

# Thyroid Function and Suicidal Behavior

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Thyroid disease is a very common condition that influences the entire human body, including cognitive function and mental health. As a result, thyroid disease has been associated with multiple neuropsychiatric conditions. However, the relationship between thyroid dysfunction and suicide is still controversial.

Keywords: suicide ; thyroid function ; hypothyroidism ; hyperthyroidism

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## 1. Introduction

Suicide is one of the main causes of mortality around the globe, accounting for about 800,000 deaths every year <sup>[1]</sup>. Deaths by suicide are more frequent in individuals with psychiatric disorders, such as major depression and alcohol use disorder. By far the single most important risk factor for suicide is a prior suicide attempt <sup>[2]</sup>. Therefore, suicide and suicide attempt/ideation are serious public health problems, as these disorders deeply affect families and communities and have long-lasting effects on the people left behind.

Thyroid dysfunction is the most common endocrine disorder <sup>[3]</sup>. Most current estimates showed that around 12% of Americans will develop a thyroid condition during their lifetime and that around 20 million have a thyroid disorder <sup>[4]</sup>. Additionally, it has been estimated that one in eight women will develop a thyroid disorder during their lifetime <sup>[5]</sup>. Some endocrine disorders have been correlated with psychiatric conditions, such as major depression, anxiety, etc. <sup>[6][7][8][9]</sup>. This is not the case for suicidal behavior, as its relationship with thyroid dysfunction is controversial, and mostly based on observational studies.

A nationwide Danish register-based study, including 111,565 participants, reported that mortality due to suicide was increased (0.10% vs. 0.07%,  $p < 0.001$ ) in patients with Hashimoto's thyroiditis compared to matched controls, suggesting a possible role of Hashimoto's thyroiditis in the pathophysiologic mechanisms of suicidal behavior <sup>[10]</sup>. Similarly, a study including 1718 patients with a history of major depressive disorder showed that those with history of suicide attempt had higher levels of thyroid-stimulating hormones (TSH) and thyroid autoantibodies compared with those without history of suicide attempt, suggesting a potential role of alterations in thyroid function tests in the risk of suicide attempts <sup>[11]</sup>. In contrast, in a large prospective cohort study of women with thyroid dysfunction that explored the risk of cause-specific mortality after nearly 30 years of follow-up, neither hyperthyroidism nor hypothyroidism were associated with higher rates of suicide <sup>[12]</sup>.

## 2. Current Insights on Thyroid Function and Suicidal Behavior

Here, we found that patients with suicidal behavior have lower levels of FT3 and TT4 compared with controls, but we found no difference in TSH, FT4, or TT3 levels. Furthermore, the subgroup of patients with history of suicide attempt had lower FT3 and FT4 levels, and higher TSH levels compared to controls. This study represents the first summary about the relationship between suicidal behavior with thyroid function.

Our results are in line with previously published evidence regarding the risk/association of thyroid disorders with suicide behavior <sup>[10][13][14]</sup>. Heiberg-Brix et al. found that patients with Hashimoto's thyroiditis had an increased frequency of death by suicide (HR = 1.31; 95% CI, 1.04–1.65,  $p = 0.024$ ) compared to euthyroid controls in a register-based Danish study <sup>[10]</sup>. In contrast, this frequency is not increased in patients with Graves' disease compared to controls without Graves' disease or euthyroid controls from the general population <sup>[15][16]</sup>. According to these findings, suicide possibly has a stronger association with autoimmune hypothyroidism rather than autoimmune hyperthyroidism. Similar results have been reported for suicidal attempt/ideation and thyroid disorders. A cross-sectional study showed that the prevalence of hypothyroidism in a group of 31 patients with bipolar disorder and suicide attempt was higher (25.8%) compared with a prevalence of 15.9% in a group of 63 patients with bipolar disorder with no suicide attempt <sup>[13]</sup>. Sanna et al. reported a 6.5% prevalence of thyroid disorders in males with history of suicidal ideation, compared with a 1.9% prevalence in males without history of

suicidal ideation [14]. Nevertheless, these results should be analyzed carefully as all these studies are observational with relatively small sample size and analyses are not adjusted for confounders.

The development of suicide, depression, and other affective disorders has been previously associated with autoimmune diseases, including thyroid-specific diseases [10][17][18][19]. In a meta-analysis published by Siegmann et al., patients with Hashimoto thyroiditis and either subclinical or overt hypothyroidism showed significantly higher scores on standardized depression instruments compared to euthyroid controls [20]. A second meta-analysis published in 2019, found that patients with subclinical hypothyroidism had higher risk of depression than euthyroid controls. However, there was no difference in the mean TSH level between individuals with depression and healthy controls [21]. Although the majority of patients with depression and other mood disorders have completely normal thyroid function tests, several test abnormalities have been described including elevated TT4 levels, low TT3 and FT3 levels, blunted TSH response to thyrotropin-releasing hormone, and positive antithyroid antibodies [19][22][23][24][25][26][27][28]. Interestingly, thyroid hormone in the form of liothyronine has been used for the treatment of depression, mainly as an augmentation therapy in severe forms of depression [29][30][31][32]. In addition, in the setting of suicidal behavior, there is evidence suggesting that thyroid hormones might have a role in the regulation of the neurotransmitters involved in suicide pathogenesis, such as serotonin and norepinephrine [33][34][35][36]. As demonstrated by our results, where most of the participants had concomitant affective disorders (depression or bipolar disorder) or schizophrenia, patients with suicidal behavior had significantly lower levels of FT3 and TT4, albeit not clinically meaningful, when compared with the control group.

To our knowledge, this is the first systematic review and meta-analysis of available evidence evaluating the relationship between suicide and thyroid function tests. There were some limitations to our study. First, due to the observational nature of all the studies included in this meta-analysis, it was not possible to establish causality. Second, although we used clear and standardized inclusion criteria and comprehensive search strategies, there remains possible sources of bias such as incomplete searching, publication bias, and the influence of confounding factors (current therapies, psychiatric comorbidities, environmental factors, etc.) in our results. Third, there was heterogeneity of the criteria used to define suicide behavior in the included studies (based on clinical records, psychiatric assessment, self-reported, etc.) and the presence of other concomitant psychiatric diseases which can affect the risk of suicidal behavior. Importantly, suicide is a very complex phenomenon related to many mental health diagnoses and with a multitude of biological, psychological, and social variables which should be considered when interpreting our findings.

### 3. Conclusions

In conclusion, we found that the available evidence regarding the association of hypothyroidism or hyperthyroidism with suicidal behavior is limited. In our best effort to summarize all the available evidence, we have described that patients with suicidal behavior had significantly lower levels of FT3 and TT4 levels compared with controls. However, the data in this field are scarce and have significant heterogeneity. Future large, well conducted studies are needed to increase our confidence in the findings presented here, especially studies reporting the specific association of hypothyroidism/hyperthyroidism in this population, which can provide a better understanding, evaluation, and follow-up of patients with thyroid dysfunction and suicidal behavior.

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