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Review article

Prospective role of thyroid disorders in monitoring COVID-19 pandemic

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ABSTRACT

COVID-19 pandemic has affected more than 200 countries and 1.3 million individuals have deceased within eleven months. Intense research on COVID-19 occurrence and prevalence enable us to understand that comorbidities play a crucial role in spread and severity of SARS-CoV-2 infection. Chronic kidney disease, diabetes, respiratory diseases and hypertension are among the various morbidities that are prevalent in symptomatic COVID-19 patients. However, the effect of altered thyroid-driven disorders cannot be ignored. Since thyroid hormone critically coordinate and regulate the major metabolism and biochemical pathways, this review is on the potential role of prevailing thyroid disorders in SARS-CoV-2 infection. Direct link of thyroid hormone with several disorders such as diabetes, vitamin D deficiency, obesity, kidney and liver disorders etc. suggests that the prevailing thyroid conditions may affect SARS-CoV-2 infection. Further, we discuss the oxidative stress-induced aging is associated with the degree of SARS-CoV-2 infection. Importantly, ACE2 protein which facilitates the host-cell entry of SARS-CoV-2 using the spike protein, are highly expressed in individuals with abnormal level of thyroid hormone. Altogether, we report that the malfunction of thyroid hormone synthesis may aggravate SARS-CoV-2 infection and thus monitoring the thyroid hormone may help in understanding the pathogenesis of COVID-19.

1. Introduction

An outbreak of betacoronavirus designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in China in December 2019. COVID-19, the disease associated with SARS-CoV-2 infection rapidly spread across the Globe. Since then the world is experiencing an outbreak of COVID-19 pandemic with 1.3 million deaths and 57 million symptomatic cases worldwide as on 20 November 2020 [1]. Individuals infected with SARS-CoV-2 show various types of clinical signs including fever, respiratory tract infections, diarrhea, breathlessness, memory loss etc. depending on person's health conditions [2]. Progression of SARS-CoV-2 infection increases in case of comorbidities such as diabetes [3], cardiovascular diseases [4], hypertension, chronic kidney diseases and respiratory disorders [5]. Figure 1 displays the comorbidities found in COVID-19 symptomatic patients and Table 1 describes the prevalence of these diseases or symptoms in different cohort studies [6, 7, 8, 9, 10, 11, 12, 13, 14]. Based on thyroid hormone functions and their association with other ailments, in this review a link has been established between aggravations of SARS-CoV-2 infection with thyroid disorders.

Thyroid disorders such as hypothyroidism and hyperthyroidism are more common in India being 11%, compared to only 2% in the UK and 4.6% in the USA [15, 16, 17, 18]. The thyroid hormone is secreted from thyroid gland that controls the growth, development of an organism and plays a vital role in maintaining normal human physiology and homeostasis. The primary hormone secreted by the thyroid gland is thyroxine (T4) but the gland also secretes smaller amounts of T3 (tri-iodothyronine). An active thyroid gland produces appropriate amounts of T3 and T4 under the influence of thyroid stimulating hormone (TSH), which is secreted from the pituitary gland [19]. The function of thyroid gland is influenced during hypothyroidism, hyperthyroidism, follicular thyroid carcinoma, papillary thyroid carcinoma and undifferentiated thyroid carcinoma. In hyper- and hypothyroidism, the thyroid gland is over- or underactive respectively and fails to produce appropriate hormone level that leads to deregulated secretion of T3 and T4 into the blood [20]. Altered thyroid state is a type of thyroid dysfunction that shows potentially devastating health consequences and is more common in women than men [21, 22]. The common symptoms of hypothyroidism such as fatigue, muscle weakness, dry skin, excessive hair fall, weight gain, increased sensitivity to cold etc. (Table 2) [23, 24,

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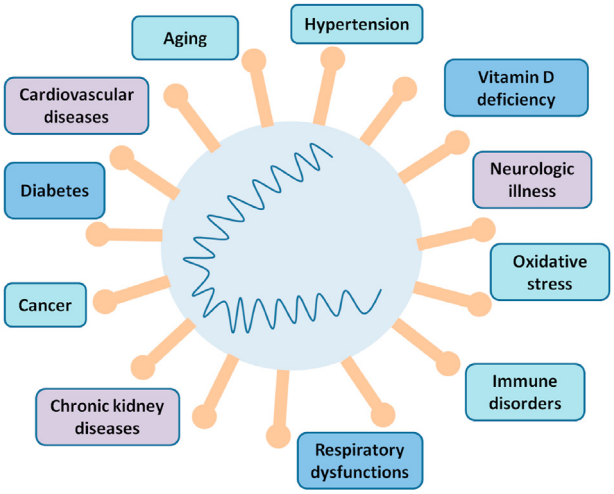

Figure 1. COVID-19 and associated comorbidities. Risk of severe COVID-19 symptoms increases in case of multiple disorders that includes respiratory dysfunctions, hypertension, cardiovascular diseases, chronic kidney disease, diabetes, deregulated immune response, oxidative stress, reduced level of vitamin D, neurologic illness and cancer.

25, 26, 27, 28], are drastically affect the professional productivity of people [29, 30, 31, 32]. Thyroid disorder may occur due to several factors that include I) Autoimmunity: The most common cause of hyper- and hypothyroidism is an immune disorder called Graves' and Hashimoto's thyroiditis. Here, the immune system produces antibodies that attack their own body tissues thereby named autoantibodies. In autoimmune hyper- and hypothyroidism, the immune system attacks the cells in the thyroid gland thereby the production of thyroid hormone is compromised [33]. II) Thyroid surgery: In some people, part or the entire thyroid gland is removed due to the detection of thyroid nodules that leads to deregulated thyroid hormone levels or even thyroid carcinoma [34]. III) Radiation therapy: People with Graves' disease, nodular goiter, or thyroid cancer are treated with radioactive iodine (^{131}I). Radiation may affect the thyroid gland that can result into thyroid dysfunction [35]. IV) Congenital hypothyroidism: Babies that are born with defective thyroid, without thyroid or partly formed thyroid gland, are born with either permanent or transient congenital hypothyroidism at birth. Transient hypothyroidism at birth is caused due to placental transfer of maternal anti-thyroid antibodies inhibiting fetal thyroid function [36]. Defects in thyroid hormone biosynthesis, resistance to thyrotropin, developmental defects, central hypothyroidism, thyroid hormone resistance, abnormal thyroid hormone transport into the cell and thyroid dysgenesia which includes thyroid ectopia, athyreosis, hypoplastic gland in situ are major reasons for permanent congenital hypothyroidism [37]. V) Damage to the pituitary gland: If pituitary gland is damaged by injury, radiation, tumor or surgery, it will not be able to produce TSH that directs thyroid gland to produce hormones. VI) Treatment and medications: Some drugs can interfere with the normal functioning of thyroid gland such as Lithium that are prescribed for certain psychiatric disorders. These medications may lead to abnormalities of thyroid gland [38] and VII) Iodine deficiency: Thyroid gland produces thyroxin by utilizing iodine that comes into our body from foods. Decreased iodine intake can lead to hypothyroidism and on the otherhand too much of iodine may worsen the disease. The present treatment approach is to normalize thyroxin hormone levels, specifically T4 and TSH by prescribing oral thyroid hormone (L-thyroxine) preparation to alleviate the hormone deficiency in case of hypothyroidism. Similarly, hyperthyroid patients are treated with n-propyl thiouracil (PTU) or methimazole to lower the thyroid level. Although the present treatment of thyroid disorders substantially maintains the level of hormone in the blood, it fails to improve well-being and quality of life of patients that have to be under medication for life-time [39].

Thyroid hormones are critically involved in the metabolism and thus their deregulated levels lead to abnormal metabolic state which may be hypermetabolic or hypometabolic. Action of thyroid hormone determines the function of heart, lung, liver, kidney and other organs thus playing a central role in human healthcare system. With increasing age, prevalence of thyroid disorders such as subclinical hypothyroidism is increased [40, 41]. Furthermore, hypermetabolic rate in hyperthyroid individuals is believed to be due to increased mitochondrial reactive oxygen and nitrogen species, thereby indicating the role of thyroid hormone in oxidative stress management [42] which in turn is linked with aging [43, 44]. Besides, oxidative stress leads to several age-related disorders that include diabetes, arthritis, osteoporosis, dementia, cancer and metabolic syndromes [45, 46, 47]. Intricate relation of thyroid hormones with aging, oxidative stress and other diseases suggests the crucial role of thyroid hormone in adverse outcome of SARS-CoV-2 infection. Herein, we discuss in detail the association of thyroid disorders with comorbidities including oxidative stress and aging.

2. Disorders and diseases associated with thyroid dysfunction

Risk of morbidities and mortalities in individuals with thyroid disorders is well established [48, 49, 50]. Several reports suggest critical association of thyroid dysfunction with diabetes [51, 52], cardiovascular diseases [53, 54], respiratory dysfunctions [55, 56], cancer [57, 58], chronic kidney diseases, hypertension, bacterial and viral infections. In the following sections, we discuss the association of several physiological disorders with thyroid dysfunctions (Figure 2).

2.1. Immune dysfunctions

Immune response in viral infections play determining role in disease outcome and thus immunotherapy can be promising treatment strategy [59]. Bidirectional link between neuroendocrine system and immune system is well established from previous research [60, 61]. Thyroid hormones play important role in modulating immune cell activities at cellular level. The intimate relationship between increased levels of T3 and proinflammatory activities such as the respiratory burst, nitric oxide synthase activity, and tumor necrosis factor-α expression in Kupffer cells has been extensively studied [62]. Thyroid hormones are also known to play vital role in maturation of dendritic cell and increased secretion of interleukin-12 (IL-12), which suggests their profound implications on immunopathology [63]. Nevertheless, immune system is known to regulate the function of thyroid hormone [64]. Autoimmune thyroiditis is a T-cell mediated autoimmune disease characterized by lymphocytic infiltration followed by fibrosis and atrophy of the gland [65, 66, 67]. Similarly, hyperthyroidism affects the functional aspects of monocytes and macrophages by inhibiting pro-inflammatory actions. The pro-inflammatory markers such as macrophage inflammatory protein-1a (MIP-1α) and IL-1β was found to be masked in T4-induced hyperthyroidism [68]. Action of thyroid hormone is significantly associated with innate immune response that suggests the complex adaptive responses in immunopathology [69]. Abnormal production of antibody was reported in patients with hyperthyroidism [70]. Similarly, a drastic reduction of lymphocytic function has been observed in patients with severe hypothyroidism [71] and congenital hypothyroidism [72]. Increased adherence of neutrophils and their reduced migration was detected in patients with primary hypothyroidism in comparison to healthy individuals [73] which strongly suggest increased risk of bacterial infections in hypothyroid individuals.

2.2. Major physiological disorders

Thyroid hormone have a central role in cardiovascular homeostasis, thus supplementation of thyroid hormone have been suggested in ischemic heart disease [74]. On the other hand, hypothyroidism is a known risk factor for coronary artery diseases [75] and elevated cardiac

Table 1. Prevalence of comorbidities in COVID-19 patients.

Symptoms	[6] Zhu *et. al.* 2020	[7] Zhang *et. al.* 2020	[8] Liu *et.al.* 2020	[9] Chen *et. al.* 2020	[10] Jin *et.al.* 2020	[11] Li Jitian *et. al.* 2020	[12] Jiang *et. al.* 2020	[13] Li *et. al.* 2020	[14] Guan *et. al.* 2020
Fever	80.40%	91.70%	81.80%	83%	85.14%	92.1%	98%	88.50%	43.80%
Elevated C-reactive protein levels	73.60%	Significantly high (all $P < 0.001$)	83.90%	-	-	-	-	44.30%	-
Lesions involving bilateral lungs	75.70%	89.60%	84.70%	75%	-	-	-	-	-
Cough	63.10%	75.00%	48.20%	82%	71.62%	42.10%	76%	68.60%	67.80%
Lymphopenia	56.50%	75.40%	-	-	-	-	-	64.50%	83.20%
Fatigue	46%	75.00%	32.10%	31.08	-	28.10%	44%	35.80%	-
Expectoration	41.80%	-	4.40%	-	39.19%	25.80%	28%	28.20%	-
Anorexia	38.80%	-	-	-	-	-	-	-	-
Elevated D-dimer	37.20%	Significantly high (all $P < 0.001$)	-	-	-	-	-	-	-
Chest tightness	35.70%	-	-	2% (Pain in chest)	-	12.70%	-	-	-
Shortness of breath	35%	-	7.3% (Heart palpitations)	31%	10.81%	5%	-	-	-
Dyspnea	33.90%	-	19%	-	-	-	55%	21.90%	-
Leukopenia	25.90%	-	-	-	-	-	-	-	-
Abnormal liver function	29%	-	-	-	-	-	-	-	-
Lesions involving single lung	25.80%	-	-	-	-	-	-	-	-
Abnormal renal function	25.50%	-	-	-	-	-	7% (Acute kidney injury)	-	-
Elevated procalcitonin	17.50%	-	-	-	-	-	-	-	-
Headache	15.40%	-	9.50%	8%	21.62%	-	8%	12.10%	-
Pharyngalgia	13.10%	-	-	-	-	-	-	-	-
Diarrhea	12.90%	-	8%	2%	-	5%	3%	4.80%	3.80%
Leukocytosis	12.60%	-	-	-	-	-	-	29.40%	-
Shivering	10.90%	-	-	-	-	-	-	-	-
Eosinopenia	-	52.90%	-	-	-	-	-	-	-
Gastrointestinal symptoms	-	39.60%	-	-	-	-	-	-	-
Hypertension	-	30.00%	9.50%	-	16.22%	-	-	-	23.70%
Diabetes mellitus	-	12.10%	10.20%	-	9.46%	-	-	-	-
Drug hypersensitivity	-	11.40%	-	-	-	-	-	-	-
Fatty liver and abnormal liver function	-	5.70%	-	-	10.81%	-	-	-	-
Chronic gastritis and gastric ulcer	-	5%	-	-	-	-	-	-	-
Coronary heart disease	-	5%	-	-	1%	-	-	-	-
Cholelithiasis	-	4.30%	-	-	-	-	-	-	-
Arrhythmia	-	3.60%	-	-	-	-	-	-	-
Thyroid diseases	-	3.60%	-	-	-	-	-	-	-
Urticaria	-	1.40%	-	-	-	-	-	-	-
Chronic obstructive pulmonary disease	-	1.40%	-	-	-	-	-	-	-
Smokers	-	1.40%	-	-	4.23%	-	-	-	-
Malignancy	-	-	1.50%	-	-	-	-	-	-
Hemoptysis	-	-	5.10%	-	4.05%	-	5%	-	-
Cardiovascular disease	-	-	7.30%	-	-	59.30%	12%	-	-
Chronic obstructive pulmonary disease	-	-	1.50%	-	-	-	-	-	-
Acute respiratory distress syndrome	-	-	-	17%	-	-	29%	-	-
Multiple mottling and ground-glass opacity	-	-	-	14%	-	-	-	-	56.40%
Muscle ache	33%	-	-	11%	13.51%	11.90%	-	-	-
Confusion	-	-	-	9%	-	-	-	-	-
Sore throat	-	-	-	5%	8.11%	10.70%	-	-	-
Rhinorrhoea	-	-	-	4%	-	6.30%	-	-	-
Nausea	-	-	-	1%	-	3.40%		3.90%	
Vomiting	-	-	-	1%	-	2.90%		3.90%	5.00%

(*continued on next page*)

Table 1 (*continued*)

Symptoms	[6] Zhu *et. al.* 2020	[7] Zhang *et. al.* 2020	[8] Liu *et.al.* 2020	[9] Chen *et. al.* 2020	[10] Jin *et.al.* 2020	[11] Li Jitian *et. al.* 2020	[12] Jiang *et. al.* 2020	[13] Li *et. al.* 2020	[14] Guan *et. al.* 2020
Pneumothorax	-	-	-	1%	-	-	-	-	-
Nasal obstruction	-	-	-	-	2.70%	4.60%	-	-	-
Increase of lactic dehydrogenase	-	-	-	-	-	-	-	28.30%	-
Elevated ESR	65.60%	-	-	-	-	-	-	-	-
Oxygenation index decreased	63.60%	-	-	-	-	-	-	-	-

troponins are reported to be associated with severe hypothyroidism [76]. At the same time, high serum level of brain natriuretic peptide has been detected in hyperthyroid subjects compared to euthyroid controls [77]. Similarly, the levels of D-dimers, and fibrinogen in impaired thyroid individuals have been negatively correlated with free-thyroxin levels [78, 79]. Hypothyroidism increases the risk of atherosclerotic cardiovascular diseases by increasing the levels of low-density-lipoprotein cholesterol particles, affecting smooth muscle and inducing diastolic hypertension [80]. This risk is exaggerated with insulin resistance and cigarette smoking.

Thyroid malfunctioning is associated with insulin resistance and is a known comorbid disorder for type-2 diabetes mellitus [81, 82, 83, 84]. Thyroid dysfunction is prevalent in individuals with diabetes and shows significantly increased serum levels of T3 and TSH [85]. Diabetic patients with hypothyroidism are susceptible to periodic hypoglycemic episodes. In addition, severe hyperthyroidism may lead to hyperglycemia [86, 87, 88]. Reports suggest that diabetic individuals are more likely to develop thyroid nodules [89]. Intimate relation between insulin resistance and thyroid cancer is apparently responsible for increased prevalence of thyroid cancer worldwide [90] and vice versa [91, 92].

Endocrine diseases in general have critical association with respiratory system [93] and thyroid hormones in particular play an important role in development of lungs and maturation of pulmonary surfactant [94]. Functional lung impairment has been observed in patients with hypothyroidism [95, 96, 97]. Moreover, respiratory dysfunctions has been studied to be more prevalent in hypothyroid patients [98]. For instance, reduced percentage of diffusing capacity of the lungs for carbon monoxide (DLCO), force expiratory flow (FEF) and force vital capacity (FVC) was detected in individuals with hypothyroidism [99, 100]. Under or overactive thyroid leads to diaphragmatic dysfunction [101] and weak reversible respiratory muscle [102, 103, 104].

Hypertension, which may be defined as systolic and/or diastolic blood pressure more than 160/95 mm Hg, was found more common in hypothyroid patients than in euthyroid individuals [105]. Nevertheless, hyperthyroidism is also a causal factor of hypertension. Atherosclerotic changes due to deregulated lipid metabolism in altered thyroid conditions may be the basis of vasculature changes in the blood vessels thus leading to high blood pressure. Along with this, some genetic mutations may be contributing towards thyroid disorders-mediated hypertension [106].

Thyroid hormones regulate renal function directly, thus modulate renal blood flow and glomerular filtration rate (GFR) [107]. Association of hypothyroidism and hyperthyroidism with GFR and increased renin-angiotensin-aldosterone activation underscores the link of thyroid diseases and kidney dysfunctions [108, 109]. Chronic kidney disease (CKD) caused by hypothyroidism is characterized by reduced levels of hormone T3 and can lead to renal fibrosis and renal failure with severe thyroid conditions [110]. Hypothyroidism has been reported to increase the risk of CKD incidence, progression and mortality in individuals with kidney dysfunction [111].

Thyroid dysfunctions and cancer of breast, prostate and thyroid are closely associated [112, 113]. Increased risk in the incidence of colorectal and thyroid carcinoma as well as increased cancer mortality has been reported in individuals with subclinical hypothyroidism [114]. Recently, overt thyroid dysfunction has been found to predict response to anti-PD-1 immunotherapy in association with anti-thyroid antibodies and is of clinical relevance for overall patient survival of non-small-cell lung carcinoma patients [115]. In recent times, a strong association between primary malignancies of thyroid and melanoma has been established [116]. At the same time increased TSH level is associated with poor prognosis for endometrial carcinoma patients [117]. A meta-analysis study reported an elevated risk of colorectal cancer in patients with hypothyroidism and thyroid replacement therapy has a protective role [118].

2.3. Renin-angiotensinogen system and thyroid disorders

Blood pressure and sodium homeostasis of electrolytes in the body are coordinately balanced by the renin-angiotensinogen system (RAS) which in turn is influenced by hormones in general and thyroid hormones in particular [119, 120]. RAS also controls cardiovascular and renal functions. In this system, angiotensinogen is cleaved by an aspartyl protease called renin into a decapeptide angiotensin I (AI) which is further cleaved into an octapeptide angiotensin II (AII) by angiotensin-converting enzyme (ACE). ACE cleaves AI into AII by removing the Carboxyl-terminal His-Leu residues from AI [121]. ACE2 is the homolog of ACE that exhibits 60% homology and is resistant to ACE inhibitors [122]. The primary function of ACE2 is to counterbalance the effect of ACE. ACE2 cleaves the Phe from carboxyl-terminal of AII and hydrolyzes into the vasodilator angiotensin (1–7) thereby lowering the blood pressure. AII is the active peptide that acts on the body tissues by binding to G-protein coupled receptors such as AII type receptor 1 (AT1) and AII type receptor 2 (AT2) (Figure 3). ACE2 counteracts the activity of the ACE by reducing the amount of AII and increasing Ang (1–7) which makes ACE2 a promising drug target for treating cardiovascular diseases [123]. All the components of RAS are influenced by the thyroid hormones and thus RAS is deregulated in individuals with altered thyroid states. Moreover, thyroid hormones play an essential role in development of lung and kidney which are the major sites of ACE and renin synthesis. The levels of thyroid hormones in plasma modulate both the synthesis and secretion of RAS components [119, 124, 125]. Though ACE is primarily located on pulmonary vascular endothelium, ACE is also found in tissues of heart, kidney, lungs, liver and brain. ACE2 plays critical role in SARS-CoV-2 infection by facilitating the virus entry into the host [126]. Serum level of ACE2 determines pathophysiological process of viral spread leading to lung injury. Li et. al. 2020 studied the expression of ACE2 in 31 healthy human tissues in both male and females of different age groups. ACE2 was highly expressed in several organs including thyroid, kidney, heart, small intestine, testis and adipose tissues. Nevertheless, a reduced expression of ACE2 was observed in blood vessels, blood, spleen, bone marrow, muscle and brain [127]. On the other hand, activity of ACE is tissue-specific and is highly influenced by thyroid dysfunctions [128]. For instance, treatment with glucocorticoids such as dexamethasone induces the activity of ACE in endothelial cells and rat lungs *in vivo* [129]. Moreover, during experimental hypothyroidism, significantly reduced ACE activity was found in serum and liver but was unaltered in lungs and kidney. However, in hyperthyroid animals, increased ACE activity was observed in kidney and reduced activity was detected in lungs with no effect on serum and liver [130]. Activity of ACE in serum is found to be increased in patients with hyperthyroidism [131,

Table 2. Clinical manifestations of patients with hypothyroidism.

Symptoms and Signs	[23] Kostoglou-Athanassiou and Ntalles, 2010	[24] Paudel, 2014	[25] El-Shafie, 2003	[26] Dutta et.al. 2019			[27] Paul and Dasgupta, 2012			[28] Sethi et.al. 2017
	Hypothyroidism	Subclinical Hypothyroid (n = 17)	Subclinical Hypothyroid (n = 30)	Severe Primary Hypothyroism (n = 91)	Non-severe overt Primary Hypothroidism (n = 130)	Subclinical Hypothyroidism (n = 240)	Hypothyroid (n = 41)	Overt Hypothyroid (20)	Subclinical Hypothyroid (21)	Hypothyroidism (n = 1499)
Fatigue	88%	58.80%	25%	91.20%	68.46%	56.67%	-	-	-	60.17%
Cold intolerance	84%	58.80%	-	69.23%	13.07%	1.67%	-	-	-	4.40%
Dry skin	77%	70.60%	10%	-	-	-	-	-	-	-
Voice hoarseness	74%	-	-	69.23%	16.92%	5.41%	-	-	-	-
Decreased hearing	40%	-	-	-	-	-	-	-	-	-
Sleepiness	68%	-	3%	-	-	-	-	-	-	-
Impaired memory	66%	29.40%	-	79.12%	25.38%	22.08%	-	-	-	19.81%
Weight gain	72%	-	10%	48.35%	40%	32.08%	-	-	-	36.22%
Paresthesia	56%	-	-	-	-	-	-	-	-	-
Constipation	52%	58.80%	20%	-	-	-	-	-	-	18.15%
Hair loss	41%	5.90%	-	76.92%	26.92%	32.08%	-	-	-	30.89%
Dry coarse skin	90%	-	-	72.52%	3.07%	7.08%	-	-	-	17.01%
Asthma	-	-	-	-	-	-	34.10%	40%	28.57%	-
Diabetes	-	-	-	-	-	-	31.70%	30%	33.33%	13.54%
Obesity	-	-	-	-	-	-	31.70%	25%	38.10%	1.27%
Hypertension	-	-	-	-	-	-	29.30%	45%	14.28%	11.34%
Voice hoarseness	87%	-	-	-	-	-	-	-	-	8.74%
Facial periorbital edema	76%	-	-	-	-	-	-	-	-	-
Slowed movements/ Delayed tendon reflex	73%	-	-	69.23%	-	-	-	-	-	7.47%
Mental impairment	54%	-	-	-	-	-	-	-	-	-
Bradycardia <60/min	10%	-	-	-	-	-	-	-	-	3.20%
Bradycardia>60/min	90%	-	-	-	-	-	-	-	-	-
Anxiety/Depression	-	29.40%	-	-	-	-	-	-	-	-
Tingling sensation	-	52.90%	-	-	-	-	-	-	-	-
Muscle pain/muscle weakness	-	47.10%	-	-	-	-	-	-	-	-
Dysarthria	-	-	3%	-	-	-	-	-	-	-
Dysphagia	-	-	3%	-	-	-	-	-	-	-
Snoring	-	-	3%	-	-	-	-	-	-	-
Goiter	-	-	10%	-	-	-	-	-	-	-
Menstrual irregularities	-	-	-	73.62%	28.46%	16.25%	-	-	-	10.41%
Amenorrhea	-	-	-	14.29%	-	-	-	-	-	-
Oligomenorrhea	-	-	-	27.47%	28.46%	16.25%	-	-	-	-
Meno-metrorrhagia	-	-	-	9.89%	-	-	-	-	-	-
Menorrhagia	-	-	3%	21.97%	-	-	-	-	-	-
Carpal tunnel syndrome	-	-	10%	13.18%	-	-	-	-	-	1.27
Odema of lower limbs	-	-	10%	81.31%	43.07%	28.33%	-	-	-	18.08%
Shortness of breath	-	-	-	93.40%	40.76%	32.92%	-	-	-	16.74%
Pero-orbital edema	-	76.50%	-	90.10%	26.15%	18.33%				11.47%
Feeling cold	-	-	-	-	-	-	-	-	-	15.21%
Hypervitaminosis	-	-	-	-	-	-	-	-	-	5.94%
Dyslipidemia	-	-	-	-	-	-	-	-	-	4.27%
Hypocalcemia	-	-	-	-	-	-	-	-	-	2.87%
Vitamin D deficiency	-	-	-	-	-	-	-	-	-	1.73%
Anemia	-	-	-	-	-	-	-	-	-	1.27%
Lethargy	-	-	-	-	-	-	-	-	-	1.07%
Mineral deficiency	-	-	-	-	-	-	-	-	-	0.87%
Iron deficiency	-	-	-	-	-	-	-	-	-	0.80%
Basedow's disease	-	-	-	-	-	-	-	-	-	0.53%
Neuralgia	-	-	-	-	-	-	-	-	-	0.53%
Vitamin B12 deficiency	-	-	-	-	-	-	-	-	-	0.53%
Pericardial effusion	-	52.90%	-	-	-	-	-	-	-	-
Pleural effusion	-	52.90%	-	-	-	-	-	-	-	-
Ascites	-	41.20%	-	-	-	-	-	-	-	-

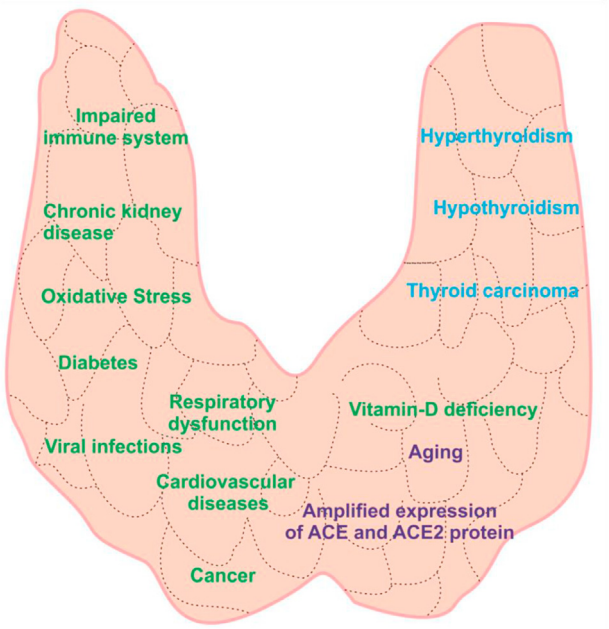

Figure 2. Physiological disorders and diseases associated with thyroid dysfunctions. Abnormal thyroid hormone action leads to several ailments including diabetes, cardiovascular diseases, respiratory dysfunctions, immune disorders, chronic kidney disease, vitamin D deficiency, deregulated RAS system, oxidative stress, hypertension, aging and various cancer. Importantly, thyroid hormone action regulates the expression of ACE and ACE2 protein on endothelial cells.

132, 133] and reduced in hypothyroid state during treatment with anti-thyroid drugs [122]. A strong positive correlation between serum ACE activity and T3 hormone concentration was observed in patients with thyroid dysfunctions. Moreover, in a recent study, amplified expression of ACE and ACE2 has been witnessed in thyroid carcinoma cases [134].

2.4. Viral infections

Farina et al. 2020 reports the pharmacology and kinetics of viral clearance in COVID-19 patients [135]. Evidences for presence of viruses such as retroviruses, human T-lymphotropic virus type 1 (HTLV-1), rubella, mumps and many more in thyroid disorders such as Graves' and Hashimoto's disease [136] advocates the relationship between thyroid gland dysfunction and viral infection. Previously, it was reported that patients who recovered from SARS showed low serum T3 and T4 levels which were due to damage caused by the SARS coronavirus to follicular cells of the thyroid gland [137]. Viral disease caused by hepatitis C virus (HCV) is also associated with rise in incidence and prevalence of thyroiditis [138]. A recent report suggests the prevalence of thyroid dysfunction in HIV infected adults [139]. Neuroendocrine functions of the thyroid gland affect the entire body including the immune system [66]. Earlier studies suggest that people with hypothyroidism have impaired immunity and are at higher risk of viral infection. Patients with hypothyroidism are at a significant risk of Human herpes virus-6 (HHV-6) infection [140, 141, 142]. A significantly increased prevalence of remote cytomegalovirus [143] infection was observed in primary hypothyroid subjects [144]. Increased risk of thyroid cancer is potentially associated with viral infections as suggested by recent meta-analysis studies [105, 145]. According to a recently conducted study, thyroid function abnormalities was observed in COVID-19 patients as compared to control group [146]. A significantly lower level of T3 and TSH was observed in COVID-19 patients compared to control group. Viral attack and damage to thyroid-pituitary axis might be the primary reason for thyroid dysfunction in COVID-19 patients. Interestingly, after recovery, no significant difference in TSH, TT3, T4, FT3 and FT4 levels is observed between COVID-19 patients and control group [147].

2.5. Oxidative stress and aging

The effect of oxidative stress is evident in many disorders along with hormonal imbalance. The elevated level of reactive oxygen species (ROS) was found during altered hormone level in hyperthyroidism that promotes oxidative stress and downregulates efficiency of antioxidants

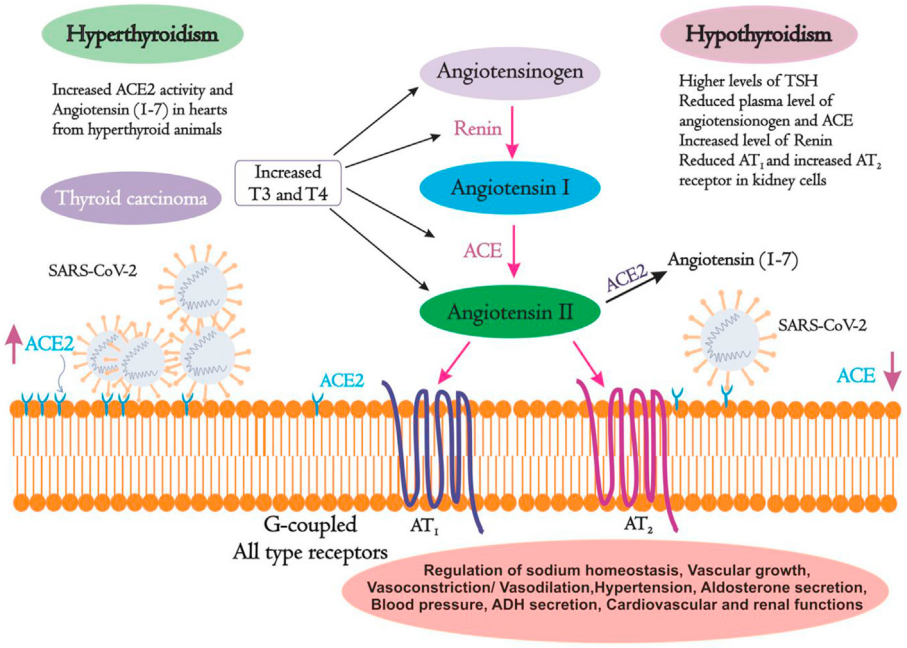

Figure 3. Effect of thyroid hormones on Renin-Angiotensinogen System. RAS plays a crucial role in normal human physiology. Thyroid hormones directly regulate the levels of RAS components. Hyper- and hypothyroid individuals show deregulated levels of RAS components. T3: Tri-iodothyronine; T4: Thyroxine; TSH: Thyroid stimulating hormone; ACE: Angiotensin-converting enzyme; AT1: All type receptors 1; AT2: All type receptors 2.

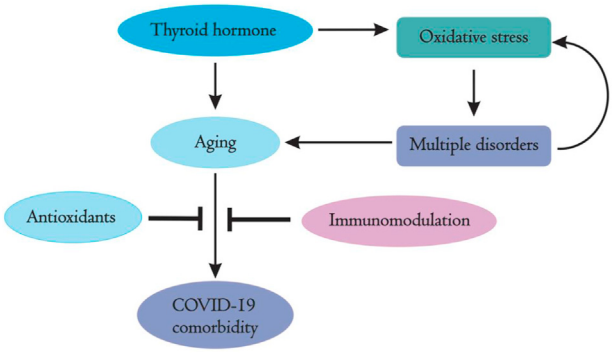

Figure 4. Intricate relation of thyroid hormone with oxidative stress, age-related multiple disorders and thus with COVID-19. Thyroid hormones are the master regulators of metabolism and its malfunctions induce oxidative stress which in turn leads to multiple disorders including aging. Deregulated thyroid hormones are closely associated with aging and SARS-CoV-2 infection. Administration of anti-oxidations and/or immunomodulators may prove to be helpful in COVID-19 disease management.

through the activation of the nuclear factor erythroid 2–related factor 2 (Nrf-2) [148]. Immune response to various pathogens is strongly regulated by oxidative stress and inflammatory processes [149]. The innate immune response was also found to be stimulated by oxidative stress through activation of the toll-like receptors and the nuclear factor kappa-B (NF-κB) during viral infections [150]. Oxidative stress occurs due to imbalance between oxidants and antioxidants. The disproportion between ROS, nitric oxides, lipid peroxidases and exogenous antioxidants (polyphenols, Vitamin E, Vitamin C, and carotenoids), endogenous antioxidants (reduced glutathione, urea, and albumin) as well as endogenous antioxidant enzymes (Superoxide dismutase, Glutathione peroxidase, and Catalase) leads to oxidative stress [151]. In long lasting viral infections such as Human immunodeficiency virus [152] and Epstein-Bar Virus [153], chronically elevated oxidative stress occurs and is associated with damaged immune system [154]. Viral infections cause increase in free radicals production and deplete antioxidants [155]. Both inflammation and endothelial damage found to play an important role in SARS-CoV-2 infection [156]. ROS production in COVID-19 patients was evaluated by cytokine shock with release of Il-2, Il-6, Il-7, TNF-α etc. that leads to hyperinflammation [157]. Oxidative stress-induced increased ROS accumulation is accompanied by reduced level of nicotinamide adenine dinucleotide (NAD^+) that is a single substrate for poly-ADP-ribose polymerase and act as a crucial electron transporter in mitochondrial respiration and oxidative phosphorylation [158]. Recognition, addition and removal of ADP-ribosylation are critical in host-virus encounters [159]. SARS-CoV-2 deregulates NAD^+ synthesis and utilization as well as induces expression of PARP [160]. Additionally, in response to SARS-CoV-2 infection, ROS has been observed to act as initiator of induced toxic innate immune response in aging population [161]. A critical analysis reveals drastic impact of COVID-19 on elderly population than young and adults [162]. Elderly people suffer from various diseases such as Alzheimer's, pulmonary dysfunction, cardiac malfunctioning, kidney failure, diabetics and others [163]. Most of such age-related diseases are reported as cause or effect of oxidative stress [43]. As shown in Figure 4, oxidative stress is critically associated with multiple disorders including aging under the influence of thyroid hormone that can be associated with COVID-19 comorbidities.

Since the endocrine functions in general and thyroid in particular is compromised with progress of age, collectively they influence oxidative stress status in individuals [164, 165, 166]. Increase or decrease in production of free radicals in hypermetabolic and hypometabolic state [167] have been noticed in hyperthyroidism [168, 169] and hypothyroidism [170] respectively. Both hypo- as well as hyperthyroid states are shown to influence antioxidant defence system in brain [171, 172, 173], liver [174, 175], heart [176], kidney [177] and testis [178]. Furthermore, thyroid hormones have been found to prevent lung congestion and improve cardiac functions by reducing the levels of reactive oxygen species in male Wistar rats [179]. Although supplementation of antioxidants do not modify thyroid hormone levels in hypo or hyperthyroid states, but they are capable of rescuing organs from oxidative stress [173, 175, 177, 180, 181, 182, 183, 184, 185]. Reduced oxidative stress was recently observed in rat upon treatment with Vitamin E/curcumin under altered thyroid state via NF-kB signaling [186]. Thus, use of exogenous antioxidants against oxidative stress-induced disorders may help the patients in general and aged population in particular to fight against COVID-19.

3. Management of thyroid dysfunctions during COVID-19

Thyroid dysfunctions are strongly associated with comorbid conditions that are found to be significantly associated with COVID-19 disease outcome which includes diabetes, cardiovascular disorders, chronic kidney disease, and hypertension etc. (Tables 1 and 2). Prevailing disease conditions determine the severity of COVID-19 disease outcome. Thus, management of endocrine diseases that affect the function in other glands including pituitary, thyroid, adrenal and gonad during SARS-CoV-2 infection is a prerequisite [187, 188]. Deregulated levels of cardiac troponin I, brain natriuretic peptide (BNP), D-dimers, and fibrinogen have been used as diagnostic markers to assess the risk of cardiovascular disorders in COVID-19 patients [189] and are equally imbalanced in patient with thyroid disorders. Similarly, Vitamin D is thought to play an important role in SARS-CoV-2 infection. For illustration, people having deficiency of Vitamin D are said to be at a higher risk of SARS-CoV-2 infection [190, 191]. Other conventional link for existing thyroid disorders and COVID-19 disease progression may be acceptable with the fact that low Vitamin D status is significantly associated with thyroid dysfunction [192, 193]. Above argument signifies that Vitamin D supplements may reduce the severity of viral infections such as influenza and SARS-CoV-2 [194,195]. Moreover, mortality of COVID-19 patients has been observed more in elderly patients than in young and middle-aged persons [196]. At the same time, old-aged hyper- or hypothyroid patients are more prevalent to hypertension [197]. Notably, thyroid hormones play indispensable role on cardiovascular system and altered thyroid accompanies congestive heart failure [198]. Oxidants play important pathogenic role in acute and chronic lung diseases [199, 200, 201] and administration of antioxidants may be effective against chronic obstructive pulmonary disease (COPD) [202]. Level of NADPH oxidase-2 (NOX-2)-induced oxidative stress is closely associated with troponin level and play important role in myocardial damage in COVID-19 patients [203]. Antioxidants can be considered as a plausible approach to reduce oxidative stress in viral infections including SARS-CoV-2. The efficacy of antioxidants such as melatonin, Vitamin E and Vitamin C is suggested and reported against obstructive pulmonary disease and multiple newborn diseases including COVID-19 [157,203,204]. Host cell entry of SARS-CoV-2 is facilitated by the spike (S) protein which binds to host ACE2 along with transmembrane serine-protease-2 (TMPRSS2). Differential ACE activity in hypothyroid and hyperthyroid experimental animals and patients elucidates the indispensable role of thyroid hormones in renin-angiotensinogen system that is critically involved in cardiovascular and renal functions [112]. Relation of ACE2 expression level during SARS-CoV-2 infection is intricate. Higher expression of ACE2 favors increased SARS-CoV-2 host cell entry, whereas, reduced expression of ACE2 after infection may lead to severe illness. Yang et. al. 2014, reported that reduced ACE2 resulted in severe H7N9-induced lung injury [205]. At the same time, recombinant ACE was found to improve pulmonary hemodynamics in human pulmonary arterial hypertension [206]. Studies suggest the role of genetic background as well as the level of hormones like estrogen in differential expression of ACE2 in the body [207, 208]. Level of ACE and ACE2 is the determining factor for the regulated functioning of RAS. Thyroid hormones play critical role in defining the expression of ACE and ACE2 in plasma and different tissues that in turn might contribute in SARS-CoV-2 infection as well as disease

severity. Increased expression of ACE2 and other components of RAS in hyperthyroidism, suggest the modulatory role of thyroid hormones on RAS-regulated metabolic pathways (Figure 3) which advocates the possible role of thyroid hormone in SARS-CoV-2 outcome. Levels of thyroid hormones T3, T4 and TSH not only govern the thyroid condition but also help to assess the function of other organs of the body. Moreover, reports suggest that increased incidence of subclinical thyroid dysfunctions is noticed in elderly people [209]. Thyroid hormone has been suggested for treatment of critically ill COVID-19 patients based on the experimental evidence that deregulated thyroid hormone metabolism occurs during acute illness such as sepsis, trauma and myocardial infarction [210, 211]. According to a recent report, thrombocytopenia was observed in COVID-19 patient having autoimmune hypothyroidism or hyperthyroidism after treatment with amoxicillin–clavulanic acid, heparin and oxygen [212]. Thyroid hormone related dysfunctions including immune response may keep individuals at a higher risk for adverse outcome for SARS-CoV-2 infection. Nevertheless, association of COVID-19 and thyroid dysfunctions is not well studied and documented due to which there are no guidelines from World Health Organization [1] for assessment of thyroid function during COVID-19 treatment. However, reports and editorials suggest the possible connection of existing thyroid-related disorders and SARS-CoV-2 infection [213, 214, 215, 216]. Therefore, like other risk factors, deregulated thyroid may significantly influence the severity of SARS-CoV-2 infection.

4. Conclusions

Since thyroid hormones play major role in metabolism, growth and development of human body, dysfunctions due to thyroid hormone may have significant clinical consequences on immune response and thus on human health. Increased prevalence of other comorbidities has been observed in individuals with abnormal thyroid that keep them at a higher risk for susceptibility towards bacterial or viral infections. Thus, deregulated thyroid hormone may have considerable risk in aggravating the infection and spread of SARS-CoV-2. Intricate association of thyroid hormone and oxidative stress suggest that supplementation of antioxidants in elderly COVID-19 patients with thyroid diseases may strengthen the immune system. Moreover, in view of existing global disaster due to COVID-19, monitoring of thyroid hormones may help in understanding the pathogenesis of COVID-19.

Declarations

Author contribution statement

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Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

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