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REVIEW ARTICLE

Structural and Functional Effects of Lithium Carbonate on the Thyroid Gland: A Review

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ABSTRACT

Lithium carbonate is considered the gold standard to treat and prevent bipolar disorders, especially in developing countries. The treatment is prolonged, which may be associated with thyroid toxicities of a variable nature. The present mini-review is written to explore the current status of knowledge regarding the impact of Lithium treatment on the structure and function of the thyroid gland which will help the clinicians in better management of patients on lithium therapy. PubMed databases and Google Scholar were searched for structural and functional effects of Lithium carbonate therapy on the thyroid gland. The pathophysiology of Lithium carbonate is intricate yet may incorporate increasing intrathyroidal iodine content, repressing the formation and release of thyroid hormones, modifying the hypothalamus-pituitary axis, and Wnt/β-catenin flagging. Goiter is commonly observed in 50% of patients and 25% of patients have hypothyroidism. Patients receiving lithium therapy have less incidence of hyperthyroidism than the general population. Lithium, given over a prolonged period, causes large and mini follicular goiter with hyperplastic epithelium and hyperchromatic nuclei, hyperplasia of stroma with expanded vascularity, sometimes hemorrhages, and finally may lead to thyroiditis, like the picture. Sometimes it may lead to eosinophilic infiltrates into the stroma of the thyroid gland, known as Hurthle cell infiltrate, which is the precursor of thyroid carcinoma. Thus, it is exhorted that those on lithium treatment ought to be periodically assessed for thyroid dysfunction.

KEYWORDS

• Lithium carbonate • Thyroiditis • Hypothyroidism, • Goiter • Hurthle cell

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INTRODUCTION

Lithium carbonate (Li_2CO_3), a salt form of Lithium, is frequently used in the management of acute mania and prophylaxis of mania in bipolar depressive disorder.[1,2] The regular therapeutic utilization of lithium additionally includes its use as an augmenting agent in depression, hostility, schizoaffective confusion, motivation control problems, a lack of ability to concentrate consistently jumble, dietary issues, and different subgroups of alcoholism. Apart from this, the use of Lithium has also been used in other medical disorders, like rare headaches disorder cluster headaches, and some dermatological disorders (eczematoid dermatitis, seborrheic dermatitis, genital herpes, etc.).[3,4] Though, as of now use of Lithium carbonate in psychiatric disorders has dwindled, still the drug continues to be used and discussed in literary forums. In the previous year, some articles regarding Lithium appeared in the *Indian Journal of Psychological Medicine*.[1,3] When we discuss the pathophysiology, clinical course, and treatment of bipolar disorder, the Thyroid gland, and the associated hypothalamic-pituitary-thyroid (HPT) axis have a major role to play. Also, the impact of long-term lithium therapy on the thyroid gland is one of the primary side effects of therapy with this drug. As compared to the plasma concentration, lithium is accumulated in the thyroid gland at higher concentrations.[4] In the present review, the PubMed database and Google Scholar were used to search for structural and functional effects of Lithium carbonate therapy on the thyroid gland up to December 2021. Keywords used to search were lithium therapy, goiter, hyperthyroidism, hypothyroidism, thyroiditis, Bipolar disorder and lithium therapy, lithium and structure of thyroid gland. The article connects the perspective of the basic science regarding the structural and functional effects of Lithium carbonate on the thyroid gland with the clinical sciences.

Pharmacokinetics

Lithium (Greek word lithos meaning stone) with the symbol Li, is an alkaline silver-white metal soft in consistency with an atomic number of three. This element is considered to be the lightest metal with the lowest density under the standard conditions of temperature and pressure.[5] Lithium reaches its peak plasma level in 2-4 hrs. After it is readily absorbed via oral administration. After the absorption of lithium carbonate, 95% is excreted in urine; 4-5% in sweat, and about 1% in feces. [1,6] Lithium has a very high affinity to very low-molecular-weight ligands but binds poorly to high and low-molecular-weight plasma proteins.[7] To reach the level of steady concentration in blood and expected therapeutic responses, it may require almost 6-8 days, as it passes slowly from an extracellular compartment to intracellular space.

Lithium is well dispersed in the human organs; it is well concentrated in the tissues like the brain, kidney, liver, thyroid, bone, and muscle cells against a concentration gradient.[1] Lithium is additionally widely scattered inside the focal sensory system and shows interactions with different synapses, diminishing norepinephrine and expanding the amalgamation of serotonin. It has been accounted for that lithium can change the glucose metabolic set point and repress phosphoglucomutase.[8] An increase in fructose 2, 6- diphosphate levels has been seen with lithium treatment but it does not affect cytochrome P-450.[9] Many studies on animals and humans have revealed that lithium intensifies the intrathyroidal iodine content and impedes the coupling of iodotyrosine residues to form iodothyronine form. For the maintenance treatment of patients with bipolar disorder, Lithium is considered the gold standard. It is a drug with a very narrow therapeutic index, so to enhance its effectiveness and reduce the toxicity and adverse drug effects; careful therapeutic drug monitoring is required. Close and acceptable monitoring of patients on lithium therapy is required for optimum dose up and initial identification of patients with (potential) adverse drug effects.[10,11]

Mechanism of Lithium on the thyroid gland

Because of the high vascular supply of the thyroid gland, Lithium tends to get exceedingly concentrated in it against a strong concentration gradient and interferes with the synthesis and metabolism of thyroxine hormone.[4,12] The unique pathway of synthesis and transport of thyroid hormone in the blood

and its subsequent metabolism offer abundant targets for drug interaction.[13] Lithium may inhibit the coupling of iodotyrosine residues in the formation of thyroxine (T4) and triiodothyronine (T3), and subsequent release of these hormones into the blood.[14] The accurate mechanism behind this process is still not well established, what we know is that the pinocytosis of colloid from the lumen of the follicles is reduced, leading to inhibition of colloid droplet formation and finally the blockade of cellular events which is mediated by cyclic adenosine monophosphate (cAMP). This cascade may be possible due either to directly inhibiting adenyl cyclase as a substitute for cationic enzymatic co-factors (e.g. Na+ or K+) or through the blockade of cAMP at any step in the cellular microenvironment.[15.16] Here, lithium is seen to influence deiodinase activity, which is a group of enzymes that either activate thyroid hormones by promoting the conversion of T4 to T3 or inactivate thyroid hormones by converting either T4 to reverse triiodothyronine (rT3) or T3 to inactive di iodothyronine (T2).[16] Predominantly, lithium is said to inhibit the type II deiodinase enzyme (5'-monodeiodinase), which carries out the peripheral conversion of T4 to T3.[17] In addition, lithium can lead to an increase in intrathyroidal iodine content, which prevents the release of T4 and T3 through a feedback mechanism.[18] The initial fall in serum tetraiodothyronine (T4) and triiodothyronine (T3) is because of the inhibition of organic iodine formation and inhibition of thyroid hormone secretion.[19]There may also be an effect on the hypothalamic-pituitary axis as lithium gets concentrated in the pituitary gland and hypothalamus as well.[20]

Effects of lithium on the thyroid gland (structural and functional)

The structural and functional effects of Lithium carbonate on the thyroid gland have been studied by various researchers from time to time.[4,5,21] Lithium gets concentrated in the thyroid gland by active transport against the concentration gradient.[12] Animal and human studies have shown that lithium leads to an increase in iodine content within the thyroid gland, which hinders the coupling of iodotyrosine deposits to form iodothyronine. Patients on long-term lithium therapy have a chance to develop goiter, hyperthyroidism and hypothyroidism which can be manifested as macro or micro-follicular goiter on histological examination.[21] The goiter formation occurs because of the proliferation of thymocytes which occurs because of the enactment of the proliferative tyrosine kinase and Wnt/beta-catenin flagging pathways.[21] The thyroid follicles are lined with hyperplastic epithelial cells having hyperchromic nuclei and there may be augmented vascularity followed by rare interfollicular hemorrhages present within the stroma.[21-24] If there was a prior subclinical thyroid problem the effects of lithium on the thyroid organ would be more pronounced.[7] It has been observed in various studies that the majority of patients who develop hypothyroidism after lithium therapy have either thyroid peroxidase antibodies and/or an exaggerated stimulation of TSH. Different studies have shown varieties in counter-acting agent titers over lithium treatment, contradicting the likelihood that lithium increases these antibodies. It is conceivable that the uptake of iodine by the thyroid gland is reduced because of lithium, it likewise impedes the coupling of iodotyrosinase and meddles with the release of hormones from the thyroid gland. The lympho-eosinophilic infiltrates have been reported in some clinical cases, which bear a resemblance to the picture of Hashimoto thyroiditis.[21] These eosinophilic infiltrates are known as Hurthle cell infiltrates. Hurthle cells are recognized as enlarged epithelial cells having profuse eosinophilic cytoplasm because of transformed mitochondria. These cells are present in Hashimoto's thyroiditis which may change into an adenoma, having the capacity to become malignant.[25,26] Because of the lithium carbonate treatment cell infiltration has been recognized that is steady with immune system thyroiditis, as certain investigations have announced an increment in the frequency of thyroid antibodies in the blood tests of certain patients who are put on lithium treatment. In animal models, it has been observed that Lithium administered over a prolonged period causes macro and micro follicular goiter with hyperplastic epithelium and hyperchromatic nuclei. In addition, there can be hyperplasia of the stroma with increased vascularity and sometimes hemorrhages in between the follicles. Because of cellular infiltration into the thyroid gland stroma, there can be thyroiditis like picture (*Figure 1*).[21]

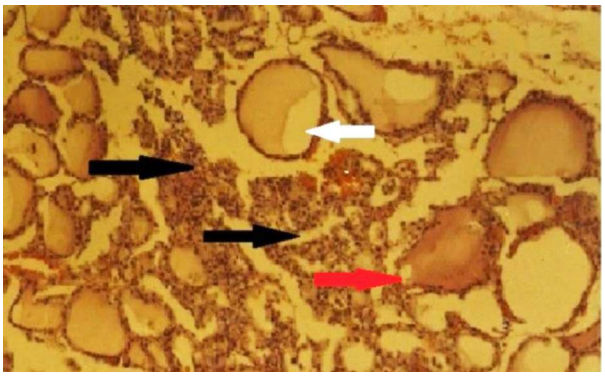

Figure 1: Photomicrograph of the thyroid gland in an animal model (rat) after 12 weeks of lithium therapy, showing vacuolations of thyroid follicles (white arrow), lymphocytic infiltrations (black arrow), and disruption of thyroid follicles (red arrow) (H and E x 100).

Clinical correlation

In many clinical studies, the most as often as possible experienced anomaly associated with lithium was a goiter. The frequency assessed was estimated to be 40-50% of the patients treated with lithium.[21] Lithium is related to a 7% (2-15%) increase in clinical hypothyroidism, a 5% increase in the risk of goiter, and infrequently (0.7%) hyperthyroidism among those who consume it. Subclinical hypothyroidism is viewed as more normal than clinical hypothyroidism, and minor elevation of thyroid-stimulating hormone (TSH) may standardize without treatment. Chemical hypothyroidism with lithium is around about 50%, where lithium gets accumulated in the thyroid gland against the concentration gradient by a dynamic active transport mechanism.[12] Lithium inhibits the glandular release of thyroid hormones (T4 and T3) by diminishing the endocytosis of thyroid chemical-laden thyroglobulin on the luminal side of the thyroid follicle; this causes a transient increase in the thyrotropin levels in more than a third of lithium carbonate-treated patients. The glandular release inhibition interceded by cyclic adenosine monophosphate (cAMP) takes place inside the thyrocytes. The blockage of iodine take-up occurs and its organification inside the thyroid organ occurs on account of higher portions of lithium within the follicles. Without thyrotropin incitement, lithium was found to rejuvenate the multiplication of cells. However, affected by thyrotropin, lithium inhibited thyrocyte multiplication at higher concentrations.[27] Lithium affects many aspects of cellular and humoral immunity in vitro as well as in vivo. The prevalence of thyroid-specific antibodies among lithium-treated patients fluctuates across studies. Women have shown enhanced expression of thyroid autoimmunity than men, especially in the middle-aged group. Thyroid autoimmunity has been found associated with affective disorders, irrespective of lithium use. So, it is unclear whether lithium treatment itself can lead to thyroid autoimmunity. As lithium is said to inhibit thyroid hormone release from the thyroid gland, it can help as an adjunct therapy in managing severe hyperthyroidism. The prevalence of thyroid explicit antibodies among lithium-treated patients vacillates across contemplate studies. Women have shown enhanced articulation and expression of thyroid autoimmunity than men, and it is more found in the moderately aged population. So likewise, thyroid autoimmunity has been found related to affective disorders, irrespective of lithium use. Along these lines, it is uncertain whether lithium as such can incite thyroid autoimmunity or not. As lithium is said to hinder thyroid hormone delivery from the thyroid gland, it very well may be utilized as an adjuvant treatment in overseeing serious hyperthyroidism. It also intensifies thyroidal radioiodine retention and might be much more effective in the decrease of administered action in hyperthyroidism.[27] There is evidence that female patients with rapid cycling and patients with auto-immune thyroiditis are prone to lithium-induced hypothyroidism. Lithium-induced goiter is typically described by smooth, small, and non-tender nodules; sometimes, nodules may regress with time. The reason for lithium-initiated thyrotoxicosis isn't clearly understood; some authorities have speculated that lithium may directly cause autoimmune reactions.[27] Because of the active transport of Na^+/I^- ions lithium is accumulated in the thyroid gland at a concentration 3-4 times higher than that in the plasma irrespective of the concentration gradient.[28] Lithium induces sporadic thyroiditis by direct toxic effects. It directly damages thyroid cells, with consequent release of thyroglobulin.[29] Before starting lithium prophylaxis in bipolar patients, assessment of thyroid function should include measurement of serum concentrations of TSH, FT3, FT4, AbTPO, and ultrasonic scanning.[30]

CONCLUSION

Lithium is a successful and cost-effective prescription, regularly used in the treatment of bipolar psychiatric diseases in developing countries. Lithium causes goiter and hypothyroidism in many patients who are on long-term medication. It leads to an increased titer of antibodies and thus exacerbates preexisting autoimmune thyroiditis. Lithium administered over a prolonged period causes macro and micro follicular goiter with hyperplastic epithelium and hyperchromatic nuclei. In addition, there can be hyperplasia of the stroma with increased vascularity and sometimes hemorrhages in between the follicles. Because of cellular infiltration into the thyroid gland stroma, there can be a thyroiditis-like picture. The presence of thyroid function abnormalities may not make up an outright contraindication to lithium treatment but should be managed with early and vigorous treatment. It is proposed that at the onset of lithium treatment thyroid capacity and function should be taken into consideration. Subsequently, thyroid function needs to be assessed every 6-12 months.

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