Pathophysiologica and clinical aspects of interaction between coronavirus disease 2019 and thyroid

Abstract. In patients who were not previously diagnosed with any thyroid conditions, the scenario of COVID-19 related anomalies of the thyroid may include either: a process of central thyroid-stimulating hormone 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 to the gland or low triiodothyronine syndrome (non-thyroidal illness syndrome) which is not specifically related to the COVID-19 infection, but which is associated with a very severe illness status. This review aimed to investigate thyroid changes resulted from 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/acute phase of COVID-19 are encouraged to detect thyrotoxicosis. After recovery, thyroid function should be assessed to identify potential hypothyroidism. There remain unanswered questions related to the predictive value of interleukin-6 in infected patients, especially in cases of cytokine storm, and the necessity of thyroid hormone replacement in subjects with hypophysitis-related central hypothyroidism.

Keywords: COVID-19; thyroiditis; Graves' disease; hypothyroidism; SARS-CoV-2

Introduction
Thyroid dysfunction has been observed in patients with COVID-19, and endocrinologists are requested to understand this clinical issue. Pandemic-related restrictions may affect thyroid disease management.

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 mainstay of viral transmission into the human body, every organ may be potentially affected and shut down [3]. Severe dysfunction is particularly found in previously damaged organs and in cases when the human-virus communication goes through a cytokine storm [4]. However, despite the massive amount of data gathered nowadays concerning this virus, we cannot rely on predictive models as multiple factors are involved in the disease evolution and prognosis as well as in the patient’s recovery [5]. Endocrine-related conditions that are likely to be correlated with a more severe prognosis are diabetes mellitus (DM), obesity, and arterial hypertension, including secondary endocrine causes [6].

Research aim and methods
This narrative review aims to update the changes in thyroid conditions after the COVID-19 infection; to analyze and discuss the relationship between COVID-19 and thyroid diseases from several perspectives. For this pur-
A comprehensive literature search was performed on PubMed/MEDLINE, Google Scholar, Scopus, Clinical-Trial.gov using free text words and medical subject headings as follows: “sars cov 2”, “covid 19”, “subacute thyroiditis”, “atypical thyroiditis”, “chronic thyroiditis”, “hashimoto’s thyroiditis”, “graves’ disease”. Data were collected, analyzed, and discussed to answer the following clinical questions: “What evidence suggests that COVID-19 may induce detrimental consequences on thyroid function?”; “Could previous or concomitant thyroid diseases deteriorate the prognosis of COVID-19 once the infection has occurred?”; “Could medical management of thyroid diseases influence the clinical course of COVID-19?”; “Does medical management of COVID-19 interfere with thyroid function?” The level of statistical evidence varies from original studies to reviews, opinions, case reports or position statements.

Results
Autopsy studies have shown that the virus can enter almost every endocrine gland including the thyroid [7]. The dysfunction may be transitory or definitive [8]. The mechanisms underlying COVID-19 related endocrine anomalies consist of inflammation, vessel damage, necrosis, degeneration, corresponding immune and autoimmune processes [9]. To date it is known that in patients who were not previously diagnosed with any thyroid conditions the scenario of COVID-related thyroid anomalies may include either: a process of central thyroid-stimulating hormone (TSH) disturbances via virus-related hypophysitis; or 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 to the gland [10]. A third category, namely euthyroid sick syndrome or low T₃ (triiodothyronine) syndrome or non-thyroidal 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 [11].

Early reports in 2020 showed an atypical subtype of thyroiditis in COVID-19 patients. Many patients with the COVID-19 infection, especially those with severe forms or admitted to intensive care units, presented with anomalies of thyroid hormones and TSH [12]. Thus, a novel etiology of subacute thyroiditis was identified [13]. This condition presents with thyroid hormonal flare-up and usually the thyrotoxicosis is self-limited and does not require specific anti-thyroid drugs [14]. A study of COVID-19 positive patients admitted to intensive care units in Milan, Italy, showed a 10% prevalence of thyrotoxicosis; statistically significantly higher than the 0.5% prevalence in COVID-19 negative patients who were admitted one year to the same units one year before [13]. 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 [15]. The clinical picture also includes thyrotoxicosis, and glucocorticoid therapy may improve the evolution to severe forms. Some authors suggest that COVID-19 related subacute thyroiditis might be actually underestimated in many cases [17]. Besides, there are reports of COVID-19 related subacute thyroiditis in patients who were not critically ill [18]. 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 [19].

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 [20]. The THYRCOV study provides early evidence that patients with acute coronavirus infection presenting with thyrotoxicosis have statistically significantly higher levels of interleukin-6 (IL-6) [21]. This was a single-center retrospective study of 287 adult subjects with an average age of 66 years who were admitted to non-intensive care units. Thyrotoxicosis was confirmed in 20.2% of cases while 5% of patients experienced hypothyroidism. IL-6 is a major player of the pro-inflammatory status in addition to IL-1 and tumor necrosis factor which may also act at the thyroid level [22]. Based on another retrospective study of 728 adult COVID-19 positive patients, IL-6 was found to be independently associated with the severity of the disease and also the mortality during hospitalization. It may become a new standard in disease assessment as a predictive factor including the follow-up period.

The coronavirus may also damage the pituitary gland, and mostly transient hypophysitis has been reported developing central hypocortisolism and central hyperthyroidism (less frequently) by decreasing the synthesis of adrenocorticotropic hormone and TSH [23]. The condition is difficult to diagnose, and there is current debate whether levothyroxine replacement has a major impact on the improvement of the clinical outcome.

Another issue relates to the primary hyperthyroidism developed during the pandemic period [24]. When a patient is COVID-19 positive, then there is a higher risk of developing arrhythmia and thromboembolic events while specific anti-thyroid drugs may be associated with agranulocytosis, thus worsening the overall prognosis [25].

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 [26]. Much information has been published to date on the risk of using pharmacological doses of glucocorticoids, especially during COVID-19 related cytokine storm [27].

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 [28]. Some data suggest a higher risk of autoimmune disorders (including autoimmune thyroiditis and Graves’ disease) after recovery from the cytokine storm [6]. 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 herpetiformis, hypophosphitis, autoimmune hepatitis, Sjögren’s syndrome, premature ovarian failure, primary adrenal insufficiency, type 1 DM, rheumatoid arthritis, atrophic gastritis, lupus, scleroderma, vasculitis, and celiac disease [29].

A severe situation is observed in the particular situation of COVID-19 positive diabetic patients of either type (including type 1 as seen in polyglucal in autoimmune syndrome also associating autoimmune thyroiditis or antibody-related chronic primary adrenal insufficiency) [30]. In COVID-19 patients, the prognosis is more severe and the glycemic profile may be worse due to the virus attack against the pancreas at the level of β-cells [31].

The term “covidiatology” has been suggested for covering the immense area of overlap of DM and COVID-19 [32]. 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 [33].

Higher doses of glucocorticoid replacement are needed. 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, apart from bone status anomalies [34].

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) [35].

Overall, the viral and immune-mediated thyroid status due to the coronavirus infection represents a small part of an otherwise complex, large and dynamic picture of the disease. Since the virus challenges the native immunity of the host organism, thyroid interaction is expected [36].

Conclusions

The 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 to detect thyroiditis. After recovery, thyroid function should be assessed to identify potential hypothyroidism. There are still unanswered questions related to the predictive value of IL-6 assays or thyroid hormone replacement therapy necessity due to virus-related hypophysitis underlying central hypo-thyroidism.

Patients with comorbid thyroid diseases are not at higher risk of contracting or transmitting SARS-CoV-2, and baseline thyroid dysfunction does not foster a worse progression of COVID-19. However, it is unclear whether low levels of free triiodothyronine, observed in seriously ill patients with COVID-19 may worsen the disease clinical progression and, consequently, if triiodothyronine supplementation could be a tool for reducing this burden. Glucocorticoids and heparin may affect thyroid hormone secretion and measurement, therefore leading to possible misdiagnosis of thyroid dysfunction in severe cases of COVID-19.

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Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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Received 28.05.2021
Revised 14.06.2021
Accepted 21.06.2021
Резюме. Коронавірусна інфекція SARS-CoV-2 швидко набула статусу пандемії та вразила мільйони людей по всьому світу. Незважаючи на те, що основною мішенню коронавірусу є дихальна система, науковці усе більше турбує проблема ураження COVID-19 інших органів та систем. Оскільки рецептори до ангіотензинперетворювального ферменту 2-го типу, через які коронавірус потрапляє в клітини, були виявлені на щитоподібній залозі, існує висока ймовірність ураження цього органа. Останнім часом надходить усе більше повідомлень про розвиток підгострого тиреоїдиту та хвороби Грейвса після перенесеного COVID-19. У пацієнтів, яким раніше не діагностували жодних захворювань щитоподібної залози, варіанти розвитку порушень стану щитоподібної залози, пов’язаних із COVID-19, можуть включати: атипівий перебіг підгострого тиреоїдиту, асоційований з поширенням вірусу або надмірною продукцією цитокінів, у тому числі деструктивний процес з необоротним пошкодженням залози або синдромом низького рівня трийодтироніну (синдром нетиреоїдної патології), конкретно не пов’язаний з інфекцією COVID-19, але зумовлений тяжким станом пацієнта. Метою цього огляду було дослідження змін функціонального стану щитоподібної залози внаслідок інфекції COVID-19. Поточна оцінка наслідків пандемії COVID-19 дозволить виявити більше інформації про захворювання щитоподібної залози, спричинені коронавірусом. Для виявлення тиреотоксикозу рекомендується проводити планові аналізи функціонального стану щитоподібної залози в пацієнтів у гострій фазі COVID-19. Після одужання слід оцінити тиреоїдну функцію для виявлення потенційного гіпотиреозу. Залишаються без відповіді питання, пов’язані з прогностичним значенням інтерлейкіну-6 в інфікованих пацієнтів, особливо у випадках із цитокіновим штормом, та необхідністю замісної терапії препаратами гормонів щитоподібної залози у суб’єктів із центральним гіпотиреозом, пов’язаним із гіпофізитом. Для виявлення тиреотоксикозу також рекомендується регулярне дослідження стану щитоподібної залози в пацієнтів із тяжким перебігом/гострою фазою COVID-19.

Ключові слова: COVID-19; тиреоїдит; хвороба Грейвса; гіпотиреоз; SARS-CoV-2