EXPLORING THE INTRIGUING INTERPLAY BETWEEN THYROID DISEASES AND BIPOLAR DISORDER

MINHAJ, R.[1] – TAHER, B.[2,3] – JABER, J.[2,3] – CHEBLI, D.[2,3] – MSHEIK, L.[2,3*]

[1] *University of Health Science, Lahore, Pakistan.*

[2] *Faculty of Medical Sciences, Lebanese University, Beirut, Lebanon.*

[3] *Medical Learning Skills Academy, Beirut, Lebanon.*

**Corresponding author*
e-mail: Layalmsheik96[at]gmail.com

(Received 30th June 2023; accepted 28th August 2023)

Abstract. Thyroid diseases, which include hypothyroidism and hyperthyroidism, and bipolar disorder are two separate yet interrelated areas of mental and endocrine health. Research has revealed a link between both illnesses, suggesting that thyroid dysfunction may impact the onset and prognosis of bipolar disorder, and vice versa. This review digs into the complex relationship between thyroid diseases and bipolar disorder, with an emphasis on therapeutic interactions, common risk factors, and the probable dysfunction of the Hypothalamic-Pituitary-Thyroid (HPT) axis in bipolar disorder. The purpose of this review is to thoroughly investigate the multidimensional association between thyroid illnesses (hypothyroidism and hyperthyroidism) and bipolar disorder. Among the objectives are: (1) Therapy Implications: Looking into the bidirectional effects of medications like lithium-induced hypothyroidism and the possible use of levothyroxine in bipolar therapy; (2) Shared Risk variables: Investigating the genetic, autoimmune, inflammatory, environmental, and gender-related variables that contribute to thyroid illness and bipolar disorder co-occurrence; and (3) HPT Axis Dysfunction: Investigating the possible involvement of HPT axis dysfunction in bipolar illness, as well as the consequences for mood regulation and symptom severity. The complex link between thyroid disorders and bipolar illness emphasizes the importance of ongoing studies in this area. Shared risk factors and bidirectional treatment impacts provide exciting opportunities for further investigation into the relationships between these illnesses. The possibility of HPT axis disruption in bipolar illness provides fresh insights into mood control mechanisms. As our understanding grows, targeted treatment therapies addressing both thyroid dysfunction and bipolar symptoms may develop, eventually improving the well-being of those dealing with these linked issues.

Keywords: *thyroid diseases, hypothyroidism, hyperthyroidism, bipolar disorder, treatment interactions, shared risk factors*

Introduction

Bipolar disorder, also known as manic depression, is a complicated and difficult mental health disease that affects millions of individuals throughout the world. Bipolar disorder, which is characterized by severe and fluctuating fluctuations in mental and physical health levels, provides a unique and often perplexing path for people who experience its ups and downs (Carvalho et al., 2020). Bipolar disorders rank as the 17th leading source of disability among all diseases worldwide with suicide rates 20 to 30 times as high as the rates of general population (Plans et al., 2019; Vigo et al., 2016). Bipolar episodes can range from depressed lows of profound sorrow and tiredness to manic or hypomanic highs of heightened attitude, higher energy levels, and aggressiveness. It has two types that differ in the severity of symptoms (Jain and Mitra, 2020a). Bipolar I is distinguished by severe mood swings that include both manic and

depressed states. Its manic episodes are characterized by strong moments of enhanced mood, energy, and higher activity levels. Whereas, depressive episodes are characterized by extreme sorrow, lack of interest, exhaustion, and thoughts of worthlessness. The second type is Bipolar II that is characterized by separate mood episodes; hypomania and depression. It differs from Bipolar I by its hypomanic episodes that are milder than full-blown mania. Several medical conditions can resemble the clinical appearance of bipolar disorder, particularly hypothyroidism, which mimics the disorder's early stages (Carvalho et al., 2020). The thyroid, a little small butterfly-shaped gland situated in the neck, is critical in maintaining the body's delicate balance. Thyroid diseases, which include a variety of ailments, upset this homeostasis and can have serious consequences for both physical and mental health. Hypothyroidism and hyperthyroidism are the two most common symptoms of thyroid dysfunction. Hypothyroidism is characterized by a decrease in thyroid hormone synthesis, namely thyroxine or tetra iodothyronine (T4) and triiodothyronine (T3). Bradycardia, cold intolerance, constipation, weariness, and weight gain are all symptoms commonly encountered in this condition. Hyperthyroidism, on the other hand, is caused by an excess of these hormones. Weight loss, heat intolerance, diarrhea, fine tremor, and muscular weakness are the most common symptoms (Khan et al., 2023).

The relationship between thyroid diseases and bipolar disorders has been a hot study area because neuropsychiatric symptoms are very common in thyroid diseases. Thyroid diseases are more prevalent in cyclic and refractory forms of bipolar disorder (Chakrabarti, 2011). Hypothyroidism was more prevalent than hyperthyroidism in patients with bipolar disorder. With several exceptions, a study found that hypothyroidism was mostly associated with depressive bipolar disorder, whereas hyperthyroidism was associated with manic bipolar disorder. Patients with hypothyroidism usually have symptoms related to depression and less commonly mania. Moreover, patients who develop a true manic episode while thyrotoxic, frequently have an underlying mood disorder, or a family history of mood disorder. Lithium, a treatment used in bipolar disorders, is also known to have and antithyroid effect. Levothyroxine, on the other hand, has been shown to stabilize mood in people with bipolar illness. The hypothalamo-pituitary thyroid (HPT) axis function was evaluated in order to examine this connection. Such an approach demonstrates that HPT axis anomalies have also been observed in bipolar illness patients. This malfunction, no matter how slight, has a significant influence on the prognosis of bipolar illness, thus clinicians must be aware of the link between these two disorders (Bocchetta et al., 2016; Chakrabarti, 2011; Gutman and Nemeroff, 2003). This narrative review will emphasize how one condition, and its most often used therapy, affects the onset and prognosis of the other. To explain this relationship, we will also throw light on shared risk factors and HPT dysfunction.

Discussion

Effect on onset

Thyroid hormones are essential for neurocognitive development and function, and therefore the association between thyroid dysfunction and mood disorders has been extensively studied over the last decades. Both hypo- and hyperthyroidism have been associated with MDD and/or BD in several observational studies (Kuś et al., 2021). In fact, a recent study has noticed that the prevalence of hypothyroidism with early onset

affective disorders higher than that compared with late onset affective disorders, suggesting the role of thyroid hormones variations in the early onset of affective diseases including bipolar disorder (Zhao et al., 2022). However, it is still unclear whether these associations are causal or not (Kuś et al., 2021). It has been proven that thyroid hormones are essential for both the development and maturation of the human brain, affecting diverse events such as neuronal processing and integration, glial cell proliferation, myelination, and the synthesis of key enzymes required for neurotransmitter synthesis. In fact, thyroid deficiency during the perinatal period results in irreversible brain damage and mental retardation (Bauer et al., 2002). In addition to that, some studies have shown that thyroid hormones influence the activity of serotonin as well as the functioning of its receptors (Bauer and Whybrow, 2021). Hypothyroidism specifically has been linked with reduced 5-HT responsiveness. Also, thyroid hormone application may increase cortical serotonergic neurotransmission via two independent mechanisms: (1) a loss of auto inhibitory serotoninergic receptor type 1A (5-HT1A) receptor sensitivity mediated by T3 which results in desensitization of auto inhibitory 5-HT1A receptors, and thus increase of cortical and hippocampal serotonin release; (2) an increase in the cortical serotoninergic receptor type 2 (5-HT2) receptor sensitivity, creating a potentially independent way of increasing 5-HT transmission (Ahmed et al., 2008). Such imbalances in the monoamines level, especially serotonin and dopamine, as well as glutamate, have been implicated in bipolar disorder and extensively studied. Bipolar disease has been associated with an increase of serotonin transporter in the thalamus and other regions and reductions in the pons. In the manic phase, reduction of dopamine D1 receptor in the cerebral cortex 24 and decrease of serotonin 2 receptor has been noticed (Kato, 2019). Therefore, thyroid hormones may have a role in the development of bipolar disorder through causing such imbalances for the neurotransmitters. A recent study has shown that coinciding thyroid hormone abnormalities, cognitive dysfunction, and neurometabolic alterations of the prefrontal cortex-thalamic circuitry occur in an early course of BD II depression (Lai et al., 2021).

Effect on prognosis

In addition to what has been previously mentioned, the coinciding presence of both conditions thyroid disease and bipolar disorder may have an impact on the prognosis of either of the two conditions, or both. First, symptoms of thyroid dysfunction can be mistaken for bipolar symptoms, leading to misdiagnosis or inadequate treatment. For example, the typical symptoms of Graves' disease, which is the most common cause of hyperthyroidism in children are tachycardia, weight loss despite increased appetite, tremor, restlessness, heat intolerance, and weakness, among others. It is not uncommon that children and adolescents presenting with these symptoms are first diagnosed with a mental health disorder including mood disorders (Zader et al., 2019). Second, Hypo or hyperthyroidism can lead to exacerbation of the symptoms of bipolar disorder and make them more difficult to manage or even trigger manic episodes in individuals with bipolar disorder. It has been shown that mania is likely to be precipitated by high starting LT4 doses, though recent reports have shown that symptoms can still arise even at lower doses and with more gradual titration, especially in long-standing hypothyroidism (Yu et al., 2017). Third, several medications used for thyroid disease treatment have been shown to favor the better prognosis of bipolar disorder. High dose thyroid (HDT), defined as doses of T3 > than 50mcg and T4 > 200mcg, is remarkably helpful in the treatment of bipolar depression, often helping even the most refractory

cases reach full remission (Kelly, 2015; Kelly and Lieberman, 2009). Equally remarkable is the absence of thyrotoxic side effects when treating bipolar disorders in doses that give non-bipolar individuals significant thyrotoxicity. It is likely that HDT therapy offers more than symptomatic relief of bipolar symptoms (Kelly, 2016). In fact, it is important to mention that HDT is recommend by major treatment guidelines for both bipolar I and bipolar II depressions (Yatham et al., 2018). HDT has been shown to be as safe as or safer than most psychiatric medications used to treat the bipolar disorders though still have not gained wide acceptance yet (Kelly, 2016). Furthermore, Lithium has been a cornerstone of the treatment of acute mania and the prevention of mood episodes during the maintenance phase of the disease. Despite its narrow therapeutic range, which requires careful monitoring of drug serum levels, lithium has proven effective in treating patients, particularly in those with a family history of BD, with non-rapid cycling BD, and without comorbid substance use disorders. It appears to have neuroprotective properties, and reduces suicidal behavior (Lambert et al., 2016). However, potentially severe side effects have also been reported, including hypothyroidism particularly in middle-aged women, for whom rates as high as 37% have been reported (Yu et al., 2017). In favor of preventive measures, Current guidelines for lithium treatment in patients with BD recommend thyroid function studies prior to treatment, once or twice during the first 6 months of therapy, and every 6–12 months (Lambert et al., 2016).

Treatment interaction

Lithium

To elaborate more, the presence of thyroid diseases can complicate the treatment of bipolar diseases and vice versa. Certain medications used in bipolar diseases, such as lithium, may affect normal thyroid function or exacerbate pre-existing disease. On the other hand, some medications used in treatment of thyroid diseases, particularly levothyroxine for hypothyroidism, have potential impact on mood-stabilizing activity of psychiatric medications in bipolar diseased patients (Chakrabarti, 2011). These treatment interactions are elaborated. Lithium has been successfully used as a psychiatric medication in bipolar depressive disorder. It is currently a widely used medication for the treatment of people with unipolar and bipolar depression, as well as for the prevention of bipolar disorders and acute mania. Lithium carbonate's antithyroid effects are extensively reported in the literature, and individuals using lithium appear to have significantly greater rates of overt and subclinical hypothyroidism, goiter, and increased antibody titers than the general population and non-bipolar controls (Chakrabarti, 2011). A complicated mechanism of action underlies lithium's ability to stabilize mood. Despite its concentration gradient, lithium is actively transported by Na+/I- ions and accumulates in the thyroid gland at a concentration that is three to four times greater than that of the plasma. It can prevent the production of colloid in thyrocytes, prevent the gland from absorbing iodine, alter the composition of thyroglobulin, reduce the strength of tyrosine iodination, and prevent the conjugation of tyrosines. Additionally, it decreases the excretion of free thyroxine in the serum, which indirectly decreases the activity of 5-deiodinases type 1 and 2 and decreases their deiodination in the liver. Each of these leads to lithium-induced hypothyroidism (Czarnywojtek et al., 2020). In patients receiving long-term lithium therapy, overt hypothyroidism was noticed. Low or normal T4 levels and raised TSH levels are

recorded in other patients, suggesting that an even higher proportion of patients developing subclinical hypothyroidism. However, the development of hypothyroidism is not a contraindication to continuing lithium treatment because high rates of thyroid hypo-function continue to drop with continuous lithium treatment to resemble rates in the general population after several years (Chakrabarti, 2011). Another effect of lithium on thyroid is the elevation of antithyroid antibodies that was reported in patients with preexisting auto-antibodies, but not denovo, leading to acceleration of preexisting thyroiditis and subsequent hypothyroidism (Shine et al., 2015).

Goiter can occur up to 50% in patients receiving long-term lithium therapy (McKnight et al., 2012) and is believed to be triggered by two different mechanisms: inhibition of thyroid hormone synthesis and release, that raises serum TSH levels and enlarges the thyroid gland subsequently; or due to thyrocyte proliferation caused by the activation of tyrosine kinase by lithium ions and its impact on intracellular signaling (Lazarus et al., 2013). Lithium-induced hyperthyroidism is rarely reported in the literature, and its incidence ranges from 0.1% to 1.7% (Carmaciu et al., 2003), and it can occur in the form of asymptomatic thyroiditis, Graves' Disease or toxic nodular goiter (Nefzi et al., 2015). On the contrary, Lithium is utilized prior to the administration of 131 I therapy in hyperthyroid patients with low iodine uptake because it further improves the retention of 131 I in the thyroid gland, and thus successfully prevents transitory hyperthyroidism exacerbations. As a result, the use of lithium adjuvant therapy allows for the most satisfying results in 131 I therapy and perhaps facilitates the treatment of hyperthyroidism (Czarnywojtek et al., 2020).

Levothyroxine

A promising innovative method for treatment of bipolar disorders is to supplement regular treatment with high-dose levothyroxine (LT4). This has shown efficacy in rapid cycling and prophylaxis-resistant bipolar disorder, and with acute refractory unipolar or bipolar depression (Bauer and Whybrow, 2021). Bauer and Whybrow conducted the first open-label trial of supplemental supraphysiological T4 dosages in 11 individuals with treatment-refractory rapid cycling bipolar disease. Adjunctive T4 treatment lowered the intensity of manic and depressive episodes in both amplitude and frequency, and resulted in complete remission in some patients (Chakrabarti, 2011). Regional and whole-brain analyses recorded an increase in the activity of the right subgenual cingulate cortex, left thalamus, medial temporal lobe (right amygdala, right hippocampus), right ventral striatum, and cerebellar vermis, but with the LT4 treatment the activity was reduced. This drop was found to be strongly associated to a decrease in depression scores. We conclude that bipolar depression patients have impaired prefrontal and limbic brain function and that LT4 may boost mood through influencing circuits that involve these areas. Although the exact mechanism underlying this is yet unknown, it has been hypothesized that supplemental T4 counteracts the effects of subclinical hypothyroidism on neural adaptation. Contrary to this belief, the majority of individuals who reacted had normal thyroid function. This has given rise to a number of alternate theories, including that this advantageous impact is caused by T4 positively modulating catecholaminergic systems, reversing isolated CNS hypothyroidism, and overcoming peripheral resistance to thyroid hormones (Bauer et al., 2005).

To sum up, there is some data suggesting that a subset of people with chronic and refractory forms of bipolar disorder may benefit from T4 augmentation of mood stabilizing treatments. Such evidence is currently scarce, though, due to insufficient

total number of patients included in earlier studies and the absence of any randomized controlled trial. Because of this, this approach should only be used as a last resort in patients who haven't responded to standard therapies (Chakrabarti, 2011).

Shared risk factors

Shared risk factors were studied in order to better understand the link between these two disorders. The shared risk factors demonstrating links between thyroid dysfunction and bipolar disorder are the following: Shared genetic vulnerability, autoimmune connection, stress and environmental triggers and the prevalence of both disorders in females.

Shared genetic vulnerability

There is evidence from numerous research studies that thyroid diseases and bipolar disorder share genetic predispositions (Soheili-Nezhad et al., 2023; Boukouaci et al., 2018; Kember et al., 2018). These studies highlight how genetic variables interact in a complicated way, causing these illnesses to co-occur or be comorbid. In a genetic epidemiology study, researchers have discovered hereditary pleiotropy amongst thyroid autoimmunity and bipolar disorder. The genetic pleiotropy between thyroid autoimmunity and mood disorders suggests that specific genetic variations or genes may be involved in the onset or susceptibility of both illnesses (Kember et al., 2018). Genome studies have uncovered the links between bipolar disorder and thyroid autoimmunity. However, no such associations have been found with hypothyroidism or hyperthyroidism. These genetic correlations were found at chromosomes 6 and 12. Through their localized genetic association analysis, they discovered two genomic regions on chromosome 6: 6p22.1 and 6p22.2 (Soheili-Nezhad et al., 2023). These regions are in proximity to the major histocompatibility complex region. There is an association of these loci with the overlapping genetic factors between thyroid disorders and mood disorders, such as bipolar disorders. The MHC region is known to be important for the immune response and is linked to a number of autoimmune diseases (Jacobson et al., 2008). In addition, a specific genetic correlation locus was found on chromosome 12. This locus is adjacent to both the MHC genes and GABBR1, which encodes a GABAergic synaptic receptor. This study provides evidence of a shared genetic predisposition between bipolar disorder and thyroid autoimmune diseases, particularly in relation to chromosomes 6 and 12 (Soheili-Nezhad et al., 2023).

Another shared genetic factor for thyroid dysfunction and bipolar disorders is the CRP gene (Boukouaci et al., 2018). CRP gene plays a role in the regulation of inflammation. Different variants of this gene have been associated with numerous autoimmune and inflammatory disorders (Dehghan et al., 2011). In a study, genotyping was conducted on both BD patients and healthy subjects and the CPR gene was observed. The CRP gene's particular genetic variant of interest was rs1130864, and the study looked at whether subjects were carriers of the A allele. The presence of the CRP rs1130864 A allele was observed to have a significantly higher occurrence among the bipolar disorder (BD) patients who also had thyroid problems compared to BD patients without thyroid conditions. The results also indicated that bipolar disorder (BD) patients experiencing rapid cycling exhibited a higher occurrence of the carrier state of the CRP rs1130864 A allele compared to those without rapid cycling. This study provides

evidence for shared genetic factors, specifically the CRP gene, between thyroid dysfunction and bipolar disorder (Boukouaci et al., 2018).

Autoimmune connection

There Autoimmunity is also a shared background for both conditions. Certain thyroid disorders such as Hashimoto's thyroiditis and Graves' disease, are classified as autoimmune conditions. Similarly, autoimmune factors have been implicated in bipolar disorder, particularly in a subset of cases with co-occurring autoimmune conditions. Many studies illustrate an autoimmune connection between both disorders (Chen et al., 2021; Rosenblat and McIntyre, 2015). There is a notable rise in the incidence of bipolar disorder among individuals diagnosed with autoimmune diseases in comparison to those without autoimmune diseases [38]. Understanding the possible immunological dysfunction pathways in mood disorders is crucial for identifying novel drug targets. The high prevalence of inflammatory medical comorbidities in BD is one potential sign that suggests a link between the disease and immunological dysfunction (Rosenblat and McIntyre, 2015; Young and Grunze, 2013). Rosenblat and McIntyre (2015) has outlined potential immune dysfunctional processes in their research overview. According to this, an inflammatory reaction in the body can be brought on by a number of causes, which also include autoimmune dysfunction (Rosenblat and McIntyre, 2015). This inflammatory state involves the conversion of arachidonic acid into prostaglandin E2, which leads to the release of cytokines that cause inflammation (Kawahara et al., 2015). Activation of these cell signaling molecules stimulates microglial cells and the hypothalamic-pituitary-adrenal axis, which in turn induces the activity of indoleamine 2,3-dioxygenase. Tryptophan, an important amino acid, is transformed into kynurenine by indoleamine 2,3-dioxygenase. This is further metabolized into kynurenic acid and quinolinic acid, both of which have been associated with depressive symptoms. This process also causes a decrease in tryptophan, resulting in lower serotonin levels, an important neurotransmitter involved in mood regulation. In this study, the relationship between BD and inflammatory comorbidities has been well established; however, the cause-effect relationship is still not entirely evident (Rosenblat and McIntyre, 2015).

Female gender

Moreover, multiple studies have indicated that women have a significantly higher likelihood of developing thyroid and bipolar disorder compared to men (Parial, 2015; Bauer et al., 2014). A literature review conducted by Bauer M includes various research studies illustrating a higher prevalence of thyroid disease in women compared to men, which seems to get worse as they get older (Bauer et al., 2005). Subclinical hypothyroidism was the most frequently seen anomaly, a moderate form of underactive thyroid that can affect up to 20% of postmenopausal women. It also revealed that thyroid autoimmunity occurs at higher rates in women. Moreover, it includes citations from numerous studies that show that bipolar disorder is more common among women (Bauer et al., 2005). Bipolar I rates are approximately the same in both gender, while bipolar II is higher in females. Post-partum phase is the most sensitive one, thus some suggest giving prophylactic mood stabilizers (Parial, 2015).

Environmental factors

The onset and progression of thyroid diseases, as well as bipolar disorder, have both been linked to infections. Although the precise mechanisms are not fully known, data from numerous research suggests that infections play a role in these disorders (Aldinger and Schulze, 2017; Wiersinga, 2016). It has been suggested that infections, notably Yersinia enterocolitica, may contribute to the initiation of autoimmune thyroid disorders, particularly Graves' disease (Wiersinga, 2016). A history of suicide attempts and mental symptoms have also been linked to influenza B. Due to limited sample sizes and the incidence of viral infections during epidemics, it is crucial to be cautious when interpreting these data. Toxoplasma gondii is another virus that has been linked to bipolar illness. Studies conducted on adult bipolar patients reveal an increased incidence of Toxoplasma gondii infection among individuals with the disorder (Aldinger and Schulze, 2017). Stress is another common environmental factor that is shared between thyroid and bipolar disorder. In a review article, Wilmar M. cites various studies to highlight the role stress plays as a catalyst for the onset of Graves' disease. These studies have reported an increased rate of stressful life events in the year leading up to the diagnosis of Graves' hyperthyroidism compared to control groups (Wiersinga, 2016). Similarly, in another review Fanny Aldinger MD cites numerous research studies to demonstrate involvement of stress in the development of bipolar disorder. According to them, stress can interfere with the biological circadian rhythms that are important for mood stability. Disruptions to these rhythms can impact individuals with the bipolar disorder. Various life events were found to affect the age at which bipolar disorder begins and the course it takes over time, including unemployment, living in mixed urban rural areas and other minor life events (Aldinger and Schulze, 2017).

Smoking is a known risk factor for thyroid dysfunction (Wiersinga, 2016). However, it has not been thoroughly investigated for bipolar disorder. However, there is some evidence that maternal smoking could be a risk factor for bipolar disorder (Aldinger and Schulze, 2017). These common risk factors suggest that there is an increased likelihood of comorbidity of thyroid and bipolar disorder. The relationship between these disorders is complex and likely influenced by variables. More research is needed to further comprehend the relationship between these conditions and investigate the specific ways in which shared risk factors contribute to their development and advancement.

HPT dysfunction in bipolar disorder

Another approach was based on assessing the function of HPT in patients with bipolar disorder in order to assess this connection. The HPT axis is a fundamental component of the endocrine system that affects thyroid hormone regulation in the body. This axis is characterized by an intricate interaction between the hypothalamus, pituitary gland, and thyroid gland, each of which helps maintain healthy thyroid hormone levels. The HPT axis is controlled by a feedback loop system that maintains the balance of thyroid gland hormones according to the body's demands. Thyroid releasing hormone (TRH) stimulates the pituitary gland to produce thyroid stimulating hormone (TSH). TSH will then increase the production of T3 and T4. TSH response to TRH is exaggerated in hypothyroidism and blunted in hyperthyroidism (Ortiga-Carvalho et al., 2011).

For many years, the relationship between this axis disruption and a variety of mental diseases was a hot study area. Bipolar disorder individuals have been shown to have HPT axis abnormalities. Disruptions in the HPT axis may contribute to symptom severity or treatment response in illnesses such as bipolar disorder, emphasizing the

necessity of investigating these complex interrelationships. Both instances were seen. Some bipolar illness patients, whether in mania, depression, or rapid cycling, have a reduced TSH response to TRH, indicating hyperthyroidism. Others, on the other hand, display an increased TSH response to TRH, indicating hypothyroidism. Rapid cycling is connected with greater morbidity in bipolar individuals. When TSH levels are measured in such individuals, higher TSH levels and an exaggerated TSH response to TRH are consistent with the high incidence of subclinical hypothyroidism reported in this group of people. This shows that rapid cycling bipolar individuals have a greater frequency of hypothyroidism than other bipolar subtypes. Furthermore, Zhong S. in his study showed that individuals with bipolar II depression had lower TSH levels but greater than those with bipolar I. According to Zhong S., this might be utilized to distinguish between bipolar I and II during diagnosis (Zhong et al., 2019; Chakrabarti, 2011; Gutman and Nemeroff, 2003). In a comparative perspective, T3 and free T4 where measured in patients during manic and depressive episodes. During manic episode, the level of these hormones was higher indicating that the severity of HPT dysfunction is worse (Zhao et al., 2021).

Coexistance of these condition

Finally, dealing with patients suffering from the two illnesses is a bit competitive. Diagnosing thyroid disease and bipolar disorder involves a thorough evaluation of clinical symptoms and specific biochemical tests. By closely monitoring thyroid function and distinguishing between different thyroid conditions, healthcare professionals can make accurate diagnoses (Khan et al., 2023). Likewise, adhering to the DSM-5 framework helps differentiate between Bipolar I and Bipolar II disorders based on specific episode characteristics. Following these diagnostic approaches allows clinicians to implement appropriate treatment strategies, leading to better patient outcomes and overall well-being (Jain and Mitra, 2020b; Bobo, 2017).

Understanding the link between endocrine and mental illnesses is essential for improving the patient's quality of life (Mishra et al., 2022). This link is bidirectional; a patient with primary endocrine disease might exhibit neuropsychiatric symptoms, and mental diseases can produce symptoms due to hormone disruption (Salvador et al., 2021). Treatment of a patient with hypothyroidism or hyperthyroidism without improvement in psychiatrist symptoms indicates a fundamental psychiatric disorder (Mishra et al., 2022; Salvador et al., 2021). Patients suffering from mental disorder, such as bipolar, will need to be tested for endocrine disease, such as thyroid hormone levels and other hormones. The combination of these two disorders is undoubtedly associated with worse patient quality of life, decreased treatment adherence, and increased care expenditures. In such circumstances, strong collaboration between endocrinologists and psychiatrists is essential for a thorough examination, precise diagnosis, and appropriate treatment plan that addresses both illnesses (Salvador et al., 2021).

Conclusion

The complex interaction between thyroid function and bipolar illness emphasizes the inescapable link between physical and mental well-being. Thyroid hormone abnormalities, according to emerging research, can profoundly impact the course and severity of bipolar disease, altering mood swings, treatment responsiveness, and overall

quality of life for afflicted persons. As our understanding of the interaction of these two complex systems grows, healthcare providers are provided with new opportunities for more focused and comprehensive treatment methods. The fact that these two conditions share common risk factors and do have treatment interactions increased the focus on this topic. Furthermore, HPT dysfunction was investigated in various types and forms of BD in order to be better aware of prospective scenarios and diagnoses.

Acknowledgement

The research study is self-funded.

Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

[1] Ahmed, O.M., El-Gareib, A.W., El-Bakry, A.M., Abd El-Tawab, S.M., Ahmed, R.G. (2008): Thyroid hormones states and brain development interactions. – International Journal of Developmental Neuroscience 26(2): 147-209.

[2] Aldinger, F., Schulze, T.G. (2017): Environmental factors, life events, and trauma in the course of bipolar disorder. – Psychiatry and Clinical Neurosciences 71(1): 6-17.

[3] Bauer, M., Whybrow, P.C. (2021): Role of thyroid hormone therapy in depressive disorders. – Journal of Endocrinological Investigation 44(11): 2341-2347.

[4] Bauer, M., Glenn, T., Pilhatsch, M., Pfennig, A., Whybrow, P.C. (2014): Gender differences in thyroid system function: relevance to bipolar disorder and its treatment. – Bipolar Disorders 16(1): 58-71.

[5] Bauer, M., London, E.D., Rasgon, N., Berman, S.M., Frye, M.A., Altshuler, L.L., Mandelkern, M.A., Bramen, J., Voytek, B., Woods, R., Mazziotta, J.C. (2005): Supraphysiological doses of levothyroxine alter regional cerebral metabolism and improve mood in bipolar depression. – Molecular Psychiatry 10(5): 456-469.

[6] Bauer, M., Heinz, A., Whybrow, P.C. (2002): Thyroid hormones, serotonin and mood: of synergy and significance in the adult brain. – Molecular Psychiatry 7(2): 140-156.

[7] Bobo, W.V. (2017): The diagnosis and management of bipolar I and II disorders: clinical practice update. – In Mayo Clinic Proceedings, Elsevier 92(10): 1532-1551.

[8] Bocchetta, A., Traccis, F., Mosca, E., Serra, A., Tamburini, G., Loviselli, A. (2016): Bipolar disorder and antithyroid antibodies: review and case series. – International Journal of Bipolar Disorders 4: 1-18.

[9] Boukouaci, W., Oliveira, J., Etain, B., Bennabi, M., Mariaselvam, C., Hamdani, N., Manier, C., Bengoufa, D., Bellivier, F., Henry, C., Kahn, J.P. (2018): Association between CRP genetic diversity and bipolar disorder comorbid complications. – International Journal of Bipolar Disorders 6(1): 1-6.

[10] Carmaciu, C.D., Anderson, C.S., Lawton, C.A. (2003): Thyrotoxicosis after complete or partial lithium withdrawal in two patients with bipolar affective disorder. – Bipolar Disorders 5(5): 381-384.

[11] Carvalho, A.F., Firth, J., Vieta, E. (2020): Bipolar disorder. – New England Journal of Medicine 383(1): 58-66.

[12] Chen, M., Jiang, Q., Zhang, L. (2021): The prevalence of bipolar disorder in autoimmune disease: a systematic review and meta-analysis. – Ann Palliat Med 10(1): 350-361.

[13] Chakrabarti, S. (2011): Thyroid functions and bipolar affective disorder. – Journal of Thyroid Research 14p.
[14] Czarnywojtek, A., Zgorzalewicz-Stachowiak, M., Czarnocka, B., Sawicka-Gutaj, N., Gut, P., Krela-Kazmierczak, I., Ruchala, M. (2020): Effect of lithium carbonate on the function of the thyroid gland: mechanism of action and clinical implications. – Journal of Physiology & Pharmacology 71(2): 191-199.
[15] Dehghan, A., Dupuis, J., Barbalic, M., Bis, J.C., Eiriksdottir, G., Lu, C., Pellikka, N., Wallaschofski, H., Kettunen, J., Henneman, P., Baumert, J. (2011): Meta-analysis of genome-wide association studies in> 80 000 subjects identifies multiple loci for C-reactive protein levels. – Circulation 123(7): 731-738.
[16] Gutman, D.A., Nemeroff, C.B. (2003): Persistent central nervous system effects of an adverse early environment: clinical and preclinical studies. – Physiology & Behavior 79(3): 471-478.
[17] Jacobson, E.M., Huber, A., Tomer, Y. (2008): The HLA gene complex in thyroid autoimmunity: from epidemiology to etiology. – Journal of Autoimmunity 30(1-2): 58-62.
[18] Jain, A., Mitra, P. (2020a): Bipolar affective disorder. – StatPearls Publishing 13p.
[19] Jain, A., Mitra, P. (2020b): Catatonic schizophrenia. – StatPearls Publishing 8p.
[20] Kato, T. (2019): Current understanding of bipolar disorder: Toward integration of biological basis and treatment strategies. – Psychiatry and Clinical Neurosciences 73(9): 526-540.
[21] Kawahara, K., Hohjoh, H., Inazumi, T., Tsuchiya, S., Sugimoto, Y. (2015): Prostaglandin E2-induced inflammation: Relevance of prostaglandin E receptors. – Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids 1851(4): 414-421.
[22] Kelly, T. (2016): A hypothesis on the mechanism of action of high-dose thyroid in refractory mood disorders. – Medical Hypotheses 97: 16-21.
[23] Kelly, T. (2015): An examination of myth: a favorable cardiovascular risk-benefit analysis of high-dose thyroid for affective disorders. – Journal of Affective Disorders 177: 49-58.
[24] Kelly, T., Lieberman, D.Z. (2009): The use of triiodothyronine as an augmentation agent in treatment-resistant bipolar II and bipolar disorder NOS. – Journal of Affective Disorders 116(3): 222-226.
[25] Kember, R.L., Hou, L., Ji, X., Andersen, L.H., Ghorai, A., Estrella, L.N., Almasy, L., McMahon, F.J., Brown, C., Bućan, M. (2018): Genetic pleiotropy between mood disorders, metabolic, and endocrine traits in a multigenerational pedigree. – Translational Psychiatry 8(1): 12p.
[26] Khan, M., Jose, A., Sharma, S. (2023): Physiology, Parathyroid Hormone. – StatPearls Publishing 6p.
[27] Kuś, A., Kjaergaard, A.D., Marouli, E., Del Greco M, F., Sterenborg, R.B., Chaker, L., Peeters, R.P., Bednarczuk, T., Åsvold, B.O., Burgess, S., Deloukas, P. (2021): Thyroid function and mood disorders: a Mendelian randomization study. – Thyroid 31(8): 1171-1181.
[28] Lai, S., Zhong, S., Zhang, Y., Wang, Y., Zhao, H., Chen, G., Chen, F., Shen, S., Huang, H., Jia, Y. (2021). Association of altered thyroid hormones and neurometabolism to cognitive dysfunction in unmedicated bipolar II depression. – Progress in Neuro-Psychopharmacology and Biological Psychiatry 105: 10p.
[29] Lambert, C.G., Mazurie, A.J., Lauve, N.R., Hurwitz, N.G., Young, S.S., Obenchain, R.L., Hengartner, N.W., Perkins, D.J., Tohen, M., Kerner, B. (2016): Hypothyroidism risk compared among nine common bipolar disorder therapies in a large US cohort. – Bipolar Disorders 18(3): 247-260.
[30] Lazarus, J.H., Kirov, G., Harris, B.B. (2013): Effect of lithium on the thyroid and endocrine glands. – In Lithium in Neuropsychiatry, CRC Press 11p.

[31] McKnight, R.F., Adida, M., Budge, K., Stockton, S., Goodwin, G.M., Geddes, J.R. (2012): Lithium toxicity profile: a systematic review and meta-analysis. – The Lancet 379(9817): 721-728.
[32] Mishra, K.K., Sawant, N., Garg, S. (2022): Management of psychiatric disorders in patients with endocrine disorders. – Indian Journal of Psychiatry 64(Suppl 2): S402-S413.
[33] Nefzi, R., Abid, Y., Ouanes, S., Johnson, I., Ghachem, R. (2015): Lithium Associated Hyperthyroidism. – European Psychiatry 30: 1p.
[34] Ortiga-Carvalho, T.M., Chiamolera, M.I., Pazos-Moura, C.C., Wondisford, F.E. (2011): Hypothalamus-pituitary-thyroid axis. – Comprehensive Physiology 6(3): 1387-1428.
[35] Parial, S. (2015): Bipolar disorder in women. – Indian Journal of Psychiatry 57(Suppl 2): 16p.
[36] Plans, L., Barrot, C., Nieto, E., Rios, J., Schulze, T.G., Papiol, S., Mitjans, M., Vieta, E., Benabarre, A. (2019): Association between completed suicide and bipolar disorder: a systematic review of the literature. – Journal of Affective Disorders 242: 111-122.
[37] Rosenblat, J.D., McIntyre, R.S. (2015): Are medical comorbid conditions of bipolar disorder due to immune dysfunction? – Acta Psychiatrica Scandinavica 132(3): 180-191.
[38] Salvador, J., Gutierrez, G., Llavero, M., Gargallo, J., Escalada, J., López, J. (2021): Endocrine disorders and psychiatric manifestations. – Endocrinology and Systemic Diseases 34p.
[39] Shine, B., McKnight, R.F., Leaver, L., Geddes, J.R. (2015): Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. – The Lancet 386(9992): 461-468.
[40] Soheili-Nezhad, S., Sprooten, E., Tendolkar, I., Medici, M. (2023): Exploring the Genetic Link Between Thyroid Dysfunction and Common Psychiatric Disorders: A Specific Hormonal or a General Autoimmune Comorbidity. – Thyroid 33(2): 159-168.
[41] Vigo, D., Thornicroft, G., Atun, R. (2016): Estimating the true global burden of mental illness. – The Lancet Psychiatry 3(2): 171-178.
[42] Wiersinga, W.M. (2016): Clinical relevance of environmental factors in the pathogenesis of autoimmune thyroid disease. – Endocrinology and Metabolism 31(2): 213-222.
[43] Yatham, L.N., Kennedy, S.H., Parikh, S.V., Schaffer, A., Bond, D.J., Frey, B.N., Sharma, V., Goldstein, B.I., Rej, S., Beaulieu, S., Alda, M. (2018): Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. – Bipolar Disorders 20(2): 97-170.
[44] Young, A.H., Grunze, H. (2013): Physical health of patients with bipolar disorder. – Acta Psychiatrica Scandinavica 127: 3-10.
[45] Yu, M.G., Flores, K.M., Isip-Tan, I.T. (2017): Acute mania after levothyroxine replacement for hypothyroid-induced heart block. – Case Reports 3p.
[46] Zader, S.J., Williams, E., Buryk, M.A. (2019): Mental health conditions and hyperthyroidism. – Pediatrics 144(5): 7p.
[47] Zhao, Y., Wang, N., Chen, J., Guan, Q., Yuan, X., Shen, Y., Zhang, X., Hao, W., Zhang, R., Zhai, D. (2022): Association between early-onset affective disorders and hypothyroidism in a larger number of psychiatric drug-free patients. – Journal of Affective Disorders 299: 31-36.
[48] Zhao, S., Zhang, X., Zhou, Y., Xu, H., Li, Y., Chen, Y., Zhang, B., Sun, X. (2021): Comparison of thyroid function in different emotional states of drug-naïve patients with bipolar disorder. – BMC Endocrine Disorders 21: 1-7.
[49] Zhong, S., Chen, G., Zhao, L., Jia, Y., Chen, F., Qi, Z., Huang, L., Wang, Y. (2019): Correlation between intrinsic brain activity and thyroid-stimulating hormone level in unmedicated bipolar II depression. – Neuroendocrinology 108(3): 232-243.