COVID-19-related thyroid conditions (Review)

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Abstract. In patients who were not previously diagnosed with any thyroid conditions, the scenario of COVID-19-related anomalies of the hypothalamus-pituitary-thyroid axes may include either: A process of central thyroid stimulating hormone (TSH) disturbances via virus-related hypophysitis; an atypical type of subacute thyroiditis which is connected to the virus spread or to excessive cytokine production including a destructive process with irreversible damage of the gland or low T3 (triiodothyronine) syndrome (so called non-thyroid illness syndrome) which is not specifically related to the COVID-19 infection, but which is associated with a very severe illness status. Our objective here was to briefly review thyroid changes due to the COVID-19 infection. Ongoing assessment of the effects of the COVID-19 pandemic will reveal more information on coronavirus-induced thyroid conditions. Routine thyroid assays performed in patients with severe infection/at acute phase of COVID-19 are encouraged in order to detect thyrotoxicosis. After recovery, thyroid function should be assessed to identify potential hypothyroidism. There remain unanswered questions related to the prognostic value of interleukin-6 in infected patients, especially in cases with cytokine storm, and the necessity of thyroid hormone replacement in subjects with hypophysitis-related central hypothyroidism.

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Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; IL-6, interleukin-6; SARS-CoV, severe acute respiratory syndrome coronavirus; TSH, thyroid stimulating hormone; T3, triiodothyronine; TNF, tumor necrosis factor

Key words: thyroiditis, thyroid, interleukin-6, thyrotoxicosis, COVID-19

Contents

1. Introduction

Human coronaviruses such as COVID-19 (Coronavirus Disease 2019) are part of a large virus family, specifically causing respiratory tract infections that underlie a heterogeneous area of severity from mild to fatal diseases, including severe acute respiratory syndrome coronavirus (SARS-CoV) (1,2). Angiotensin-converting enzyme 2 (ACE2), the functional receptor of SARS-CoV-2, plays a crucial role in the pathogenesis of COVID-19, as it provides viral entry into human cells. Because the virus follows ACE2 expression as a key player of viral transmission into the human body, every organ may be potentially affected and shut down (2,3). Severe dysfunction is particularly found in previously damaged organs and in cases when the human-virus communication goes through a cytokine storm (1-4). However, despite the massive amount of data gathered to date concerning this virus, we cannot rely on predictive models as multiple factors are actually involved in the disease evolution and prognosis as well as in patient recovery (5). Endocrine-related conditions that are likely to be correlated with a more severe prognosis are diabetes mellitus, obesity and high blood pressure, including secondary endocrine causes (6-8). In addition, a specific impact on virtually

each endocrine gland might be expected due to particular virus tropism (1,9).

2. Research aim and methods

Aim. Our objective of this review is a brief update of changes in thyroid conditions due to COVID-19 infection including immune-mediated changes.

Methods. This is a narrative review. Most papers were accessed through the PubMed database. Up until the preparation of the paper, 108 PubMed articles were selected by searching the key words 'COVID-19 and thyroid'. A total number of 61 studies were referenced (52 of them were published in 2020 and many were published ahead of print). The level of statistical evidence varies from original studies to reviews, opinions, case reports or position statements.

3. Endocrine focus during the pandemic

Autopsy studies have shown that the virus can enter almost every endocrine gland including the endocrine pancreas, pituitary gland, thyroid, parathyroids, adrenals and testis (9). The dysfunction may be transitory or definitive (9,10). The mechanisms underlying COVID-19-related endocrine anomalies consist of inflammation, vessel damage, necrosis, degeneration, respective immune and autoimmune processes (9-12).

To date it is known that, in patients who were not previously diagnosed with any thyroid conditions, the scenario of COVID-199-related hypothalamus-pituitary-thyroid axis anomalies may include either: i) A process of central thyroid stimulating hormone (TSH) disturbances via virus-related hypophysitis; or ii) an atypical type of subacute thyroiditis which is connected to the virus spread or to excessive cytokine production including a destructive process with irreversible damage of the gland (9,13). A third category, namely euthyroid sick syndrome or low T3 (triiodothyronine) syndrome or non-thyroid illness syndrome, is not specifically related to the COVID-19 infection, but is also diagnosed in other severe conditions such as sepsis, trauma, severe kidney and liver failure or acute myocardial infarction (14,15). It is an adjustment of the body to the new conditions and it does not require thyroid hormone replacement (14,15). However, molecular studies have revealed the benefits of T3 action on p38 MAPK signal transduction pathways on sepsis-related conditions thus there are ongoing trials to assess the potential benefits for critically ill COVID-19 patients to receive T3 (16,17).

4. Thyroiditis

Early reports in 2020 showed an atypical subtype of thyroiditis in COVID-19 patients. Many patients with COVID-19 infection, especially those with severe forms or admitted to intensive care units, displayed anomalies of thyroid hormones and TSH (13,14). Thus, a novel etiology of subacute thyroiditis was identified (18,19). This condition presents with thyroid hormone flare-up and usually the thyrotoxicosis is self-limited and does not require specific anti-thyroid drugs (18,19). A study on COVID-19-positive patients admitted to intensive care units in Milan, Italy showed a 10% prevalence of thyrotoxicosis; statistically significant higher than the 0.5% prevalence in COVID-19 negative patients who were admitted one year prior to the same units (18).

The overlap of a typical episode of non-COVID subacute De Quervain thyroiditis (such as coxsackie virus, mumps virus, cytomegalovirus, enterovirus and adenovirus-induced) to COVID-19 infection has been reported (19). The clinical picture also includes thyrotoxicosis, and glucocorticoid therapy may improve the severe evolution (19). Some authors suggest that COVID-19-related subacute thyroiditis might be actually underestimated in many cases (20). In addition, there are reports of COVID-19-related subacute thyroiditis in patients who were not critically ill (21,22). Subacute thyroiditis associated with thyrotoxicosis overlaps with destructive thyroiditis as autopsy studies have shown (as well as some cytology reports) but thyroid inflammation can be immune-mediated (9,23,24).

Immune-related thyroiditis is described in critically ill COVID-19-positive patients, especially at the moment of cytokine storm in addition to multiple organ failure (4,25). The THYRCOV study provides early evidence that patients with acute coronavirus infection presenting with thyrotoxicosis have statistically significant higher levels of interleukin-6 (IL-6) (26). This was a single center, retrospective study on 287 adult subjects with an average age of 66 years who were admitted to non-intensive care units (26). Thyrotoxicosis was confirmed in 20.2% of cases while 5% of them experienced hypothyroidism (26). IL-6 represents a major player of the pro-inflammatory status in addition to IL-1 and tumor necrosis factor (TNF)α which may also act at the thyroid level (9,27). Based on another retrospective study on 728 adult COVID-19-positive patients, IL-6 was found to be independently associated with the severity of the disease and also to mortality during hospitalization (27). It may become a new standard in disease assessment as a predictive factor including during follow-up (27).

5. Thyroid assessments during the pandemic period

The coronavirus may also damage the pituitary gland, and mostly transient hypophysitis has been reported developing central hypocortisolism and central hypothyroidism (less frequently) by decreasing the synthesis of adrenocorticotropic hormone (ACTH) and TSH (9,28). The condition is difficult to diagnose, and there is current debate whether levothyroxine replacement has a major impact on improvement of the clinical outcome (28).

Another issue relates to the primary hyperthyroidism developed during the pandemic period (9). When a patient is COVID-19-positive, then there is a higher risk of developing arrhythmia and thrombo-embolic events while specific anti-thyroid drugs may be associated with agranulocytosis, thus worsening the overall prognosis (9,29,30).

Regarding the patients with previously known thyroid conditions, the majority are not at a higher risk of contracting the coronavirus, or at risk of being admitted for more severe infections unless the subject is currently being treated with glucocorticoid medication against Graves' orbitopathy (31,32). Massive information has been published to date on the risk

of using pharmacological doses of glucocorticoids, especially during COVID-19-related cytokine storm (33,34).

Changes during the pandemic period are reflected in the telemedicine concept which is largely applicable to subjects who have a prior history of different endocrine pathologies (35). Other issues associated with the lockdown, the altered access to usual medical care services and new daily habits such as wearing facial mask, social distancing, and isolation, are reflected in the approach of individuals with a pre-pandemic diagnosis of thyroid diseases (36,37). Apart from the COVID-19 infection itself, we need to take into consideration the pandemic-related stress which may act as a trigger for various autoimmune conditions (38). Some data suggest a higher risk of autoimmune disorders (including autoimmune thyroiditis and Graves' disease) after recovery from the cytokine storm (9). This remains a topic of debate but actually we do not have enough longitudinal data to sustain this observation. The current increasing prevalence of coronavirus worldwide will unfortunately provide the necessary data on the follow-up of endocrine autoimmune conditions. Generally, patients with autoimmune thyroiditis have a higher risk of developing other antibody-related conditions such as vitiligo, alopecia areata, dermatitis herpatiformis, hypophysitis, autoimmune hepatitis, Sjogren's syndrome, Raynaud's syndrome, premature ovarian failure, primary adrenal insufficiency, type 1 diabetes mellitus, rheumatoid arthritis, atrophic gastritis, lupus, sclerodermia, vasculitis, and celiac disease (39,40).

A severe situation is observed in the particular situation of COVID-19-positive diabetic patients of either type (including type 1 as seen in polyglandular autoimmune syndrome also associating autoimmune thyroiditis or antibody-related chronic primary adrenal insufficiency) (41,42). In COVID-19 patients the prognostic is more severe and the glycemia profile may be worse due to the virus attack against the pancreas at the level of β-cells (43,44). The term 'covidiabetology' has been suggested for covering the immense area of overlap of diabetes mellitus and COVID-19 (45). Moreover, we need to take into consideration the association of thyroiditis with autoimmune primary adrenal insufficiency which is a condition with a higher risk of COVID-19 infection or other infections of different etiologies (46). Higher doses of glucocorticoid replacement are needed (46). Pre-pandemic studies have shown that conditions associated with thyroid autoimmune disorders such as celiac disease and rheumatoid arthritis are associated with vitamin D deficiency, a part from bone status anomalies (47-49). Pandemic data have shown an increased risk of developing hypovitaminosis D due to low sun exposure or the use of facial masks. Thus, under these circumstances it becomes necessary to supplement vitamin D (regardless of the real immune role of vitamin D when cross talk to the virus molecule) (50).

Another domain of thyroid conditions is related to thyroid cancer and the COVID-19 era. Consequently, physicians must rethink the strategies of approach (51). Most of these patients do not seem at a higher risk of COVID-19 infection but we still need convincing data (52). Risk-benefit analysis in each case will indicate the adequate approach considering the reality of the pandemic period (53). New models of telemedicine allow medical access based on a stratified risk strategy including criteria for deciding thyroid surgery (54). A study on the expression of 5 genes which may interact with the virus such as *ACE2*, *TMPRSS11D*, respective *TMPRSS2*, *CLEC4M* and *DPP4* showed significant alterations in thyroid cancer for the last mentioned three genes (55). However routine genetic testing in non-medullar thyroid cancer is hardly encouraged (56).

Overall, the viral and immune-mediated thyroid status due to coronavirus infection represents a small part of an otherwise complex, large and dynamic picture of the disease (57-59). Due to the fact that the virus challenges the native immunity of the host organism, thyroid interaction is expected (59).

6. Conclusions

Ongoing reality of the COVID-19 pandemic will reveal more information on virus-related thyroid conditions. Routine thyroid assays in patients with severe infection/acute phase of COVID-19 are encouraged in order to detect thyrotoxicosis. After recovery, thyroid function should be assessed to identify potential hypothyroidism. Still unanswered questions are related to the prognostic value of IL-6 assays or thyroid hormone replacement therapy necessary due to virus-related hypophysitis underlying central hypothyroidism.

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FS performed the critical review of the manuscript for its content. MC reviewed the findings and wrote the manuscript. AV checked and revised the manuscript and is the corresponding author. RCP revised the literature data. AAGG and AP researched the studies that were included as references. MCD critically revised the manuscript and approved the current form of the article in order to be submitted to the journal for publishing. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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