the placenta than Methimazole (MMI), and as a result, PTU has long been recognized as the preferable ATD for treating pregnancy-related hyperthyroidism. However, later research employing *in vitro* perfusion methods was unable to show differences between PTU and MMI's placental transfer kinetics, and both constituents were testified to have similar effects on fetal thyroid function [35].

Thyroid storm

The 'Thyroid Storm' appeared in the literature around the 1920s. For Instance, in 1928, Lahey gave an early statement putting forward the statement that remarks concerning the thyroid crisis and its regulation are prompted by the fact of multiple patients reporting to the hospital with advanced stages of thyroid crisis as so many of these patients were inoperable despite every measure taken in the medical books. At that time, the standard measures to treat this condition were Iodine, morphine, fluids, and glucose [38]. Toxic multinodular goiter, toxic adenoma, and graves disease can occasionally result in a thyroid storm, a severe hyperthyroid condition. When defining whether a thyroid storm is existing, the Burch-Wartofsky score is useful [6]. Dysfunctional cardiovascular system, thermoregulatory system and central nervous system, and gastrointestinal-hepatic system have been the latest definitions. In 1993, Burt and Wartofsky developed a novel scoring system to systemize the diagnosis. In the current scenario, physicians have to face constant difficulties in identifying this condition and medical groups around the world are trying to establish clear diagnostic benchmarks based on universal clinical parameters [39].

Thyroid gland as a consequence of sars-coronavirus-2

The WHO avowed COVID-19 caused by SARS-CoronaVirus-2 to be a global epidemic on the 11th of March, 2020 [49]. The ACE2 (i.e., Angiotensin-converting enzyme 2) receptor is the route through which the SARS-CoronaVirus-2 can enter human cells [50]. It was discovered that the epithelial cells of the thyroid gland, adipose tissue, small intestine, testicles, heart, and blood arteries expressed ACE2 higher than those of other tissues [51]. Therefore, thyroid follicular cells possibly will be a target for covid virus (SARS-CoronaVirus-2) entrance as a result [13]. Recent research has shown that COVID-19 may affect many different parts of the body, inclusive of the endocrine organs, which may be a detriment by a variety of mechanisms involving direct virus injury to the gland or a direct impression on the hypothalamus-pituitary gland axis, systemic inflammation brought on by the production of cytokines and chemokines, vascular derangement, and immunological responses as shown in fig. 5 [52]. Cell culture tests revealed that the thyroid gland expressed more of the enzymes TMPRSS2 (i.e., Transmembrane protease serine 2) and ACE2 than the lung. Therefore, COVID-19 may target the thyroid gland [53]. Additionally, a retrospective analysis of 287 consecutive COVID-19 sufferers who were hospitalized in non-intensive care units and had their thyroid function examined revealed an elevated frequency of hyperthyroidism and an inverse connection of thyrotropin levels [54]. The COVID-19 disease had a significant impression on our daily lives and has suddenly changed the direction of medical research. Additionally, we encountered a wealth of medical material that was frequently at odds with itself, even on the subject of thyroid health [55].

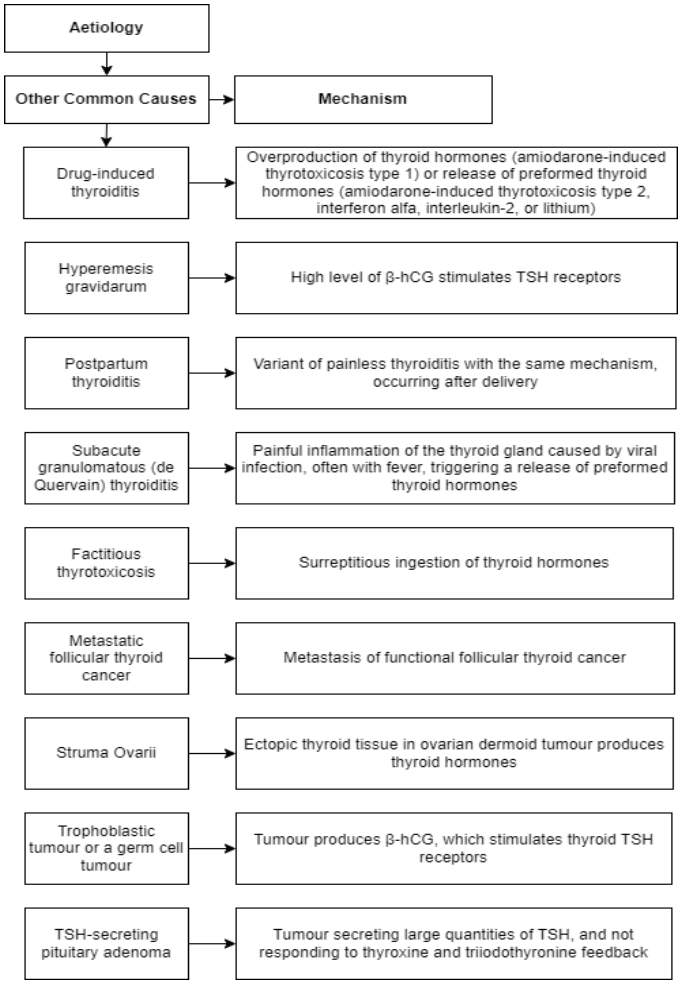

Fig. 4: Flow chart shows the other common causes or etiology of hyperthyroidism along with their mechanisms [40–48]

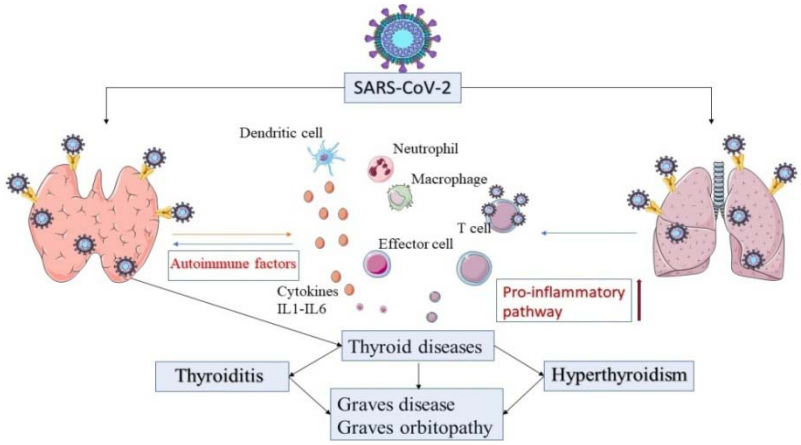

Fig. 5: SARS-Coronavirus-2-induced thyroid dysfunction. The image depicts both the direct infection of the thyroid and the viral receptor, host protein ACE2, which is highly expressed in the gland. Injury to the follicular and parafollicular cells, the building blocks of the thyroid, is the direct result of a viral infection, which leads to thyroid dysfunction. Infections that target the host's lungs or other organs lead to a "cytokine storm" that activates many pro-inflammatory pathways, causing the thyroid to become dysfunctional as well [52]

Role of SARS-corona virus-2 inducing hyperthyroidism

Hyperthyroidism is overblown by the stimulation of TSH receptors by antibodies referred to as Graves disease or as a repercussion of the autonomous production of thyroid hormones by thyroid nodules [56], if the sufferers do not take any precautions, hyperthyroidism may lead to cardiac hypertrophy. According to reports, hyperthyroidism activates the heart RAAS (i.e., Renin-angiotensin aldosterone system), which could worsen cardiac Angiotensin II (Ang II) levels and its renin function. Additionally, it has been demonstrated that the cardiac Ang II receptor type 2 known as the AT2 receptor, is increased in response to hyperthyroidism, indicating that the primary RAAS axis major molecules are altered in hyperthyroidism. Because thyroid hormone production is increased

when Ang II receptor type 1 known as the AT1 receptor inhibitors and ACE stands for angiotensin-converting enzymes are used, it is possible that RAAS plays a crucial role in thyroid hormone-mediated cardiac hypertrophy [57] as shown in fig. 6. It has been revealed that ACE can be hyperactivated by hypertrophy-induced autoregulatory factors. These findings show that the RAAS's counter-regulatory mechanisms are increased in hyperthyroidism, which may help to control how the heart responds to thyroid hormone [51]. After getting the SARS-CoronaVirus-2 immunization or covid vaccine, several kinds of thyrotoxicosis, including overt sub-acute thyroiditis, atypical thyroiditis, and autoimmune hyperthyroidism (Graves' disease), have been reported [58, 59].

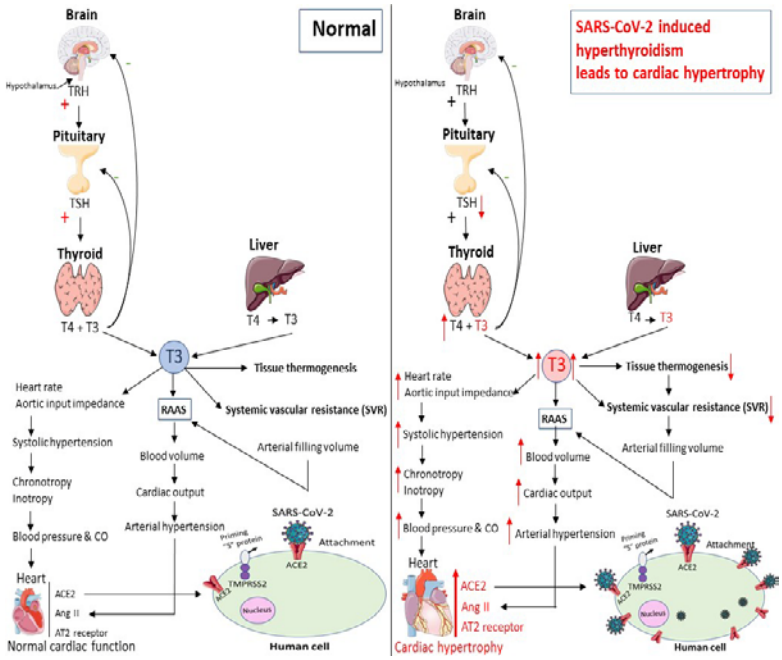

Fig. 6: SARS-CoronaVirus-2-induced hyperthyroidism leads to cardiac hyperthyroidism. The illustration on the left side shows a normal thyroid function. RAAS is one of the cellular physiological processes that is regulated by thyroid hormone, and this pathway is less susceptible to SARS-CoronaVirus-2 infection the illustration on the right side shows a SARS-CoronaVirus-2 induced hyperthyroidism leads to cardiac hypertrophy [57]

GD can be brought on by SARS-CoronaVirus-2 mRNA immunization (covid vaccine) and the SARS-corona virus-2 (covid virus)

An auto-immune thyroid condition called Graves disease is brought on by the existence of thyroid-stimulating antibodies or receptors. Graves' disease may begin or relapse as a result of the stimulation of an autoimmune response, regardless of context, which includes when COVID-19 infection is present [60]. One probable explanation, in particular, is the theory that some frequent viral infections, such as the influenza virus and the Epstein-Barr virus, cause epigenetic fluctuations in genes linked to GD vulnerability, such as the thyrotropin receptor and thyroglobulin gene [61]. This suggests that the commencement of autoimmune thyroid disorders (AITD) linked to the SARS-CoronaVirus-2 contagion should be anticipated. Indeed, after the SARS-CoronaVirus-2 contagion and covid vaccination against it, certain cases of GD and other AITD have been documented [62]. The coronavirus ailment 2019, which has stunned the entire planet to its core, may be brought under control with the help of vaccines. However, professionals have started to closely monitor any complexities that could be connected to improved vaccination at previously unheard-of levels [61]. Because the peptide sequences of thyroid peroxidase (TPO) and the viral proteins are comparable and homologous, it has been found that TPO reacts with the membrane protein, the spike protein, and the nucleoprotein of SARS-2 coronavirus [63, 64]. Consequently, the SARS-2 coronavirus spike protein formed within the host cells to elicit an immune response in contradiction of it could incite autoimmune reactions via the process of molecular mimicry, which led to graves disease [65]. Graves' illness has been linked to COVID-19 in time, suggesting that SARS-CoronaVirus-2 may cause autoimmune thyroid problems [66].

Graves' ophthalmopathy (GO)

The primary extrathyroidal symptom of Graves' illness is thyroid-associated orbitopathy, also recognized as Graves' ophthalmopathy (GO). The signs and symptoms of GO include everything from double vision to loss of vision to gritty, irritated, and red eyes. Proptosis and lid retraction are frequent. Up to 90% of those with the condition have upper eyelid retraction due to fibrosis and inflammation of the Mullers and elevator's muscles. Enlargement of the orbital fat i.e., type 1 orbitopathy, the extraocular muscles i.e., type 2 orbitopathy, or both are the causes of proptosis [67]. Hepatitis B, the human papillomavirus, and the H1N1 vaccines can all cause autoimmune hyperthyroidism, and the hyperimmune milieu that results from the SARS-CoronaVirus-2 mRNA immunization (covid vaccine) can lead to the development of autoimmune thyroid illnesses. The precise pathogenetic pathways for GO to first manifest, return, or worsen after receiving SARS-CoronaVirus-2 mRNA immunization (covid vaccine) [68].

SARS-CoronaVirus-2 mRNA immunization (covid vaccine) and the SARS-CoronaVirus-2 triggered SAT

Subacute granulomatous thyroiditis, commonly known as De Quervain's thyroiditis or giant cell thyroiditis, is a self-limiting or self-discipline inflammatory condition of the thyroid gland that typically develops after or concurrently with viral infection [69]. These abnormalities, including sub-acute thyroiditis, are thought to be caused by the interaction of the immune system and thyroid hormones as well as the direct cytotoxic effect of the virus [11]. Clusters of sickness have been documented during viral infection outbreaks, and sub-acute thyroiditis is alleged to be triggered by a postviral inflammatory process or a viral infection. This circumstance is quite similar to the COVID-19 pandemic event [70]. Interactions with ACE2 receptor-In addition to the lungs, many other organs, such as the thyroid, express ACE2 receptors [51]. It is thought that ACE2 is essential for the pathophysiology of lung damage brought on by coronaviruses. ACE2 receptors in the thyroid may therefore represent a different mechanism of harm [71]. It is

believed that the pathophysiology of SAT caused by SARS-CoronaVirus-2 infection is similar to that of SAT caused by other viral infections, either by a postviral inflammatory response or through a direct viral infection that targets the thyroid of hereditarily vulnerable people. Psychoanalysts should be aware that SARS-CoronaVirus-2 infected patients may develop subacute thyroiditis as a result [72]. The most frequently used treatments for COVID-19 induced SAT comprised analgesics, α-adrenoceptor blockers, and short-term corticosteroids. Although now hydroxychloroquine is not a recommended therapy, it has been reported that hydroxychloroquine and steroids were used in conjunction in one case. Other authors writing COVID-19-related Sub-acute thyroiditis used steroids for various causes and dates [73]. The most prevalent thyroid-related clinical condition linked to COVID-19 appears to be subacute thyroiditis [74]. One of the most successful public health interventions is immunization, which prevents lifelong disability and saves many lives. Because vaccines are very safe, very effective, and generally economical, they have enabled not only a decrease in the prevalence of illnesses but also a decrease in the mortality and morbidity associated with them [75]. Numerous vaccinations have been created, including those utilizing cutting-edge technology (virus-vector-based vaccines and mRNA-based), which can provide a strong defense against severe COVID-19 forms. Numerous tribunals have demonstrated the general safety and effectiveness of the COVID-19 vaccinations that are now on the market. However, after the administration of several types of COVID-19 vaccinations, a small number of cases of post-immunization problems, such as thyroid abnormalities, have been noted [76]. TPO reacts with the membrane protein, nucleoprotein, and protein of SARS-CoronaVirus-2. A number of thyroid peroxidase-related gene sequences show similarities with gene sequences in several covid proteins, according to BLAST matching. As a result, the development of autoimmune thyroiditis may be facilitated by antibodies produced against SARS-CoronaVirus-2 [77]. SARS coronavirus cross-reactivity with thyroid protein may cause the development of thyroiditis following COVID-19 vaccination or SARS-CoronaVirus-2 immunization. Women made up 73.6% of COVID-19 patients with the SARS-CoronaVirus-2-related SAT, who were mostly patients aged 18 to 63 [78].

Thyroid nodules and cancer relating to SARS-CoronaVirus-2

With a palpable incidence of between 3% and 7%, thyroid nodules (TNs) are one of the endocrine system's more prevalent disorders. In randomly chosen individuals, the prevalence of high-resolution ultrasonography ranges from 19% to 67%, with global annual growth trends. Thyroid cancer affects 5% to 15% of TNs [79]. The detection of thyroid incidentalomas-thyroid nodules discovered during imaging taken for purposes unrelated to the thyroid-has been put forth as a key factor in the increased incidence of thyroid cancer [80]. The likelihood of developing a major illness and passing away increases with age and the existence of other medical disorders in COVID-19 cases. Cancer patients are thought to be among the most susceptible groups to infection and the disclosure of more severe indications, presumably as a result of immune system weakness brought on both directly by the side effects of anticancer treatment and indirectly by tumor growth. However, there is little information about the effects of COVID-19 contagion on those who have thyroid cancer or a history of it [81]. A greater rate of death from COVID-19 and catastrophic results in cancer patients were documented in reports from the United States and China that described the therapeutic, demographic, and clinical outcomes of the cancer patients. Despite the slow-growing nature of thyroid cancer, more recent research has revealed that thyroid cancer is frequently diagnosed among COVID-19 patients brought to hospitals. These findings, however, are preliminary, and thyroid cancer and COVID-19 infection have not yet been linked causally. They are mostly blamed for the high incidence of thyroid nodules and malignancy [82, 83]. The likelihood of COVID-19 infection and consequences can be further impacted by treatment. Immune function is impacted by I^{131} both immediately and over time, which may have an impact on patients' COVID-19 results. Treatment with I^{131} can raise IL-6, a cytokine linked to severe pulmonary illness and death from COVID-19, in thyroid cancer patients who also have thyroid autoimmunity. A spike in IL-6 and ferritin in patients who performed particularly badly was associated with death [84, 85].

Future prospective

To create a meaningful risk/benefit analysis and accurate thyroid disorder statistics, prospective research should be conducted using vaccinated and unvaccinated populations. Further research indicates that nevertheless of underlying other etiological factors, sufferers with hyperthyroidism are likely at an increased risk of developing fatal and severe SARS-CoronaVirus-2 disease. However, the WHO did not advise hospitalized COVID-19 sufferers to undergo routine thyroid function testing. Nobody distinguishes how long the COVID-19 contagion will last, but in the near future, high demand for healthcare services unrelated to COVID-19 is anticipated. In our view, patients with symptomatic COVID-19 should take the testing of the functioning of the thyroid into consideration.

CONCLUSION

In conclusion, the etiology and pathophysiology of hyperthyroidism, as well as its common causes and therapies, were reviewed. It is crucial for both the clinician and the pathologist to be aware of these illnesses as diagnostic factors, even though the majority of them are rare, particularly when compared to toxic nodular or multi-nodular goiter and graves' disease. Theoretically, the connection of the HPT axis and thyroid must be considered when dealing with COVID-19, SARS-CoronaVirus-2 can affect any organ throughout the viraemic phase. The sort of change that predominates in thyroid damage appears to be mostly determined by the COVID-19 severity. In particular, mild COVID-19 that causes damaging thyrotoxicosis and neck pain (also known as classical subacute thyroiditis) typically develops during or shortly after. There will probably be cases of thyroid abnormalities as an outcome of vaccine-independent and/or vaccine-associated processes as the world currently engages in the largest mass vaccination campaign.

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All the authors have contributed equally.

CONFLICTS OF INTERESTS

There is no conflict of interest among all the authors of this article.

REFERENCES

1. Yussuf YA, Bhogireddy N, Vulli V, Verma A, Bhaskaran AA. Thyroid stimulating hormones and free thyroxine as an indication of thyroid dysfunction at pathology laboratory of Mnazi Mmoja Hospital, Zanzibar. Asian J Pharm Clin Res. 2014 Jan 1:67-71.
2. Stathatos N. Anatomy and physiology of the thyroid gland. The thyroid and its diseases: a comprehensive guide for the clinician; 2019. p. 3-12.
3. Klein I, Danzi S. Thyroid disease and the heart. Curr Probl Cardiol. 2016 Feb 1;41(2):65-92. doi: 10.1016/j.cpcardiol.2015.04.002. PMID 26792255.
4. Podder G, Adhikari A, De A, Banerjee J, De M. Antioxidant enzymes status and thyroid stimulating hormone level of down syndrome patient in West Bengal, India: a case-control study. Asian J Pharm Clin Res. 2013 Nov 1:1-4.
5. Giovanella L, Avram AM, Ovcaricek PP, Clerc J. Thyroid functional and molecular imaging. Presse Med. 2022 Jun 1;51(2):104116. doi: 10.1016/j.lpm.2022.104116. PMID 35124101.
6. Wiersinga WM. Graves' disease: can it be cured? Endocrinol Metab (Seoul). 2019 Mar 1;34(1):29-38. doi: 10.3803/EnM.2019.34.1.29, PMID 30912336.

7. Sharma A, Stan MN. Thyrotoxicosis: diagnosis and management. Mayo Clin Proc. 2019 Jun 1;94(6):1048-64. doi: 10.1016/j.mayocp.2018.10.011, PMID 30922695.
8. Smithson M, Asban A, Miller J, Chen H. Considerations for thyroidectomy as treatment for graves disease. Clin Med Insights Endocrinol Diabetes. 2019 Apr;12:1179551419844523. doi: 10.1177/1179551419844523, PMID 31040734.
9. Vija Racaru LV, Grunenwald S, Hindie E, Taieb D, Clerc J, Zerdoud S. Management of adenomas and toxic multinodular goiters with iodine 131. Medecine Nucleaire. 2020 Oct 1;44(4):272-6. doi: 10.1016/j.mednuc.2020.09.001.
10. Scappaticcio L, Pitoia F, Esposito K, Piccardo A, Trimboli P. Impact of COVID-19 on the thyroid gland: an update. Rev Endocr Metab Disord. 2021;22(4):803-15. doi: 10.1007/s11154-020-09615-z. PMID 33241508.
11. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395:497-506. doi: 10.1016/S0140-6736(20)30183-5, PMID 31986264.
12. Rotondi M, Coperchini F, Ricci G, Denegri M, Croce L, Ngnitejeu ST. Detection of SARS-COV-2 receptor ACE-2 mRNA in thyroid cells: a clue for COVID-19-related subacute thyroiditis. J Endocrinol Invest. 2021 May;44(5):1085-90. doi: 10.1007/s40618-020-01436-w, PMID 33025553.
13. Taylor PN, Albrecht D, Scholz A, Gutierrez Buey G, Lazarus JH, Dayan CM. Global epidemiology of hyperthyroidism and hypothyroidism. Nat Rev Endocrinol. 2018 May;14(5):301-16. doi: 10.1038/nrendo.2018.18, PMID 29569622.
14. De Leo S, Braverman LE. Iodine-induced thyroid dysfunction. The thyroid and its diseases: a comprehensive guide for the clinician; 2019. p. 435-52.
15. Wemeau JL, Klein M, Sadoul JL, Briet C, Velayoudom Cephise FL. Graves' disease: Introduction, epidemiology, endogenous and environmental pathogenic factors. Ann Endocrinol (Paris). 2018;79(6):599-607. doi: 10.1016/j.ando.2018.09.002. PMID 30342794.
16. Davies TF, Andersen S, Latif R, Nagayama Y, Barbesino G, Brito M. Graves' disease. Nat Rev Dis Primers. 2020 Jul 2;6(1):52. doi: 10.1038/s41572-020-0184-y, PMID 32616746.
17. Weetman AP. Graves' disease. N Engl J Med. 2000 Oct 26;343(17):1236-48. doi: 10.1056/NEJM200010263431707, PMID 11071676.
18. Antonelli A, Ferrari SM, Ragusa F, Elia G, Paparo SR, Ruffilli I. Graves' disease: epidemiology, genetic and environmental risk factors and viruses. Best Pract Res Clin Endocrinol Metab. 2020 Jan 1;34(1):101387. doi: 10.1016/j.beem.2020.101387. PMID 32107168.
19. Kim BW. Does radioactive iodine therapy for hyperthyroidism cause cancer? J Clin Endocrinol Metab. 2022 Feb;107(2):e448-57. doi: 10.1210/clinem/dgab700, PMID 34555150.
20. Cirocchi R, Trastulli S, Randolph J, Guarino S, Di Rocco G, Arezzo A. Total or near-total thyroidectomy versus subtotal thyroidectomy for multinodular non-toxic goitre in adults. Cochrane Database Syst Rev. 2015;2015(8):CD010370. doi: 10.1002/14651858.CD010370.pub2. PMID 26252202.
21. Abdi H, Amouzegar A, Azizi F. Antithyroid drugs. Iranian Journal of Pharmaceutical Research. 2019;18Suppl 1:1.
22. Staniforth JUL, Erdirimanne S, Eslick GD. Thyroid carcinoma in Graves' disease: a meta-analysis. Int J Surg. 2016 Mar 1;27:118-25. doi: 10.1016/j.ijsu.2015.11.027. PMID 26626367.
23. Walsh JP. Managing thyroid disease in general practice. Med J Aust. 2016 Aug;205(4):179-84. doi: 10.5694/mja16.00545, PMID 27510349.
24. Stasiak M, Lewiński A. New aspects in the pathogenesis and management of subacute thyroiditis. Rev Endocr Metab Disord. 2021 Dec;22(4):1027-39. doi: 10.1007/s11154-021-09648-y, PMID 33950404.
25. Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med. 2003 Jun 26;348(26):2609-17. doi: 10.1056/NEJMoa030288, PMID 12826635.
26. Cukier P, Santini FC, Scaranti M, Hoff AO. Endocrine side effects of cancer immunotherapy. Endocr Relat Cancer. 2017 Dec 1;24(12):T331-47. doi: 10.1530/ERC-17-0358, PMID 29025857.
27. Barroso Sousa R, Barry WT, Garrido Castro AC, Hodi FS, Min L, Krop IE. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. JAMA Oncol. 2018 Feb 1;4(2):173-82. doi: 10.1001/jamaoncol.2017.3064, PMID 28973656.
28. Joshi M, Bisht S, Singh MF. A review: mechanistic insights into the effect of thyroid disorders on estrogen level and bone mineral density. Int J Pharm Pharm Sci. 2019;11(10):9-17. doi: 10.22159/ijpps.2019v11i10.34447.
29. Biondi B, Cooper DS. Subclinical hyperthyroidism. N Engl J Med. 2018 Jun 21;378(25):2411-9. doi: 10.1056/NEJMcp1709318, PMID 29924956.
30. Donangelo I, Suh SY. Subclinical hyperthyroidism: when to consider treatment. Am Fam Physician. 2017 Jun 1;95(11):710-6. PMID 28671443.
31. Bervini S, Trelle S, Kopp P, Stettler C, Trepp R. Prevalence of iodine-induced hyperthyroidism after administration of iodinated contrast during radiographic procedures: a systematic review and meta-analysis of the literature. Thyroid. 2021 Jul 1;31(7):1020-9. doi: 10.1089/thy.2020.0459, PMID 33327840.
32. Lee SY, Rhee CM, Leung AM, Braverman LE, Brent GA, Pearce EN. A review: radiographic iodinated contrast media-induced thyroid dysfunction. J Clin Endocrinol Metab. 2015 Feb 1;100(2):376-83. doi: 10.1210/jc.2014-3292, PMID 25375985.
33. Korevaar TIM, Medici M, Visser TJ, Peeters RP. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. Nat Rev Endocrinol. 2017 Oct;13(10):610-22. doi: 10.1038/nrendo.2017.93, PMID 28776582.
34. Moleti M, Di Mauro M, Sturniolo G, Russo M, Vermiglio F. Hyperthyroidism in the pregnant woman: maternal and fetal aspects. J Clin Transl Endocrinol. 2019 Jun 1;16:100190. doi: 10.1016/j.jcte.2019.100190. PMID 31049292.
35. Illouz F, Luton D, Polak M, Besançon A, Bournaud C. Graves' disease and pregnancy. Ann Endocrinol (Paris). 2018;79(6):636-46. doi: 10.1016/j.ando.2018.08.004. PMID 30224035.
36. Kobaly K, Mandel SJ. Hyperthyroidism and pregnancy. Endocrinol Metab Clin North Am. 2019 Sep;48(3):533-45. doi: 10.1016/j.ecl.2019.05.002. PMID 31345521.
37. Akamizu T. Thyroid storm: a Japanese perspective. Thyroid. 2018 Jan 1;28(1):32-40. doi: 10.1089/thy.2017.0243, PMID 28899229.
38. Chiha M, Samarasinghe S, Kabaker AS. Thyroid storm: an updated review. J Intensive Care Med. 2015 Mar;30(3):131-40. doi: 10.1177/0885066613498053, PMID 23920160.
39. Burch HB. Drug effects on the thyroid. N Engl J Med. 2019 Aug 22;381(8):749-61. doi: 10.1056/NEJMra1901214, PMID 31433922.
40. Koren G, Ornoy A, Berkovitch M. Hyperemesis gravidarum-Is it a cause of abnormal fetal brain development? Reprod Toxicol. 2018 Aug 1;79:84-8. doi: 10.1016/j.reprotox.2018.06.008. PMID 29913206.
41. Amino N, Arata N. Thyroid dysfunction following pregnancy and implications for breastfeeding. Best Pract Res Clin Endocrinol Metab. 2020 Jul 1;34(4):101438. doi: 10.1016/j.beem.2020.101438. PMID 32651061.
42. Caron P. Thyroiditis and SARS-CoV-2 pandemic: a review. Endocrine. 2021 May;72(2):326-31. doi: 10.1007/s12020-021-02689-y, PMID 33774779.
43. Yap PS, Ali O, Truran P, Aspinall S. Thyrotoxicosis and thyroiditis. Surgery (Oxford). 2020 Dec 1;38(12):794-800. doi: 10.1016/j.mpsur.2020.10.002.
44. Cao J, Zhang M, Zhang L, Lou J, Zhou F, Fang M. Non-coding RNA in thyroid cancer–functions and mechanisms. Cancer Lett. 2021 Jan 1;496:117-26. doi: 10.1016/j.canlet.2020.08.021. PMID 32949678.
45. Siegel MR, Wolsky RJ, Alvarez EA, Mengesha BM. Struma ovarii with atypical features and synchronous primary thyroid cancer: a case report and review of the literature. Arch Gynecol Obstet. 2019 Dec;300(6):1693-707. doi: 10.1007/s00404-019-05329-z, PMID 31679038.
46. Rejlekova K, Cursano MC, De Giorgi U, Mego M. Severe complications in testicular germ cell tumors: the

choriocarcinoma syndrome. Front Endocrinol. 2019 Apr 12;10:218. doi: 10.3389/fendo.2019.00218, PMID 31031704.

47. Beck Peccoz P, Giavoli C, Lania A. A 2019 update on TSH-secreting pituitary adenomas. J Endocrinol Invest. 2019 Dec;42(12):1401-6. doi: 10.1007/s40618-019-01066-x, PMID 31175617.
48. Boelaert K, Visser WE, Taylor PN, Moran C, Leger J, Persani L. Endocrinology in the time of Covid-19: management of hyperthyroidism and hypothyroidism. Eur J Endocrinol. 2020 Jul;183(1):G33-9. doi: 10.1530/EJE-20-0445, PMID 32438340.
49. Hossain MF, Hasana S, Mamun AA, Uddin MS, Wahed MII, Sarker S. Covid-19 Outbreak: pathogenesis, current therapies, and potentials for future management. Front Pharmacol. 2020 Oct 16;11:563478. doi: 10.3389/fphar.2020.563478, PMID 33178016.
50. Murugan AK, Alzahrani AS. SARS-CoV-2 plays a pivotal role in inducing hyperthyroidism of Graves' disease. Endocrine. 2021 Aug;73(2):243-54. doi: 10.1007/s12020-021-02770-6, PMID 34106438.
51. Marazuela M, Giustina A, Puig Domingo M. Endocrine and metabolic aspects of the COVID-19 pandemic. Rev Endocr Metab Disord. 2020 Dec;21(4):495-507. doi: 10.1007/s11154-020-09569-2, PMID 32643004.
52. Urhan E, Karaca Z, Kara CS, Yuce ZT, Unluhizarci K. The potential impact of COVID-19 on thyroid gland volumes among Covid-19 survivors. Endocrine. 2022 Jun;76(3):635-41. doi: 10.1007/s12020-022-03019-6, PMID 35239124.
53. Duntas LH, Jonklaas J. Covid-19 and thyroid diseases: a bidirectional impact. J Endocr Soc. 2021 Aug;5(8):bvab076. doi: 10.1210/jendso/bvab076, PMID 34189381.
54. Trimboli P, Camponovo C, Scappaticcio L, Bellastella G, Piccardo A, Rotondi M. Thyroid sequelae of Covid-19: a systematic review of reviews. Rev Endocr Metab Disord. 2021 Jun;22(2):485-91. doi: 10.1007/s11154-021-09653-1, PMID 33843008.
55. Yamakawa H, Kato TS, Noh JY, Yuasa S, Kawamura A, Fukuda K. Thyroid hormone plays an important role in cardiac function: from bench to bedside. Front Physiol. 2021 Oct 18;12:606931. doi: 10.3389/fphys.2021.606931, PMID 34733168.
56. Barreto Chaves ML, Senger N, Fevereiro MR, Parletta AC, Takano AP. Impact of hyperthyroidism on cardiac hypertrophy. Endocr Connect. 2020 Mar;9(3):R59-69. doi: 10.1530/EC-19-0543, PMID 32101527.
57. Siolos A, Gartzonika K, Tigas S. Thyroiditis following vaccination against COVID-19: report of two cases and review of the literature. Metabol Open. 2021 Dec 1;12:100136. doi: 10.1016/j.metop.2021.100136. PMID 34693241.
58. Lee KA, Kim YJ, Jin HY. Thyrotoxicosis after covid-19 vaccination: seven case reports and a literature review. Endocrine. 2021 Dec;74(3):470-2. doi: 10.1007/s12020-021-02898-5, PMID 34637073.
59. Caron P. Thyroid disorders and SARS-CoV-2 infection: from pathophysiological mechanism to patient management. Ann Endocrinol (Paris). 2020;81(5):507-10. doi: 10.1016/j.ando.2020.09.001. PMID 32950466.
60. Bostan H, Ucan B, Kizilgul M, Calapkulu M, Hepsen S, Gul U. Relapsed and newly diagnosed Graves' disease due to immunization against Covid-19: A case series and review of the literature. J Autoimmun. 2022 Apr 1;128:102809. doi: 10.1016/j.jaut.2022.102809. PMID 35220164.
61. Murugan AK, Alzahrani AS. SARS-CoV-2: emerging role in the pathogenesis of various thyroid diseases. J Inflamm Res. 2021;14:6191-221. doi: 10.2147/JIR.S332705. PMID 34853527.
62. Vojdani A, Vojdani E, Kharrazian D. Reaction of human monoclonal antibodies to SARS-CoV-2 proteins with tissue antigens: implications for autoimmune diseases. Front Immunol. 2020;11:617089. doi: 10.3389/fimmu.2020.617089, PMID 33584709.
63. Kanduc D, Shoenfeld Y. Molecular mimicry between SARS-CoV-2 spike glycoprotein and mammalian proteomes: implications for the vaccine. Immunol Res. 2020 Oct;68(5):310-3. doi: 10.1007/s12026-020-09152-6, PMID 32946016.
64. Patrizio A, Ferrari SM, Elia G, Ragusa F, Paparo SR, Mazzi V. Graves' disease following SARS-CoV-2 vaccination: a systematic review. Vaccines. 2022 Sep 1;10(9):1445. doi: 10.3390/vaccines10091445, PMID 36146523.
65. Lui DTW, Lee KK, Lee CH, Lee ACH, Hung IFN, Tan KCB. Development of Graves' disease after SARS-CoV-2 mRNA vaccination: a case report and literature review. Front Public Health. 2021 Nov 23;9:778964. doi: 10.3389/fpubh.2021.778964, PMID 34888290.
66. Mejia Gonzalez MA, Carbone J. How suitable is intravenous tocilizumab for the treatment of graves' ophthalmopathy? Expert Rev Clin Immunol. 2021 Nov 2;17(11):1151-3. doi: 10.1080/1744666X.2021.1997591, PMID 34704876.
67. Abeillon-du Payrat J, Grunenwald S, Gall E, Ladsous M, Raingeard I, Caron P. Graves' orbitopathy post-SARS-CoV-2 vaccines: report on six patients. J Endocrinol Invest. 2023 Mar;46(3):617-27. doi: 10.1007/s40618-022-01955-8, PMID 36378488.
68. Aemaz Ur Rehman M, Farooq H, Ali MM, Ebaad Ur Rehman M, Dar QA, Hussain A. The association of subacute thyroiditis with Covid-19: a systematic review. SN Compr Clin Med. 2021 Jul;3(7):1515-27. doi: 10.1007/s42399-021-00912-5, PMID 33942028.
69. Mattar SAM, Koh SJQ, Rama Chandran SR, Cherng BPZ. Subacute thyroiditis associated with Covid-19. BMJ Case Rep. 2020 Aug 1;13(8):e237336. doi: 10.1136/bcr-2020-237336, PMID 32843467.
70. Khatri A, Charlap E, Kim A. Subacute thyroiditis from Covid-19 infection: a case report and review of literature. Eur Thyroid J. 2021 Feb 1;9(6):324-8. doi: 10.1159/000511872, PMID 33708634.
71. Campos Barrera E, Alvarez Cisneros T, Davalos Fuentes M. Subacute thyroiditis associated with Covid-19. Case Rep Endocrinol. 2020;2020:8891539. doi: 10.1155/2020/8891539, PMID 33005461.
72. Dworakowska D, Morley S, Mulholland N, Grossman AB. Covid-19-related thyroiditis: a novel disease entity? Clin Endocrinol (Oxf). 2021 Sep;95(3):369-77. doi: 10.1111/cen.14453, PMID 33650180.
73. Christensen J, O'Callaghan K, Sinclair H, Hawke K, Love A, Hajkowicz K. Risk factors, treatment and outcomes of subacute thyroiditis secondary to Covid-19: a systematic review. Intern Med J. 2022 Apr;52(4):522-9. doi: 10.1111/imj.15432, PMID 34139048.
74. MacDonald N, Mohsni E, Al-Mazrou Y, Kim Andrus J, Arora N, Elden S. Global vaccine action plan lessons learned I: recommendations for the next decade. Vaccine. 2020 Jul 14;38(33):5364-71. doi: 10.1016/j.vaccine.2020.05.003, PMID 32563607.
75. Olivieri B, Betterle C, Zanoni G. Vaccinations and autoimmune diseases. Vaccines (Basel). 2021 Jul 22;9(8):34451940. doi: 10.3390/vaccines9080815, PMID 34451940, PMCID PMC8402446.
76. Vojdani A, Kharrazian D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. Clin Immunol. 2020 Aug;217:108480. doi: 10.1016/j.clim.2020.108480. PMID 32461193.
77. Jafarzadeh A, Nemati M, Jafarzadeh S, Nozari P, Mortazavi SMJ. Thyroid dysfunction following vaccination with Covid-19 vaccines: a basic review of the preliminary evidence. J Endocrinol Invest. 2022 Oct;45(10):1835-63. doi: 10.1007/s40618-022-01786-7, PMID 35347651.
78. Jiang H, Tian Y, Yan W, Kong Y, Wang H, Wang A. The prevalence of thyroid nodules and an analysis of related lifestyle factors in Beijing communities. Int J Environ Res Public Health. 2016 Apr;13(4):442. doi: 10.3390/ijerph13040442, PMID 27110805.
79. Uppal A, White MG, Nagar S, Aschebrook Kilfoy B, Chang PJ, Angelos P. Benign and malignant thyroid incidentalomas are

rare in routine clinical practice: a review of 97,908 imaging studies. Cancer Epidemiol Biomarkers Prev. 2015;24(9):1327-31. doi: 10.1158/1055-9965.EPI-15-0292. PMID 26160694.

80. Giannoula E, Iakovou I, Giovanella L, Vrachimis A. Updated clinical management guidance during the Covid-19 pandemic: thyroid nodules and cancer. Eur J Endocrinol. 2022 Apr;186(4):G1-7. doi: 10.1530/EJE-21-0716, PMID 35073277.
81. Dai M, Liu D, Liu M, Zhou F, Li G, Chen Z. Patients with cancer appear more vulnerable to SARS-CoV-2: A multicenter study during the Covid-19 outbreak patients. Cancer Discov. 2020 Jun 1;10(6):783-91. doi: 10.1158/2159-8290.CD-20-0422. PMID 32345594.
82. Raghavan D, Tan AR, Story ES, Burgess EF, Musselwhite L, Kim ES. Management changes for patients with endocrine-related cancers in the Covid-19 pandemic. Endocr Relat Cancer. 2020 Sep 1;27(9):R357-74. doi: 10.1530/ERC-20-0229, PMID 32744242.
83. Tsang VHM, Gild M, Glover A, Clifton Bligh R, Robinson BG. Thyroid cancer in the age of Covid-19. Endocr Relat Cancer. 2020 Nov 1;27(11):R407-16. doi: 10.1530/ERC-20-0279, PMID 32810844.
84. Prete A, Falcone M, Bottici V, Giani C, Tiseo G, Agate L. Thyroid cancer and Covid-19: experience at one single thyroid disease referral center. Endocrine. 2021 May;72(2):332-9. doi: 10.1007/s12020-021-02650-z, PMID 33638758.