

# COVID-19 and Basedow disease

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## ABSTRACT

Coronavirus disease-2019 (COVID-19) heavily hits the human body through various and dramatic ways, and endocrine system is not an exception. Our purpose is to update the concepts around subjects diagnosed with Basedow disease (BD) before, after or during experiencing COVID-19 infection. This is a literature review based on full-length, English papers that are available through PubMed (published between 2020 and 2021). Angiotensin-converting enzyme 2 and transmembrane protease serine 2 receptors are expressed at thyroid level and this might explain why an active coronavirus infection activates the BD especially in patients with a potential predisposition. Also, the new diagnostic of BD might follow a COVID-19 infection (within weeks). Simultaneously dealing with both conditions requires a more challenging multidisciplinary management, while the diagnostic of thyroid condition after recovery from infection is more likely to follow the general pattern of evolution (as seen in non-COVID-19 cases). A previous diagnostic of autoimmune hyperthyroidism means mostly either: BD is remitted after prior medication treatment with anti-thyroid drugs and/or radioiodine therapy (normal thyroid function), the patient has iatrogenic hypothyroidism that was induced after thyroidectomy or after radioiodine therapy (requiring daily oral levothyroxine substitution) or the subject is under thiamazol (or similar drugs) with either controlled or uncontrolled thyroid function. Most of the clinical studies agree (but not all) that people with treated hypothyroidism and hyperthyroidism are not susceptible to a higher morbidity or mortality concerning coronavirus infection. One exception is concurrent medication with anti-thyroid drugs with a higher risk of agranulocytosis which is a prone condition to any kind of infection. Graves' ophthalmopathy may be synchronous or not with an active thyroid disease. Except for mild forms, typically the condition requires glucocorticoid therapy, preferably a short course of intravenous metiprednisolone which exposes the patient to a higher risk of an infection, including COVID-19. Recently, BD was suspected to be induced or aggravated by COVID-19 vaccination which is still a matter of discussion.

**Keywords:** SARS-CoV-2, COVID-19, coronavirus, thyrotoxicosis, hyperthyroidism, ophtalmopathy, Basedow disease, eye disease, Basedow-Graves' disease, Graves' disease

## Abbreviations

ACE2 = angiotensin-converting enzyme 2

ANCA = antineutrophil cytoplasmic antibody

AAV = antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis

COVID-19 = coronavirus disease-2019

SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2

TSH = thyroid stimulating hormone

TRAB = TSH (thyroid stimulating hormone) antibodies

TMPS2 = transmembrane protease serine 2

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## INTRODUCTION

Coronavirus disease-2019 (COVID-19) heavily hits the human body through various and dramatic ways, and endocrine system is not an exception under these circumstances, regardless the patient displays a severe form of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) or not (1,2). Among these clinical aspects, thyroid gland is situated right in the center of this particular matter involving pathologies that are reported in medical literature with different levels of statistical evidence from case reports to clinical studies (2,3). The clinical picture varies; for instance, new entities are described in relationship with thyroid status changes that are induced by COVID-19 infection like subacute thyroiditis or necrotic thyroiditis (4,5). Also, the scenario might involve prior thyroid conditions, for example coronavirus infection provides the tools to trigger previous autoimmune diseases like chronic autoimmune thyroiditis (6,7). The main thyroid-related mechanisms involve inflammation, cytokines excess, anomalies of oxidative status, high prothrombotic status, as seen in others endocrine and non-endocrine organs (8,9,10). Overall, the immune modulation is the key element of understanding the degree the infectious disease provides the aggravating circumstances of autoimmune thyroid diseases, either maladies which are associated with blocking antibodies as Hashimoto thyroiditis or activators antibodies meaning TSH (thyroid stimulating hormone) antibodies (TRAB) as seen in Basedow-Graves' disease (11,12,13).

## AIM

Our purpose is to update the concepts around subjects diagnosed with Basedow-Graves' disease before, after or during COVID-19 infection.

## METHOD

This is a brief literature review. General data following the mentioned purpose are provided by full-length, English papers that are available through PubMed database. The inclusion criteria are reflected by their clinical relevance (for different practitioners). The papers are published between 2020 and 2021, according to the COVID-19 pandemic circumstances and evolution of published data regarding medical community all over the world. The level of statistical evidence involving the papers that are focused on Basedow-Graves disease and coronavirus infection varies, from single case report to clinical studies or reviews. General data are addressed according to several sub-sections based on the thyroid background of the patient: with prior thyroid disease with or without eye involvement, with pre-

vious thyroidectomy or not; and, on the other hand, without known thyroid background. At "Discussions" section, data on vaccine against COVID-10 infection and Basedow disease, respective Graves' ophthalmopathy are also pointed out.

## GENERAL DATA

### Active COVID-19 infection and newly onset Basedow disease

Angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) receptors are expressed at the level of thyroid and this might explain why in patients with a potential predisposition an active coronavirus infection activates the Basedow – Graves' disease (meaning in subjects without a prior specific medical history) (14). Also, the new diagnostic of Basedow disease might soon follow a COVID-19 infection (within first few weeks) (15,16). Simultaneously dealing with both conditions requires a more challenging multidisciplinary management, while the diagnostic of thyroid condition after recovery from infection is more likely to follow the general pattern of evolution (as seen in non-COVID-19 cases) (17,18). Harris et al. reported the first case subscribing to this situation: a 21-year old female admitted for symptoms and signs of hyperthyroidism without prior thyroid medical history (but she was known with prediabetes mellitus) and she had a 16-day history of positive polymerase chain reaction (PCR) for SARS-CoV-2 (the infection remitted within 10 days) (19). Generally, an infection (not only coronavirus infection) might trigger autoimmune hyperthyroidism (20,21). Another potential mechanism of activating the TRAB-related disease is selenium deficiency that is induced by COVID-19 infection (22).

### Coronavirus infection in patients with prior diagnostic of Basedow-Graves disease

A previous diagnostic of autoimmune hyperthyroidism means that the clinical presentation may mostly underline one of the three following situations: Basedow disease is remitted after prior medication treatment with anti-thyroid drugs or radioiodine therapy (normal thyroid function), the patient has iatrogenic hypothyroidism that was induced after thyroidectomy or after radioiodine therapy (requiring daily oral levothyroxine substitution in order to achieve normal thyroid function) or the subject is under thiamazol (or similar drugs) with either controlled or uncontrolled thyroid function (23,24,25). A patient under thiamazol or propylthiouracil drugs might develop agranulocytosis with dramatic implications on a concurrent infection, including COVID-19 (26,27). Recently, Okuda et al. re-

ported the case of 37-year old Japanese female with antineutrophil cytoplasmic antibody (ANCA) - associated vasculitis (AAV) 12 days after vaccination against COVID-19 while she was under propylthiouracil for Basedow –Graves' disease (28). Most of the clinical studied agree that people with treated hypothyroidism and hyperthyroidism are not susceptible to higher morbidity or mortality concerning coronavirus infection (29,30). However, a meta-analysis of Damara et al. showed that hypothyroidism, not hyperthyroidism is prone to a poor prognostic of COVID-19 infection (31). Of course, as pandemic goes on, a growing body of evidence is expected (32).

### Associating conditions to Basedow disease and a potential coronavirus infection

The co-presence of thyroid nodules (with a higher prevalence in general population that Basedow disease) or even thyroid cancer requires adequate control of infection before surgery (if feasible); the discussion is similarly approached if the patient with Basedow disease (without thyroid nodules or suspected malignancy) is a candidate to thyroidectomy which should be postponed until the remission of coronavirus infection (33,34). Follow-up of patients who are known with different thyroid conditions suffered an adjustment during pandemic, thus the use of telemedicine became a must anywhere in the world (35,36). Also, people who suffered a prior thyroidectomy have a higher chance of having associated hypocalcemia, with or without hypoparathyroidism, during a coronavirus infection (37,38). For what we know so far, more than a half of the patients affected by a severe form of COVID-19 infection display hypocalcemia (39,40). Potential underlying mechanisms of COVID-19-related hypocalcemia are related to transitory (as hypoxia-related) or surgically induced hypoparathyroidism, vitamin D deficiency, renal damage due to COVID-19 infection, generally inflammatory status and anomalies of oxidative stress which are reflected at the level of abnormal calcium – parathyroid feedback and even developing or aggravating a bone metabolic disease (41,42,43).

People diagnosed with autoimmune thyroid conditions have a higher risk of others autoimmune (endocrine and non-endocrine) maladies like vitiligo, rheumatoid arthritis etc. (44,45). Several case reports showed that COVID-19 infection might trigger some of them like psoriasis vulgaris etc. (46). Yet, one of the most dramatic synchronous circumstance is the presence of type 1 diabetes mellitus which exposes the subjects to a more severe form of coronavirus infection, especially in patients with uncontrolled diabetic disease and/or associated organ damage like renal insufficiency or cardiovascu-

lar disease (47,48,49). Also, the subjects that associate primary adrenal insufficiency need a higher dose of glucocorticoid replacement during COVID-19 infection while they are generally more susceptible to any type of infection (viral, bacterial or fungal) (50,51,52).

Moreover, pregnancy in COVID-19 positive females with autoimmune thyroid diseases might associate unexpected changes of thyroid hormones status as seen in others organs (53,54,55). A few cases of postpartum thyroiditis have been reported after the women were confirmed with SARS-CoV-2 infection during pregnancy (56,57).

### Graves' disease and COVID-19

The ophthalmopathy may be synchronous or not with an active thyroid disease; except for mild forms, typically the condition requires glucocorticoid therapy, preferably a short course of intravenous treatment (58,59,60). If methylprednisolone or other similar regimes of glucocorticoids were necessary, this situation is prone to an infection, including COVID-19 (61,62,63). Additionally, the eye disease might be developed after COVID-19 vaccination (64). In 2021, a case report of a 50-year old lady who was known with Basedow disease without Graves' eyes involvement showed that the patient developed the eye complications starting with the day 3 after the second dose of immunization against coronavirus (64). This case published by Rubinstein opens up a new interesting chapter of medicine, meaning the autoimmune conditions developed after this vaccination like hepatitis, vasculitis etc. (65,66).

## DISCUSSIONS

Regarding what we know until present moment, none of the previous thyroid conditions like Basedow disease with or without Graves' ophthalmopathy, limits the indications of immunization against COVID-19 (some reports of post-vaccine subacute thyroiditis are also published) (67,68,69). Two males cases of 32 years, respective of 35 years were described by di Filippo et al. with *de novo* diagnostic of Basedow disease after 10, respective 5 days since vaccination (70). Another case showed a more severe hyperthyroidism on day 6 since first dose of COVID-19 immunization (71). Another case of relapsed Basedow disease was reported by Pierman et al. (72). Another subject (known with vitiligo and type 2 diabetes mellitus) developed Basedow disease after one month since immunization in addition to autoimmune diabetes mellitus (73). Probably, in the future global databases will be create to facilitate spreading of medical information since real life medicine data are imperious, considering the dynamics of the COVID-19 pandemic (74,75).

## CONCLUSIONS

COVID-19 pandemic showed unexpected medical issues and the field of Basedow-Graves' disease subscribes to this aspect. More statistical evidence is necessary to clearly link the thyroid and/or associated TRAB – induced eye involvement to the coronavirus infection or even with to the vaccine against the virus. Until such precise data are available,

awareness of different associations remains the key operative word in daily multidisciplinary practice.

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