Thyroid complications of SARS and coronavirus disease 2019 (COVID-19)

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Abstract. We have reviewed the available literature on thyroid diseases and coronavirus disease 2019 (COVID-19), and data from the previous coronavirus pandemic, the severe acute respiratory syndrome (SARS) epidemic. We learned that both SARS and COVID-19 patients had thyroid abnormalities. In the limited number of SARS cases, where it was examined, decreased serum T3, T4 and TSH levels were detected. In a study of survivors of SARS approximately 7% of the patients had hypothyroidism. In the previous evaluation evidence was found that pituitary function was also affected in SARS. Others suggested a hypothalamic-pituitary-adrenal axis dysfunction. One result published recently indicates that a primary injury to the thyroid gland itself may play a key role in the pathogenesis of thyroid disorders in COVID-19 patients, too. Subacute thyroiditis, autoimmune thyroiditis and an atypical form of thyroiditis are complications of COVID-19. Thyroid hormone dysfunction affects the outcome by increasing mortality in critical illnesses like acute respiratory distress syndrome, which is a leading complication in COVID-19. Angiotensin-converting enzyme 2 is a membrane-bound enzyme, which is also expressed in the thyroid gland and the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) uses it for docking, entering as well as replication. Based on the available results obtained in the SARS-CoV-2 pandemic, beside others, we suggest that it is necessary to monitor thyroid hormones in COVID-19.

Key words: Coronavirus disease 2019 (COVID-19), Severe acute respiratory syndrome (SARS), Thyroid, Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), Acute respiratory distress syndrome (ARDS)

Introduction

Most of human pathogenic coronaviruses are benign, the three notable exceptions are the three epidemics caused by the coronavirus family: the SARS (severe acute respiratory syndrome) in 2002–2003, the MERS (Middle East respiratory syndrome) in 2012 and COVID-19. The rate of case fatality for COVID-19 is approximately 3.4%, while for SARS and MERS it was 9.6% and 34%, respectively [1]. SARS is an acute respiratory disease with significant morbidity and mortality, consisting of two phases: initially an influenza-like period, followed very commonly by the outbreak of respiratory and gastrointestinal symptoms [2]. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the original virus of COVID-19, described as the seventh type of coronavirus infecting humans (86.9% of the genome of SARS-CoV-2 is equal to SARS-CoV) [1]. Six other types of coronaviruses are known as those generating human diseases, including SARS-CoV (the pathogen virus for SARS epidemic) as well as MERS-CoV (the pathogen virus for MERS epidemic).

As SARS is a disorder known to lead to multiple organ injury (lung is the major target organ), it has been presumed that SARS could have a detrimental effect on the thyroid gland, as well [3]. However, there are only a few publications reporting data on clinical observations based on blood samples from SARS patients’ specimens examined for thyroid function. Also, there are only a few direct researches published on the hypothalamic-pituitary-thyroid (HPT) axis of SARS patients [3, 4]. It has been assumed that the adenohypophyseal endocrine cells in SARS patients may be destructed [4]. Some surveys in connection with the former outbreak of SARS suggest that coronavirus can affect thyroid activity in people not previously diagnosed with thyroid disorders [5]. A study found that SARS patients had low triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH) levels [5]. Some other viruses may also lead to thyroid disorders, like subacute thyroiditis and...
autoimmune thyroid diseases. Clear evidence for the presence of viruses (or for their components) in the thyroid gland is available for retroviruses and mumps in subacute thyroiditis, for retroviruses in Graves’s disease and for human T lymphotropic virus-1, enterovirus, rubella, mumps, herpes simplex virus, Epstein Barr virus and parvovirus in Hashimoto’s thyroiditis [3]. Data on thyroid involvement by SARS-CoV-2 infection are scarce. Consequently, there are currently no data on how COVID-19 affects people with a treated or not treated hypophysitis or by hypothalamic damage [3]. COVID-19 in this respect, some knowledge in relation to COVID-19 affects people with a treated or not treated hypophysis, principally on those of the thyroid system.

To check the thyroid function in patients with SARS, the serum levels of thyroid hormone were measured in 48 patients concerned [5]. The levels of serum T3, T4, free triiodothyronine (fT3) and TSH in SARS patients were significantly lower than in controls: serum T3 and T4 levels were decreased in 94% and 46% of SARS patients during the acute phase and in 90% and 38% during the convalescent phase of SARS. It was concluded that alteration of serum levels of thyroid hormone and TSH in SARS patients depends on the outcome of the disease [5].

Changes in the level of thyroid hormones persisted also after clinical recovery of SARS. In a publication of Leow MK et al. 61 survivors of SARS were analysed for hormonal disorders 3 months after recovery [7]. Patients with pre-existing endocrine diseases were excluded from the study. 39.3% of patients had hypocortisolism and 3.3% of them also had transient subclinical thyrotoxicosis. 6.7% of the investigated subjects were biochemically hypothyroid, three-quarters of them with central hypothyroidism and one-quarter with primary hypothyroidism (most of those with central hypothyroidism had concomitant central hypocortisolism). In some cases, hypothyroidism was reversible, and thyroid hormones got normalized within 3 to 9 months. The authors hypothesize that SARS causes a reversible thyroiditis, hypophysitis or has direct hypothalamic effect, although no radionuclide scans or thyroid biopsies were performed [7]. Hypocortisolism plus hypothyroidism together can clarify the common occurrence of the wide range of nonspecific symptoms described in recovered SARS patients. These symptoms were considered as post-SARS sickness syndrome [8].

To date, the effects of SARS directly on the thyroid gland are little known because only few detailed histopathological investigations of the thyroid gland in SARS patients have been reported. A study of Wei L et al. demonstrated that the thyroid gland in patients with SARS was significantly altered [6]. Five thyroid samples were collected from autopsies of SARS patients. Ten normal thyroid samples served as the control. In contrast to normal thyroid tissue, the thyroid glands from SARS patients clearly showed devastation of the follicular epithelium and exfoliation of epithelial cells into the follicle. Also, it has been confirmed that apoptosis plays a role in the pathogenesis of SARS, because special assays have shown many cells in the thyroid gland undergoing apoptosis [6]. In vitro studies have shown that overexpression of some nonstructural SARS-CoV proteins can promote apoptosis in several cell types [9-12]. In a study of Wei L et al. SARS-CoV viral genomic sequences were missing from thyroid cells [6]. Also, SARS-CoV was detected by Ding Y et al. in many endocrine organs, including pituitary, but not in thyroid [13]. There is no explanation about how the SARS-CoV injured the thyroid gland. Several mechanisms are known in patients with SARS to describe organ damages, including host immune overreaction, destruction of lymphocytes, inhibition of the innate immune response, direct cellular destruction, and apoptosis [3, 6, 14-17].

In another study of Wei L and colleagues, they investigated the endocrine cells in the adenohypophysis as well as the immunoreactivity of the various hormonal products from pituitary endocrine cells collected from autopsies of 5 patients with SARS [4]. The patients died 21–45 days after the beginning of symptoms as the consequence of SARS-CoV infection. Five autopsied normal pituitary samples were used as control without a condition that could affect the pituitary gland. Both the number and the
immunoreactive intensity of TSH positive cells in the SARS group were significantly decreased compared with the controls. This result illustrates that the decrease in serum TSH in SARS patients might correlate with changes in TSH cells in the pituitary gland. In SARS infection, the reduced serum T3 and T4 levels would not be able to stimulate the TSH cells to produce more TSH in the negative feedback loop [4], however, the reason for the described changes in TSH cells in the pituitary is not clear. The authors have concluded, that there are two possible mechanisms that might explain these results. The first one is the direct effect of the SARS-CoV on the pituitary cells. The other one is an indirect consequence of several systemic alterations caused by the SARS infection which lead to hormonal alterations in the pituitary-endocrine axis feedback loops [4].

**SARS-CoV-2 and Thyroid**

Blood is very rarely tested allowing us to draw consistent conclusions as to the derangement of thyroid gland in COVID-19. In a retrospective analysis, clinical examinations of moderately to severely or critically ill patients with COVID-19 were performed [18]. 113 of these patients died and 161 patients recovered. The TSH and fT3 serum concentrations were significantly lower in deceased (0.7 mIU/mL and 2.8 pmol/L) than in healed patients (1.4 mIU/mL and 4.3 pmol/L). The difference between the free thyroxin (fT4) levels was not significant (15.8 pmol/L in dead and 18.3 pmol/L in recovered patients) [18]. Thyroid function was not evaluated as a predicting factor for SARS-CoV-2 infection and progression to respiratory failure.

Recently four cases of subacute thyroiditis (de Quervain’s thyroiditis) have been reported in COVID-19 patients [19-22]. Thyroid function assessments showed thyrotoxicosis, with suppressed serum TSH, elevated fT4, fT3 and thyroglobulin levels as well as the absence of thyroid autoantibodies. In patients with subacute thyroiditis thyroid dysfunction is usually triphasic: thyrotoxicosis develops in the majority of patients, followed by hypothyroidism (uncommon) and mostly 3 months later the disease is completely solved (euthyroidism). The pathogenesis of subacute thyroiditis has not been absolutely cleared up, but it is accepted that this disease is due to viral infection or to a postviral inflammatory reaction in genetically predisposed persons [19]. There are no data that patients with autoimmune thyroid disease are most sensitive to viral infection (including SARS-CoV-2), nor that they run the risk of developing more severe COVID-19. However, two case reports by Matau-Salat M et al. suggest that SARS-CoV-2 could also act as a trigger of autoimmune thyroid disease [23]. The authors describe two cases of autoimmune hyperthyroidism (Graves’ disease) occurring 1 respectively 2 months after the clinical onset of COVID-19, one with a previous history of Graves’ disease, and another without previously known thyroid dysfunction. Thyroid function assessments showed thyrotoxicosis, with suppressed serum TSH and elevated fT4 or fT3 levels and the thyroid autoantibodies were positive.

In a recently published study by Muller I et al., the prevalence of thyrotoxicosis being suggestive of subacute thyroiditis was investigated [24]. Patients treated in high intensity of care units (HICU) in 2020 due to COVID-19 (HICU-20, n = 93) were compared with SARS-CoV-2 negative patients admitted to the same HICU in 2019 (HICU-19, n = 101). Data of patients with known thyroid disease were not included. 15% of HICU-20 and only 1% of HICU-19 patients had thyrotoxicosis. In HICU-20 patients the serum TSH levels were lower than in HICU-19 patients (1.04 mIU/L vs. 1.43 mIU/L, p = 0.018), while serum fT4 levels showed no difference between the groups. There was no significant difference between the fT3 levels, the main non-thyroidal illness syndrome (NTIS) indicator, which were low in both groups. The authors conclude that a significant number of patients admitted to the HICU with COVID-19 have thyrotoxicosis and low TSH concentrations. These alterations demonstrate that SARS-CoV-2 can induce subacute thyroiditis and NTIS. To test this hypothesis, thyroid imaging was done nearly two months following discharge of some patients with former thyroid dysfunction. All were tested negative for SARS-CoV-2 at discharge. 75% of them had a diffuse mild hypoechogenic pattern at thyroid ultrasound, suggesting the presence of a former thyroiditis. Compared with data published by other authors, these patients with a severe COVID-19, did not have the typical characteristics of patients with classic cases of subacute thyroiditis. The thyroid dysfunction seemed to be milder, the HICU-20 patients did not have an undetectable TSH or extremely high T4 levels, nor typical neck pain, suggesting an atypical form of thyroiditis also characteristic for the SARS-CoV-2 infection. The prevalence for both autoimmune and non-autoimmune thyroid disease was lower in HICU-20 patients (9%) than in the HICU-19 group (23%), suggesting that thyroid disorders do not increase the risk of SARS-CoV-2 infection or the severity of COVID-19.

In a retrospective study by Chen M et al., 56% (28/50) of hospitalized SARS-CoV-2 infected patients with not known previous thyroid diseases, showed significantly lower-than-normal values for TSH (0.3 mIU/L) during the course of their COVID-19 infection compared with healthy controls (TSH = 1.57 mIU/L) and non-COVID-19 pneumonia patients with a similar degree of
severity (TSH = 1.18 mIU/L) [25]. All the cases were nonmild and divided into three clinical classifications: moderate, severe, and critical. They also found a low TSH and total T3 levels in 18% of the patients, and the degree of the decreases positively and significantly correlated with the severity of their COVID-19 infection. Beside the aforementioned mechanism, the observed decrease in TSH level in patients with COVID-19 could also be induced by the glucocorticoids with which most patients (31/50) were treated, however the dosage was low (57.3 mg methylprednisolone daily). Serum TSH levels of the patients with COVID-19 were significantly lower in the severe and critical group compared with non-COVID-19 pneumonia patients with a similar degree of severity. This finding also indicates a unique effect of COVID-19 on TSH-secreting cells. After recovery the levels of all the thyroid hormones returned to the normal value and no significant differences in thyroid function were found between the COVID-19 and control groups.

Thyroid, Acute Respiratory Distress Syndrome and Nonthyroidal Illness Syndrome

Thyroid hormone dysfunction could affect the outcome, and increase mortality in patients with a critical illness [26-29]. Like the most severe manifestations of SARS, COVID-19 can be complicated by sepsis, multi-organ failure and acute respiratory distress syndrome (ARDS) [30]. ARDS is represented by hypoxic respiratory failure with bilateral lung infiltrates frequently requiring mechanical ventilation. Almost 5% of patients with COVID-19 develop a severe form of the disorder that requires intensive care unit (ICU) admittance, and approximately two-thirds of them develop ARDS [30-32]. The Acute Physiologic and Chronic Health Evaluation II (APACHE II) score was designed as a mortality prediction tool for adult patients admitted to ICU. Also, Sequential Organ Failure Assessment (SOFA) score can be measured at all patients admitted to the ICU in order to determine the mortality risk. Both methods are applied in case of COVID-19 patients [33, 34].

In some studies, it was observed that serum fT3 was a strong predictor of ICU mortality [35]. Others described that the combination of serum fT3 levels and APACHE-II score provided the best possibility for predicting mortality in ICU admitted patients [28, 36]. In a prospective, observational study the prognostic efficacy of fT3, fT4 and TSH was analysed in addition to the APACHE II and SOFA scoring systems in order to predict ICU mortality in 206 critically ill ARDS patients [37]. For each patient the APACHE II and SOFA scores were calculated by using data from the first 24 hours of admission. Within the first 24 hours, fT3, fT4, and TSH serum concentrations were also measured. The survivors had significantly lower APACHE II (11 vs. 16) and SOFA scores (6 vs. 9), and significantly higher serum fT3 level (2.18 vs. 1.72 pg/mL) than non-survivors. According to the findings, the authors suggested that fT3 levels might have additive discriminating power to (among others) SOFA and APACHE II scores in predicting the short-term mortality in ARDS patients admitted to ICU [37]. Some of the studies described that decreased thyroid function at baseline is associated with a worse outcome of patients critically ill with sepsis or septic shock [29].

In critically ill patients, the most common endocrine disorder is NTIS (also called sick euthyroid syndrome or low T3 syndrome) [38]. The SARS-CoV-2 infection can lead to critically ill COVID-19 cases. NTIS is characterised by clearly decreased serum T3 and fT3 concentrations and increased serum reverse T3 (rT3) as well as low T4 levels. Despite of decreased T3 and low T4 levels, TSH is typically maintained within its normal range (in mild-to-moderate NTIS) or is slightly decreased (in severe NTIS). A remarkable decrease in serum T3 and T4 in NTIS patients is associated with a high possibility of death [39], and the decrease of the degree of T3 during the first 24 h after the onset of acute illness indicates the severity of disease and correlates with mortality [40]. Alterations of the HPT axis are the central components of NTIS and lead to disturbed negative feedback regulation [41]. In addition, peripheral changes in thyroid hormone metabolism also occur during NTIS [41]. These peripheral alterations, which may depend on the timing, tissue, nature and severity of the illness, include changed levels and binding affinity of the thyroid hormone binding proteins, altered thyroid hormone transporters, modifications in the expression and activity of the thyroid hormone deiodinases, and also changes in the thyroid hormone receptor expression in the peripheral tissues [40]. These pathogenic alterations are different from those described in patients with thyroid dysfunction due to SARS-CoV infection [4, 6, 7], consequently separate mechanisms are involved. In a retrospective study, 56% of 50 hospitalized moderate-to-critical COVID-19 patients showed lower-than-normal TSH values during their infection [25]. These results cannot be fully explained by NTIS.

In the case of patients with NTIS requiring mechanical ventilation the outcome in the ICU has not been fully studied. The prospective study by Rothberger GD et al. involved 162 NTIS patients who underwent mechanical ventilation and aimed to determine the impact of NTIS on the ICU outcome [26]. Serum fT3 levels were measured on the day of initiation of mechanical ventilation.
The rate of mortality and ventilator-free days (VFDs) on day 28 after the starting of mechanical ventilation was assessed. Compared to patients with normal fT3 (≥2.3 pg/mL), patients with low fT3 (<2.3 pg/mL) had significantly higher mortality (52% vs. 19%) and significantly less mean and median VFDs on day 28 (10.7 vs. 18, and 0 vs. 23). It was concluded that the presence of low fT3 measured due to NTIS is associated with poor outcome in ICU patients requiring mechanical ventilation [26].

The differentiation among NTIS, COVID-19 and other, primary thyroid disorders in patients in the ICU can sometimes be very difficult. If a similar decline in serum T3 and T4 happens in the situation of primary hypothyroidism, serum TSH would be considerably increased. In patients with a combination of primary hypothyroidism and NTIS, the serum TSH concentration is still high and reacts to levothyroxine treatment. High serum TSH level in combination with low serum T4 is indicative of hypothyroidism and can also be detected in patients recovering from NTIS [39].

Data support that host immune overreaction (cytokine storm syndrome or cytokine release syndrome) may play an important role in the pathogenesis of SARS [2, 42]. SARS-CoV infection may lead to hyperinduction of the immune system, causing an increased level of cytokines, e.g. interleukin-6 (IL-6), and chemokines have been described in SARS patients, however, contradicting results also exist [2, 43]. Data have shown that IL-6 levels are also significantly higher in COVID-19-patients with a severe status compared with those with a non-severe condition, so IL-6 is a prognostic marker in serious COVID-19 cases [44-46]. Like other cytokines, IL-6 also provokes thyroid inflammation and autoimmunity [47]. Moreover, serum IL-6 is also often elevated in NTIS (the exact mechanism is not defined yet), and its level is inversely related to T3 levels in NTIS patients [39]. In the study by Swaroopa D et al., in case of 30 patients admitted to ICU and diagnosed with ARDS, serum samples were collected and measured on day 1 and 7 for serum IL-6, and IL-8 [48]. Also, APACHE II scoring was done on day 1. ARDS was associated with increased serum IL-6 and IL-8 on day 1 compared with that in healthy controls. Compared with survivors, the cytokine levels were significantly higher in nonsurvivors measured on day 1. By using both APACHE II score, IL-6 and also IL-8, the predictable accuracy of mortality was 94% [48]. These findings are in accordance with other studies which describe a similar elevation of these cytokines in deceasing patients as compared with survivors [49].

**Angiotensin-converting Enzyme 2 (ACE2) and Thyroid**

It was confirmed that ACE2 is the functional receptor for SARS-CoV and SARS-CoV-2. ACE2 is a membrane-bound enzyme and these coronaviruses use it for docking, entering as well as for replication [50, 51]. It was also shown that ACE2 overexpression facilitated viral entry and replication in cells that were otherwise resistant to the virus [52, 53]. ACE2 is expressed dominantly in human alveolar cells, so ARDS can be explained by this lung tropism. ACE2 in the gastrointestinal tract explains the early gastrointestinal symptoms, so as ACE2 in the heart in relation with cardiac injury and myocarditis. All these symptoms have been reported in COVID-19 patients [54]. Besides, other extrapulmonary manifestations of COVID-19 are associated with the systemic distribution of ACE2 in several organs. Patients who smoke, are older, and are male also have a higher density of ACE2 receptors. Actually, increased ACE2 levels can be detected in cardiovascular diseases (CVD) and in associated comorbidities such as diabetes and hypertension [55]. Not only CVD itself but also the pharmacological renin-angiotensin system (RAS) blockade, the angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARBs) used in CVD increase the ACE2 levels, and may promote SARS-CoV-2 entry and virus replication in several organs (both ACEi and ARBs could significantly increase mRNA expression of cardiac ACE2) [52, 53].

ACE2 as counter-regulatory enzyme degrading angiotensin II to angiotensin 1-7 (which induce vasodilation, anti-fibrotic, anti-proliferative and anti-inflammatory effects) has been shown to be beneficial in ARDS. In that case ACE2 has both cardio-protective and pulmonary-protective activity. On the contrary, SARS-CoV-2 infection may downregulate ACE2 (if ARDS develops, a downregulation of ACE2 occurs), so it seems that RAS blockade decreases the risk of ARDS, myocarditis, consequently mortality in COVID-19 [52, 53].

There are contradictory results concerning ACE2 expression on thyroid tissue or some endocrine organs. ACE2 has not been shown to date to be expressed on thyroid gland [2, 6, 13], however, a recently published paper by Li MY et al. reported that a number of endocrine organs (like thyroid) express ACE2 [56]. Diniz GP et al. found that in hyperthyroid rats the cardiac ACE2 mRNA levels were significantly increased as compared with those in the control (439.1 ± 99.23% vs. 112 ± 35%) [57]. Hyperthyroidism was caused by daily intraperitoneal injection of levothyroxine for 14 days: serum fT3 and fT4 levels were significantly increased in the hyperthyroid group. Despite of the fact that cardiac ACE2 pro-
tein levels were unchanged in the hyperthyroid group, the cardiac ACE2 activity was significantly increased in hyperthyroidism (123.9 ± 13.5 vs. 100.1 ± 5.8 arbitrary units in the control group). As mentioned above, ACE2 plays a beneficial role in the cardiovascular system. Independently of unaltered ACE2 protein levels, hyperthyroidism promoted an increase in cardiac ACE2 activity. The authors found that thyroid hormones-induced cardiac hypertrophy was accompanied by higher cardiac ACE2 gene expression and unchanged ACE2 protein expression [57]. This study allows us some suggestion on ACE2 and thyroid.

In our opinion, we are dealing also in this case with a double edged sword, depending on the phase of the disease: increased baseline ACE2 expression could potentially increase infectivity and higher or high-normal tT4 level would be an addressable risk factor. Conversely, once infected, downregulation of ACE2 may be the hallmark of COVID-19 progression. Consequently, upregulation by using preferentially the levothyroxine treatment results in a higher plasma level of tT4 in the SARS but it may turn out to be beneficial, similarly to the case of ACEi/ARBs treatment. In order to clarify our speculations prospective clinical studies are necessary to analyse the thyroid function as a predictive factor for SARS-CoV-2 development and progression to respiratory failure.

Conclusion

We know that viruses may lead to thyroid disorders. Coronaviruses can also affect thyroid activity. We learned that both SARS and COVID-19 survivors had thyroid abnormalities. Based on the available results in the SARS-CoV-2 pandemic [18-25, 58-60], more attention has to be paid both to patients with not diagnosed thyroid disorder and to treated thyroid patients with COVID-19. Routine control of thyroid function is not recommended by the guidelines however, we suggest the importance of monitoring thyroid hormones in COVID-19. Beside others, we suggest routine screening of thyroid function at least in COVID-19 patients requiring hospitalization. Because subacute thyroiditis might be a late complication in COVID-19 patients, thyroid function should also be monitored during the follow-up period of COVID-19. Having reviewed the few available data, we cannot yet describe an increased prevalence of pre-existing thyroid disorder in SARS and COVID-19 patients. The thyroid gland in patients with SARS is significantly altered and transient subclinical thyrotoxicosis, central as well as primary hypothyroidism (in some cases reversible) were described. Subacute thyroiditis, autoimmune thyroiditis and an atypical form of thyroiditis are complications of COVID-19. The thyroidal complications in SARS and COVID-19 seem to be slightly different, since the SARS epidemic was more localized and the COVID-19 affects people worldwide and therefore the published data are more accurate, we presume. We have several unanswered questions at present time. What are the long-lasting thyroidal effects of COVID-19? Should we modify the treatment of hypothyroid SARS-CoV-2 infected patients according to the different phases of COVID-19 disease? The exact mechanism by which SARS-CoV-2 causes injury to the thyroid gland is unclear and also warrants further investigation.

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