Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Narrative Review

Severe acute respiratory syndrome and thyroid: A molecular point of view

Fatemeh Sadoughi [a], Parisa Maleki Dana [a], Jamal Hallajzadeh [b, *], Zatollah Asemi [a, **], Mohammad Ali Mansournia [c], Bahman Yousefi [d, e]

[a] Research Center for Biochemistry and Nutrition in Metabolic Diseases, Institute for Basic Sciences, Kashan University of Medical Sciences, Kashan, I.R. Iran
[b] Department of Biochemistry and Nutrition, Research Center for Evidence-Based Health Management, Maragheh University of Medical Sciences, Maragheh, Iran
[c] Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
[d] Molecular Medicine Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[e] Department of Biochemistry, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

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SUMMARY

SARS-CoV-2 and some other members of Coronaviridae family have recently forced a great deal of health, social, and economic issues globally. To that end, investigations have been oriented towards finding ways for reducing the burden of COVID-19. One of the occurrences which stands in the way of making the treatment of this disease less complicated is the way coronaviruses involve a variety of cells, tissues, organs, and even systems. This action is possible as a result of viral attachment to the angiotensin-converting enzyme 2 or ACE2. Thus, any kind of cell expressing ACE2 is prone to be affected by both SARS-COV and SARS-COV-2. Endocrine system is one of these at-risk systems. In this review, we have considered the relation between coronaviruses and one of the most essential organs of endocrine system: thyroid gland. This relation can be probed from two aspects: how underlying thyroid dysfunction can increase the risk of being infected by these viruses and how these viruses can alter the function of thyroid gland.

1. Introduction

COVID-19 is a severe disease clinically manifested by respiratory symptoms which is able to cause the death of 15.2% of total infected individuals after 2–8 weeks of the disease initiation [1]. Recently, expanding the research domains on the effects of SARS-CoV-2 or 2019-nCoV on other tissues, organs, and systems then respiratory system has led to some significant results [2–4]. The importance of these subsidiary-affected tissues, organs, and systems is in complicating the treatment process, decreasing the survival rate, and increasing the global economic burden. Endocrine system is one of the pivotal players of regulating the homeostasis by providing chemical signals between a diversity of cells [5]. Thyroid gland as an essential component of this system is able to regulate the rate of metabolism by secreting a class of hormones including thyroxine [5].

Currently, thyroid dysfunction has attracted a great deal of interest because of two reasons: first, its role in increasing the risk of being infected by SARS-CoV-2 as an underlying disease and second, occurring in individuals as a complication secondary to SARS-CoV-2 infection. In this paper, on one hand, we reviewed a number of evidences manifesting the characteristics of COVID-19 patients in order to find the association between thyroid dysfunction, as a metabolic disease, and the risk of SARS-CoV-2 infection. On the other hand, we have looked into thyroid-related diseases as a side effect of COVID-19. This review might give a new insight on prognostic testing and managing COVID-19 patients for a more qualified after-survival life and a lower chance of mortality.

2. Coronavirus, ACE2, and endocrine system

According to our recent knowledge of coronaviruses, ACE2 takes a critical part in COVID-19 pathogenesis [6]. ACE2 or angiotensin-

* Corresponding author. Fax: +98-31-55463377.
** Corresponding author.
E-mail addresses: rahasadoughi@gmail.com (F. Sadoughi), prs.maleki@yahoo.com (P. Maleki Dana), jamal.hallaj@yahoo.com (J. Hallajzadeh), asemi_r@yahoo.com (Z. Asemi), mansournia_ma@yahoo.com (M.A. Mansournia), bahmanusefi@gmail.com (B. Yousefi).

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converting enzyme 2 is capable of binding to the spike protein of this member of Coronaviridae family [7]. In addition to the disease severity, this connection has also another disadvantage for the human body during SARS-CoV-2 infection: decreased amounts of ACE2 on the cellular surface [7,8]. The importance of this action can be understood after discussing the functions of ACE2 in a normal state. ACE2 is a homolog of ACE which has the ability to collate its actions by forming angiotensin (Ang) 1–7 from Ang II [9]. This suggests that ACE2 is actually functioning as a regulator of the renin-angiotensin system or RAS [10]. Being involved in RAS is enabling this enzyme to have both local and systemic impacts, in addition to altering the performance of a diversity of our systems [11,12]. We can classify the roles of ACE2 by the organs which are expressing this protein on their cells (organs including brain, heart, lung, testis, and kidneys [12]):

1. Heart and vasculture: decreasing blood pressure, making some changes in cardiac structure, preventing heart failure, and enhancing cardiac remodeling [13–19].
2. Kidneys: vasodilation, preventing proliferation and inflammation, glomerular injury, decreasing fibrosis [15,20].
3. Lungs: increasing pulmonary blood pressure by Activation of the intrapulmonary RAS, developing fibrosis [11,21,22].

With respect to this expression pattern, any dysregulation in ACE2 expression leads to several metabolic and cardiovascular diseases containing hypertension [23], arrhythmia [18], myocardial infarction [17,24], diabetes [25], glomerulosclerosis [26], albuminuria [15] and etc.

Interestingly, recent investigations have revealed a relation between ACE2 and another ingredient of the endocrine system: thyroid gland [27]. As reported by Li et al. ACE2 is expressed highly in some organs including thyroid gland. Furthermore, they revealed that there is a positive correlation between ACE2 expression and CD8+ T cell enrichment and interferon response in men [28]. Recently, Rotondi et al. has also detected that the mRNA of the ACE2 gene can be found in follicular cells of thyroid sample tissues [29]. Furthermore, a recent pilot study revealed that not only thyroid cells express ACE2 gene but this expression can also be modulated by IFN-γ and TNF-α [30]. On the other hand, thyroid hormones are also capable of activating RAS by influencing the levels of other proteins such as renin and angiotensinogen [31]. Overall, infection with SARS-CoV-2 might be related to metabolic diseases because of ACE2 endocytosis after the viral attachment.

3. COVID-19 patients with underlying thyroid disease

Investigations manifesting the characteristics of COVID-19 patients identified some underlying conditions frequently repeated in these patients. Metabolic diseases seem to be a constant ingredient of these conditions [4,32,33]. However, still the booster impact of thyroid dysfunctions, as important metabolic diseases, on the risk of being infected by SARS-CoV-2 or its mortality rate needs deeper explorations. According to a report by Garg et al. [32] which examined 1482 hospitalized patients, 60 patients had an underlying metabolic disease. Among this number, 15 individuals were suffering from thyroid dysfunction while two of them had also diabetes mellitus beside their disease. In another study [34], after looking into the underlying diseases of 122,653 COVID-19 patients, it was found that only 37 individuals had an existing chronic thyroid disease. In contrast, investigations demonstrate that autoimmune thyroid disease do not put its patients into a higher risk of being infected by 2019-nCoV [35]. Recently, A review of reviews has also confirmed that having an underlying thyroid disease does not increase the risk for SARS-CoV-2 infection [36].

4. SARS-CoV-2 and thyroid gland: a precise look

There are several hypotheses suggested by researchers on how exactly coronaviruses affect thyroid gland and the level of its hormones. Studying the systemic effects of coronavirus is still in its infancy and the limited number of investigations is restricting the borders of our knowledge. In this section, we try to explain the SARS-CoV-2 cellular and molecular effects according to the explorations in this field conducted since December 2019:

Wei et al. [37] examining 5 autopsies of SARS patients concluded that this disease is able to impact follicular epithelial cells and the parafollicular cells and thereby, alter the thyroid function to some degree. They also tested the levels of both thyroid hormones, T3 and T4, and identified a considerable reduction. Furthermore, they confirmed the dual influence of coronavirus on both thyroid and hypothalamus–pituitary axis [37]. As well, Leow et al. [38] found hypothyroidism in SARS patients and suggested that this might be a result of virus-induced thyroiditis or a disturbance in the hypothalamus-piturity-thyroid axis. Furthermore, they implicated that this effect of SARS-CoV-2 is not related to autoantibodies against thyroid [38] and thus, thyroiditis or hypophysitis can define the effects of coronavirus on thyroid hormones better than autoimmune diseases [38]. There is also a paradoxical exploration which provided autopsies of SARS patients and did not detect any viruses in site of thyroid [39]. However, the chosen population in this study was composed of only 4 SARS patients [39]. Similarly, another clinical study on three COVID-19 patients detected no abnormal sign in autopsies obtained from thyroid [40].

The most recent study is conducted by Khoo et al. [41], which is a cohort study containing 621 patients, which concludes that the levels of TSH and FT4 are lower in patients diagnosed with COVID-19 while this reduction is not seen in patients admitted to the hospital without COVID-19. However, they declared that based on their definition of thyrotoxicosis (TSH <0.30 and FT4 > 23.0), "there was no suggestion of a novel COVID-19–related thyroiditis/thyrotoxicosis" [41]. Furthermore, they also suggest that reduced TSH levels might be the consequence of two different effects of SARS-CoV-2: increasing the proinflammatory cytokines such as interleukin-6 and cortisol [41]. They were able to suggest the second mechanism by excluding the patients who were receiving exogenous steroids [41]. In contrast, a retrospective study represented "a high prevalence of overt and subclinical thyrotoxicosis in patients with COVID-19" which is probably correlated with the cytokine storm and IL-6 secretion in COVID-19 patients [42]. Notwithstanding the limitations of this study, they suggested that destructive thyroiditis might be the reason why TSH and FT4 reduced due to SARS-CoV-2 infection [42]. This study disagreed with another previous study relating the low levels of TSH and TT3 to the non-thyroidal illness (NTI) [43]. On the other hand, there is an association between the time of viral nucleic acid cleaning and thyroid dysfunction which might strengthen the idea of direct viral infection [43].

The non-thyroidal illness (NTI) hypothesis indicates that during a systemic illness, a total reduction can be observed in T3, T4, and TSH which is preserving energy in the body [44]. NTI is mediated through a variety of factors including circulating cytokines including IL-6 and TNF-α. Considering the SARS-related cytokine storm, Croce and colleagues suggested that NTI is an explanation for thyroid dysfunction in COVID-19 patients [44]. Additionally, Chen and colleagues examined 50 patients and detected that there is a direct relation between the degree of TSH and TT3 reduced levels and the severity of the disease [45]. Recently, a review of reviews also declared that the most frequent thyroid dysfunction found in COVID-19 patients is non-thyroidal illness syndrome [36].

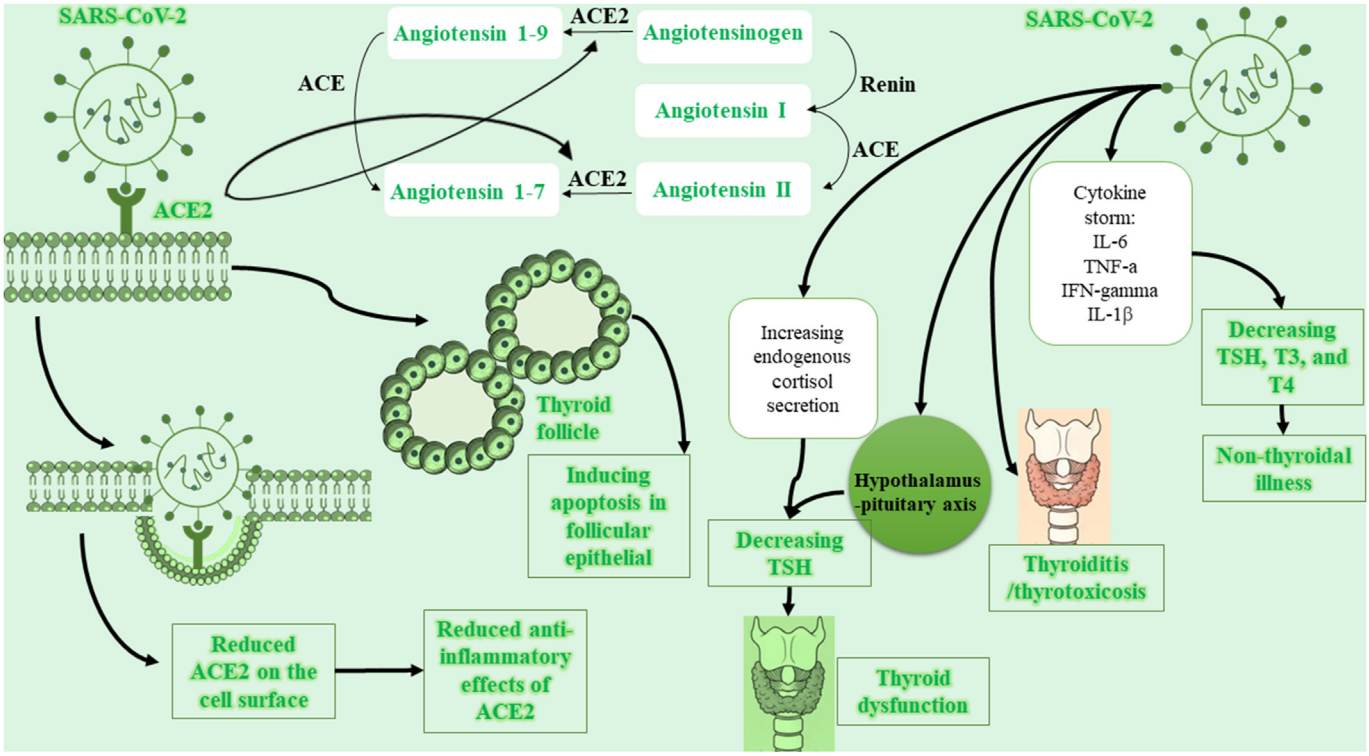

Fig. 1. Cellular and molecular mechanisms by which SARS-CoV-2 affects thyroid function. ACE, Angiotensin converting enzyme; TSH, Thyroid-stimulating hormone.

5. Conclusions

What we have observed while considering SARS-associated studies is that there is no reliable evidence on the neither higher risk of infection due to an underlying thyroid disease nor post-SARS thyroid dysfunction. Trials conducted in this area are commonly done on a limited number of patients and therefore, more investigations are required for confirming their results. Moreover, a majority of studies are using autopsies and more evidence should be established on patients with early stages of the disease. Between the papers we found, SARS-CoV-related evidence have higher number than 2019-nCoV-related evidence. However, due to the receptor which both of these viruses are sharing [46], SARS-related results might be extensible to SARS-CoV-2. We hypothesize that if coronaviruses actually cause thyroid dysfunction, four mechanisms can explain it (represented in Fig. 1): first coronavirus might affect the cells of thyroid gland directly and cause thyroiditis and/or apoptosis, second, coronavirus might affect hypothalamus-pituitary-thyroid axis through inducing hypophysitis, third, the cytokine storm initiated during COVID-19 can cause NTI, and fourth, reducing the number of ACE2 on the surface of thyroid cells might be disadvantageous (Fig. 1). Still, these hypotheses need more investigations to be confirmed. Furthermore, the effects of immunotherapy and anti-coagulant drugs used for COVID-19 patients, increased cortisol secretion, and sick euthyroid syndrome [2] should be taken into consideration, as well.

Finally, thyroid dysfunctions caused by SARS-CoVs are dynamically changing in conjunction with the course of disease and seem to recover spontaneously and therefore, therapeutic measurements in early stages might not be needed. In advanced patients, on the other hand, thyroid dysfunction is transient and after COVID-19 treatment, TSH levels get back to normal and thus it seems that treatment might be necessary only in patients with specific indicators of a serious thyroid disease.

Availability of data and material

Not applicable.

Author contributions

PMD and ZA contributed in conception, design and drafting of the manuscript.

FS, JH, MAM, BY and MMH contributed in reviewing relevant literature.

All authors approved the final version for submission.

Consent for publication

Not applicable.

Declaration of competing interest

The authors declare no conflict of interest.

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