Advances In Therapy® | *Volume 19 No. 4 July/August 2002*

Thyroid Abnormalities in Lithium-Treated Patients

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ABSTRACT

The purposes of this study were to evaluate possible effects of lithium on thyroid function, determine the relationship among thyroid function, antibody levels, and demographic/clinical variables, and establish the prevalence of lithium-related goiter, clinical hypothyroidism, and thyroid antibodies. Forty-nine patients who had taken lithium for a minimum of 6 months were enrolled, as were 46 age- and sex-matched controls naïve to lithium use. Blood was drawn to measure levels of total and free T3, T4, thyroid-stimulating hormone (TSH), and antimicrosomal and antithyroglobulin antibodies. Thyroid volume was quantified on ultrasonography. Twenty-nine patients in the study group (59%) and 7 in the control group (15%) had goiter. Free T4 levels were significantly lower in the study group, and TSH levels were higher. Among lithium-treated patients, 12% had clinical hypothyroidism and 2% had subclinical hypothyroidism. Thyroid antibodies were present in 23% of the lithium group and 15% of the control group. No significant relationship was apparent among thyroid antibodies, thyroid volume, and clinical hypothyroidism. Our findings suggested that along with its goitrogenic effects, lithium inhibited thyroid function and led to clinical hypothyroidism. Older age, family history of thyroid disorders, and the presence of thyroid antibodies significantly influenced thyroid function in the present study.

Keywords: lithium; thyroid; hypothyroidism; goiter; thyroid antibodies

INTRODUCTION

The antithyroid effect of lithium, a widely used mood stabilizer, has been recognized since the 1970s[1-3] in cell-culture, experimental, and clinical studies.[4] Disorders linked to lithium treatment range from mild disturbances in

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thyroid-stimulating hormone (TSH) response to severe myxedema; the most frequent dysfunctions are goiter and subclinical and clinical hypothyroidism. Hyperthyroidism induced by lithium is rare.[4-6]

Lithium affects the synthesis, release, and metabolism of thyroid hormone and TSH and the iodinization of thyrosine in various ways, but the result is inhibition of thyroid hormone release from the gland, the critical mechanism underlying hypothyroidism, goiter, and other thyroid disturbances.[6-8] Increases in TSH release and in iodine reuptake are among the mechanisms to compensate for this effect of lithium. When these mechanisms fail, a thyroid disorder results.[3,5,8]

High levels of thyroid antibodies in patients treated with lithium are among the indicators of autoimmune mechanisms in lithium-induced hypothyroidism,[9-14] although the prevalence of thyroid antibodies in patients with this condition is similar to that reported for the general population (5%–15%). These contradictory findings emphasize the need for further studies.[15,16]

Risk factors for lithium-related thyroid disorders include a thyroid disorder before lithium treatment, family history of thyroid disorders, female sex, increased age, long duration of lithium treatment, smoking, residence in an endemic goiter area, and concomitant use of carbamazepine.[9,14,17,18] A thyroid disorder that antedates lithium treatment is believed to be the most important predisposing factor.[1,5]

The purposes of this study were to evaluate possible effects of lithium on thyroid function, determine the prevalence of goiter, thyroid antibodies, and clinical and subclinical hypothyroidism, and investigate the association of these abnormalities with certain demographic and clinical features.

PATIENTS AND METHODS

Patients

The study enrolled 95 patients: 49 in the lithium group and 46 in the control group. Patients in the lithium group were between 19 and 67 years of age (mean, 39.8 ± 11.6 years), had a diagnosis of bipolar disorder-I, schizoaffective disorder, or recurrent major depression, according to *DSM-IV* criteria,[19] and had been receiving lithium for the past 6 months. At the time of inclusion in the study, all patients were euthymic and not suffering from any affective episodes, as determined in a clinical interview conducted by the authors. Exclusion criteria for this group were thyroid dysfunction before lithium treatment; use of a mood stabilizer other than lithium; treatment with thyroid hormone, antithyroid drugs, or glucocorticoids; current or prior substance or alcohol abuse or dependence; and systemic or neurologic disorders. The age- and sex-matched patients in the control group had newly diagnosed somatoform disorders,[19] had not received any psychotropic drugs prior to study entry, and had no history of thyroid disorders or thyroid treatment. All patients in both groups gave informed consent before participating in the study.

Assessment of Thyroid Function and Thyroid Antibodies

Blood samples were drawn from both groups to determine thyroid function and to measure thyroid antibodies and serum lithium levels. An automated chemiluminescent immunoassay system (ACS 180; Bayer, Tarrytown, NY, USA) was used to

quantify serum concentrations of TSH, total (tT3) and free triiodothyrosine (fT3), and total (tT4) and free thyroxine (fT4). The normal laboratory ranges were as follows: tT3, 85–185 ng/dL; fT3, 2.3–4.2 ng/dL; tT4, 4.5–12.5 µg/dL; fT4, 0.89–1.8 ng/dL; and TSH, 0.47–5.01 µIU/mL. Serum concentrations of fT3, fT4, and TSH were used to classify patients as having clinical or subclinical hypothyroidism or hyperthyroidism. Hyperthyroidism was defined by elevated serum level of fT4 and suppressed TSH in combination with clinical signs. Clinical hypothyroidism was defined as the presence of elevated TSH and suppressed fT4 serum levels in combination with clinical features. Subclinical hypothyroidism was diagnosed by suppressed TSH but normal fT4 levels.

Thyroid antimicrosomal antibodies (AMA) and thyroid antiglobulin antibodies (TAG) (normal range of ratios, 0–1.1) were analyzed by means of the microELISA method (Microsomal Ig G, A, M ELISA; Clark Laboratories, Jamestown, NY, USA) to detect autoimmune phenomena.

Blood was drawn from all participants in the morning after an overnight fast. All serum samples were immediately frozen at –16°C, maintained at that level until study end, and analyzed at the same time to avoid any confounding factor based on laboratory standardization.

Ultrasound Examination

Thyroid ultrasonography was carried out with an RTX scanner (400 model USG; General Electric, Waukesha, Wisc, USA) with a 7.5-mHz linear transducer. On examination, patients were supine with the neck in hyperextension. Both thyroid lobes were evaluated in three dimensions, and thyroid volume was estimated automatically by way of an ellipsoid method programmed in the scanner's software. A volume in excess of 22,000 mm^3 constituted enlargement.

Statistical Analysis

The χ^2 test or Fisher's exact test was used to analyze categorical variables; *t* tests and one-way analysis of variance (ANOVA) were performed for continuous variables. When the parametric hypothesis was not met, a nonparametric Mann-Whitney *U* test was used. All *P* values were two tailed, with statistical significance set at less than .05. SPSS® software, version 9.0 (Chicago, Ill, USA) was used for all analyses.

RESULTS

Demographic and Clinical Data

The 49 lithium-treated patients (21 men [43%], 28 women [57%]) had a mean age of 39.8 ± 11.6 years (range, 19 to 67 years). The control group of 46 (13 men [28%], 33 women [72%]) had a mean age of 36.1 ± 12.6 years. No significant between-group differences were found for age ($P = .138$) or sex ($P = .125$). In the lithium group, 35 patients (72%) had bipolar disorder-I, 6 (12%) had schizoaffective disorder, and 8 (16%) had recurrent major depression.

The average duration of lithium treatment in this group was 4.6 ± 3.6 years; 16 patients (33%) used lithium for fewer than 2 years, 17 (34%) for 2 to 5 years, and

16 patients for more than 5 years. The mean serum lithium level on entry was 0.69 ± 0.13 mEq/L, with an average dose of 1016 ± 147 mg/d (range, 600–1200 mg/d) for the entire group.

In the lithium group, 29 patients (59%) were not using any concomitant medications; 11 (22%) were using antidepressant drugs; 9 (18%) were taking antipsychotics. Thirty-one (63.2%) were smokers, and 10 (20.4%) had a family history of thyroid disorders.

Thyroid Function

Compared with control group values, fT3 and tT4 levels were significantly decreased and TSH levels were significantly increased in the lithium group (Table 1). Despite these differences, all thyroid values were within normal ranges for both groups.

Table 1. Thyroid Values* in Lithium and Control Groups

Value	Lithium Group	Control Group	*P* Value
Free T3, ng/dL	2.82±0.45	3.07±0.49	.013†
Free T4, ng/dL	1.02±0.23	1.06±0.14	.257
Total T3, ng/dL	112.9±22.3	116.0±18.8	.472
Total T4, µg/dL	7.56±1.90	8.46±1.28	.008†
Thyroid-stimulating hormone, mIU/mL	2.58±2.11	1.55±1.00	.003†
Thyroid antiglobulin antibodies, ratio	1.56±1.98	1.08±0.83	.134
Thyroid antimicrosomal antibodies, ratio	1.21±1.28	1.02±1.14	.444
Thyroid volume, mm^3	27.958±19.008	13.421±6.831	<.0001†

*All values are mean ± SD.
†Statistically significant.

When thyroid function was defined as suppressed, normal, or elevated according to hormone values, the lithium group differed from the control group in suppressed fT4 level and elevated TSH (Table 2).

In the lithium group, no relationship was apparent between thyroid function and sex, concomitant psychotropic drug use, duration of lithium treatment, or family history of thyroid disorder ($P>.05$). Lithium-treated smokers had a significantly higher fT3 level than their nonsmoking counterparts (3.0 ± 0.4 vs 2.5 ± 0.4 ng/dL, $P<.0001$). Patients older than 50 years of age had significantly lower fT4 levels compared with patients younger than 50 (0.9 ± 0.4 vs 1.1 ± 0.6 ng/dL, $P = .011$).

Thyroid volume in the lithium group was significantly elevated relative to that in the control group (see Table 1). Goiter was identified ultrasonographically in 59%

(n = 29) of the lithium group and in only 15% (n = 7) of the control group ($P<.0001$). Twenty-five lithium-treated patients with goiter were euthyroid according to serum thyroid function values. No significant relationship with the goitrogenic effect of lithium could be detected for demographic (sex, age, smoking, concomitant drug use) or clinical variables (family history of thyroid disorder, duration of lithium therapy, presence of thyroid antibodies).

Table 2. Definition of Thyroid Function by Hormone Values

	Definition	Lithium n (%)	Control n (%)	*P* Value
fT3, ng/dL	Suppressed (<2.3)	5 (10)	1 (2)	.101
	Normal (2.3–4.2)	44 (90)	43 (94)	
	Elevated (>4.2)	0 (0)	2 (4)	
fT4, ng/dL	Suppressed (<0.89)	10 (20)	0 (0)	.001*
	Normal (0.89–1.80)	39 (80)	46 (100)	
	Elevated (>1.8)	0 (0)	0 (0)	
tT3, ng/dL	Suppressed (<85)	4 (8)	0 (0)	.118
	Normal (85–185)	45 (92)	46 (100)	
	Elevated (>185)	0 (0)	0 (0)	
tT4, µg/dL	Suppressed (<4.5)	3 (6)	0 (0)	.243
	Normal (4.5–12.5)	46 (94)	46 (100)	
	Elevated (>12.5)	0 (0)	0 (0)	
TSH, mIU/mL	Suppressed (<0.47)	0 (0)	3 (7)	.025*
	Normal (0.47–5.01)	42 (85)	42 (91)	
	Elevated (>5.01)	7 (15)	1 (2)	

*Statistically significant.

Six lithium-treated patients (12%) (4 men, 2 women) had clinical hypothyroidism, and 1 patient (2%) had subclinical hypothyroidism. There was no case of clinical or subclinical hypothyroidism in the control group. One instance of hyperthyroidism was found in the control group, none in the lithium group. Among demographic and clinical variables, only a family history of thyroid disorders was significantly high in lithium-treated patients with clinical hypothyroidism ($P = .012$); all other variables were comparable to those in patients without this condition.

In the lithium group, 14.3% of women (n = 4) and 9.5% of men (n = 2) had clinical hypothyroidism ($P = .688$). The difference with the control group was not significant. The mean duration of lithium therapy was lower in women than in men, but not significantly so (9.0 ± 2.8 vs 2.6 ± 2.3 years, $P = .06$).

The prevalence of both thyroid antibodies (TAG and AMA) in the lithium group was 23%. In the control group, respective values were 15% (n = 7) and 13% (n = 6). The differences were not significant. The presence of thyroid antibodies did not correlate with clinical or demographic variables in either group; however, of six patients with clinical hypothyroidism, four (67%) demonstrated thyroid antibodies. Analyzed another way, 36.3% of patients with thyroid antibodies had clinical hypothyroidism, while only 5.2% of patients without thyroid antibodies had clinical hypothyroidism; the difference was significant (P = .026).

A search for correlations between thyroid function test values, thyroid antibodies, thyroid volume, duration of lithium treatment, serum lithium level, and age uncovered only a negative correlation between serum fT4 level and age (r = –.404, P = .004).

DISCUSSION

In this study, mean thyroid function values in both groups were within normal ranges; however, all measurements of T4 and T3 were lower in the lithium than in the control group and reached significance for fT3 and tT4. TSH levels were also significantly different (higher) in association with lithium treatment, as were suppressed fT4 and elevated TSH levels. Global assessment of these findings in our study further supports the inhibitory effects of lithium on thyroid function, which have been noted in other studies.[6,8,16,18,20,21]

Many investigations have focused on factors that might predict and affect the inhibition of thyroid function during lithium therapy. In the present study, the most significant relationship detected was a negative correlation between age and fT4 values. In another report,[8] the prevalence of thyroid dysfunction was higher in patients between 40 and 59 years of age than in patients younger than 40. Age should be borne in mind in follow-ups of lithium-treated patients, and the thyroid function of elderly patients receiving lithium should be closely monitored.

Rates of goiter in previous studies of lithium have ranged from 3.8% to 51%.[4,15,18,21,22] Prevalence in our study was 59% in the lithium group and 15% in the control group (P<.0001). Although the goitrogenic effect of lithium is unquestioned at this time, controversy still surrounds the factors leading to its occurrence in lithium-treated patients. In one study,[23] mean thyroid function values were higher in patients with than in those without a family history, a finding supported in a case report.[24] Similar to our results, no significant relationship was apparent between sex and lithium-related goiter in a controlled study,[15] whereas lithium-induced goiter and TSH levels were significantly higher in women older than 60 years of age in another report.[23] The authors of the latter report supported their findings by referring to an epidemiologic study which indicated that aging women are at an increased risk of hypothyroidism and that lithium use further increases this risk.[25]

Concomitant use of psychotropic drugs (antidepressants or antipsychotics) has not been shown to affect lithium-induced thyroid dysfunction,[4,9] a result confirmed in the present study. A significant correlation has been reported between smoking and increased thyroid volume.[9] Thiocyanate, a substance present in all cigarettes, is believed to have goitrogenic effects and to account for this relationship.[9,15,21] Of the lithium-treated patients in our study who developed goiter, 19 (65%) were smokers and 10 (35%) were nonsmokers; no significant difference vis-à-vis the control group

could be found with respect to smoking. Several authors have claimed that an increased risk of goiter parallels an increased duration of lithium treatment; others reject any such relationship.[11,12,14] One study[26] found an increased risk of goiter with more than 2 years of lithium use compared with fewer than 2 years of treatment. No significant relationship between duration of lithium therapy and goiter was evident in our patients.

Neuropsychiatric manifestations of lithium-induced hypothyroidism may make it difficult to differentiate these symptoms and those of the primary disorder. Resistance of the primary disorder to treatment, an exacerbation of its symptoms, and an increase in the frequency of recurrences may be other effects. Particularly in patients with treatment-resistant depression and rapid-cycling bipolar disorder, an assessment for hypothyroidism should be conducted.[3,6,8]

The prevalence of lithium-induced clinical hypothyroidism in the literature varies widely from 0% to 47%, possibly owing to differences in study designs, methodology, and diagnostic criteria, although most sources report rates between 5% and 20%. Subclinical hypothyroidism has been said to occur at higher rates (20% to 50%).[6,16-18,20,27,28] In the present study, the rate of subclinical hypothyroidism due to lithium exposure contradicted prior results, being less prevalent than clinical hypothyroidism. The transient nature of subclinical hypothyroidism and the absence of clinical symptoms may allow the disorder to go unrecognized in lithium-treated patients, who may progress to clinical hypothyroidism. This progression emphasizes the importance of closely monitoring thyroid function in lithium-treated patients.

In some studies, older age, female sex, increased duration of lithium treatment, and family history of thyroid disorder were closely related to clinical hypothyroidism. Although these factors have not been universally confirmed, female elderly patients have consistently been more likely to demonstrate this abnormality.[9,17,20,27] In one study,[8] female sex was cited as the main risk factor for clinical hypothyroidism during lithium treatment, leading to a prevalence of 13.8% compared with 4.5% in men. A significant difference with respect to sex could not be established in our study. In the study previously described,[8] women had a three-times-higher incidence of hypothyroidism in the first 2 years of lithium treatment than did men. Clinical hypothyroidism appeared 24 months after onset of therapy in women and after 59 months in men. The present study evaluated duration of lithium therapy only in patients who demonstrated clinical hypothyroidism and found a mean duration of 2.6 years for female patients and 9 years for male patients. Although not statistically significant ($P = .06$), the apparent 6-year difference may support the hypothesis of earlier occurrence of hypothyroidism in women.

Also noted in our study was a high rate of family history of thyroid disorders in lithium-treated patients with clinical hypothyroidism. The literature similarly contains several studies presenting high rates of hypothyroidism in such patients with relatively short-duration lithium therapy. When associated with genetic loading, lithium use may contribute to the earlier onset of hypothyroidism, with serious medical and psychiatric consequences.[23]

It has recently been postulated that the therapeutic action of lithium is mediated in part through immunologic mechanisms.[29] Development of autoantibodies against the thyroid gland during lithium therapy may reflect underlying autoimmune thyroiditis and result in some thyroid dysfunction.[11,14-16,26] Few studies indicate

a positive correlation between thyroid antibodies and lithium-induced goiter but add that lithium may also notably increase the titer of thyroid AMA and convert latent subclinical autoimmune disease into clinically overt illness.[13-15] In a controlled study, however,[12] there was no increase in the prevalence of TAG or AMA antibodies with lithium treatment, nor did lithium act as an adjuvant to raise the titers in individuals with preexisting antithyroid antibodies. The prevalence of thyroid antibodies among lithium-treated patients ranges between 20% and 40%.[14,15,21,26] Some published studies suggest a close relationship between thyroid antibodies and lithium; others do not, noting that thyroid antibody rates in lithium-treated patients are similar to the rate (5%–15%) in the general population.[15,16,29,30] The present study showed no difference between groups in prevalence of thyroid antibodies. The 23% rate was, however, consistent with findings in similar studies.[14,15,21,26]

Several limitations of our study should be borne in mind. First, there were no baseline thyroid function values that could be compared with the values during lithium treatment. A second limitation was the cohort nature of the study. Third, the small sample size prevents generalization of the results to a wider population. A large prospective study that includes baseline thyroid function values and controls for and follows up immunologic function would greatly improve our understanding of the lithium–thyroid gland association.

In conclusion, our results showed that lithium treatment apparently inhibits thyroid function, enlarges the gland, and increases the inhibitory effects parallel to the natural increases that occur with age. Women are more likely than men to show effects earlier, and a family history is a risk factor for hypothyroidism. During lithium therapy, patients should be closely monitored for the appearance of thyroid disorders and other unwanted drug effects. Early intervention may help solve potential problems complicating the primary disease and improve quality of life in a timely fashion.

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