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Original Article

Liquid Thyroxine Improves Outcomes in Hypothyroid Patients With Small Intestinal Bacterial Overgrowth and Irritable Bowel Syndrome

Brittany Bohinc Henderson, MD *, Shelby P. Smith, BS, Marlena E. Mengelkamp, BS, Emma Kate Rhymer, BS, Kensi N. Gray, BS, Abigail G. Jackson, BS, Samantha F. Henry, BS, Stacey Chuang, BA, Erin H. Stavrakas, DNP, FNP-C, Olivia M. Blair, PA-C, MAPS, Melissa Heaps, MSN, APRN, NP-C

Charleston Thyroid Center, Mount Pleasant, South Carolina

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ABSTRACT

Objective: Malabsorption of levothyroxine (LT4) is often seen in patients with hypothyroidism and gastrointestinal (GI) conditions. Our study was designed to establish the prevalence of small intestinal bacterial overgrowth (SIBO) in patients with hypothyroidism and irritable bowel syndrome (IBS), and to demonstrate that liquid LT4 is more consistently absorbed vs tablet, leading to improvement in thyroid and GI symptoms.

Methods: This was a single-center, open label, prospective cohort study of liquid LT4 in 75 adult patients with hypothyroidism and IBS. Patients were transitioned from LT4 tablets to solution at equivalent dosing. Patients returned at 6 and 12 weeks for repeat thyroid levels and completion of validated questionnaires. A standard 2-hour SIBO breath test was administered at Week 6. Patients recorded daily stool appearance and frequency.

Results: Prevalence of SIBO was 65.3%. Liquid LT4 normalized thyroid stimulating hormone (TSH) in a higher percentage of patients vs tablet (77.55% vs 57.14%); significantly decreased TSH in subjects with SIBO; improved hypothyroid symptoms, IBS symptoms, stool appearance in all groups, and significantly altered bowel frequency among those with SIBO.

Conclusion: Small intestinal bacterial overgrowth (SIBO) is common in patients with hypothyroidism and IBS. Among SIBO patients, LT4 tablets were inefficiently absorbed, leading to suboptimal thyroid control; however, transitioning from LT4 tablets to solution normalized TSH and improved hypothyroid symptoms. Liquid LT4 also significantly improved GI symptoms in all patients with hypothyroidism and IBS, regardless of SIBO status. Additionally, 1 in 5 patients had complete resolution of IBS symptoms after switching from LT4 tablets to solution, independent of changes in TSH.

Introduction

Background

In hypothyroidism, levothyroxine (LT4) replacement is standard of care. Both tablet and capsule LT4 formulations have narrow therapeutic indices, undergo dissolution in the stomach, and are absorbed in the small intestine, primarily at the jejunum and upper ileum[1]; successful treatment relies on complete dissolution and consistent drug delivery to the small intestine.

Patients with hypothyroidism and IBS often have comorbid gastrointestinal (GI) disorders detrimental to LT4 absorption.[1] Due to thyroid hormone's impact on bowel motility, irritable bowel syndrome (IBS) with constipation and/or diarrhea is very

Abbreviations: LT4, levothyroxine; GI, gastrointestinal; SIBO, small intestinal bacterial overgrowth; IBS, irritable bowel syndrome; TSH, thyroid stimulating hormone; PPIs, proton pump inhibitors; FODMOP, fermentable oligosaccharides, disaccharides, monoaccharides, and polyols; ThyTSQ, thyroid treatment satisfaction questionnaire; IBS-SSS, irritable bowel severity scoring system; IBS-GAI, IBS global assessment of improvement; BSCS, Bristol stool chart scale; FDA, food and drug administration; IRB, institutional review board; IQRs, interquartile ranges; IBS, inflammatory bowel disease; Q, questions; QOL, quality of life; OTC, over the counter; fT4, free T4; fT3, free T3; PI, prescribing information.

* Address correspondence to Dr Brittany Bohinc Henderson, Department of Endocrinology, Charleston Thyroid Center, 1054 Johnnie Dodds Boulevard, Suite A, Mount Pleasant, SC 29464.

E-mail address: charlestonthyroid@gmail.com (B.B. Henderson).

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common among patients with hypothyroidism.[2,3] IBS is associated with altered GI motility that affects the delivery of LT4.[4] Small intestine bacterial overgrowth syndrome (SIBO), defined as a clinical syndrome of GI symptoms caused by the presence of excessive numbers of bacteria within the small intestine,[5] can develop in bowel motility disorders, including hypothyroidism and IBS; symptoms of IBS and SIBO can have significant overlap. Due to high levels of bacteria in the small intestine,[6] SIBO patients may not experience consistent and complete dissolution and absorption of LT4.[1,7] Identifying and treating SIBO in this patient population is essential for ensuring consistent delivery of the drug and resolution of hypothyroid symptoms.[1,5]

Prevalence of SIBO

The prevalence of SIBO is unknown in the general population, but most experts agree that it is significantly underdiagnosed.[8] SIBO has been reported in >50% of those with hypothyroidism and in 30% to 85% of patients with IBS.[3,7-9] Any medical condition that alters gut motility or stomach pH can contribute to development of SIBO, including, but not limited to, hypothyroidism, diabetic gastroparesis, gastric bypass surgery, GI inflammatory diseases (Crohn's disease, celiac disease), systemic neuromuscular illnesses (Parkinson's Disease), and *H. pylori* infection. Any prescription medication affecting GI motility or pH may also contribute to the development of SIBO, including proton pump inhibitors (PPIs), LT4,[1,8] and opiates.

SIBO commonly presents with symptoms of abdominal pain, bloating, gas, distention, constipation and/or diarrhea. Symptoms often masquerade as other diagnoses such as IBS, functional diarrhea, functional dyspepsia, or chronic constipation. Because of the overlap of SIBO with many other GI conditions, it should be considered and tested for, particularly in those who have motility risk factors, anatomical abnormalities of the small bowel, and/or malabsorption syndromes.[5]

The gold standard for SIBO diagnosis is the lactulose breath test used to measure production of both hydrogen and methane gas from the bacteria after fermentation of lactulose in the small intestine. SIBO can be hydrogen-only, methane-only, or both hydrogen and methane-dominant depending on the type of bacteria overgrowing within the gut. Treatment is either single or dual antibiotic therapy and a low FODMAP* diet.

Rationale for Our Study

Levothyroxine (LT4) sodium oral solution should improve absorption of thyroid medicine in this patient population as it bypasses the need for gastric dissolution and may enhance small bowel absorption, allowing for down-titration of dosing and improvement of patient symptoms. Our study aimed to determine the prevalence of SIBO, demonstrate enhanced liquid LT4 absorption, evaluate thyroid-stimulating hormone (TSH) normalization, and measure improvement in clinical symptoms upon transition from LT4 tablets to the oral solution in patients with IBS and hypothyroidism.

Study Endpoints

The primary endpoint was improvement in the percent of SIBO patients achieving normal TSH levels (0.4-4.0 uIU/ml) after switching from equivalent dosing of tablet LT4 to liquid LT4 at Week 6.

The secondary endpoints were as follows: (1) reduction in mcg/kg thyroid dosing for patients with SIBO over 12 weeks, suggesting improvement in small intestinal absorption of liquid LT4, (2) improvement in hypothyroid symptoms among SIBO patients before and after the transition to liquid LT4, as assessed by the validated Thyroid Treatment Satisfaction Questionnaire (ThyTSQ), and (3) improvement in GI symptoms as measured by the Irritable Bowel Severity Scoring System (IBS-SSS) and by the IBS Global Assessment of Improvement (IBS-GAI) questionnaires as well as objective weekly average BSCS (Bristol Stool Chart Scale) scores and frequency after transition from tablet to liquid LT4 (see Supplementary File for more information on the individual questionnaires and BSC scale).

Highlights

- Small intestinal bacterial overgrowth is common in hypothyroid patients with IBS.
- Gastrointestinal (GI) issues affect levothyroxine absorption and TSH optimization.
- Switching from levothyroxine tablet to solution normalizes TSH in this population.
- Switching to levothyroxine solution improves gastrointestinal and thyroid outcomes.
- Switching to levothyroxine solution resolves GI symptoms in 1 in 5 patients.

Clinical Relevance

Irritable bowel syndrome (IBS) is a common comorbidity amongst hypothyroid patients and can lead to development of small intestinal bacterial overgrowth (SIBO). Gastrointestinal malabsorption of levothyroxine (LT4) tablets may occur as a result. Transitioning to liquid LT4 normalized TSH; improved hypothyroid symptoms, IBS symptoms, and improved stool appearance and frequency.

Methods

This was a single-center, open label, prospective cohort study of liquid LT4 oral solution in 75 adult patients with hypothyroidism and GI symptoms consistent with IBS. All patients had variable serial TSH levels within the past year on their tablet formulation (defined as TSH levels fluctuating outside of the normal reference range of 0.4-4.0 uIU/ml) or at least one unprompted dose change in the last 6 months, suggesting difficulty optimizing TSH levels on tablet formulations. Inclusion and exclusion criteria are presented in the Supplementary File. Thyroid levels including TSH, free T4, free T3 were collected at baseline, 6 and 12 weeks. At study enrollment, all patients were transitioned from T4 tablets to LT4 oral solution initially at equivalent dosing. After Week 6, thyroid doses were titrated as needed to reach a TSH level of 0.4-4.0 uIU/ml per provider discretion. Patients were counseled on dosing and administration of liquid LT4 according to the Food and Drug Administration (FDA)-approved prescribing information. At Week 6, all patients underwent a 2-hour lactulose SIBO breath test (Genova Diagnostics, details in the Supplementary File). At baseline, and at the 6- and 12-week marks, patients were administered the IBS-SSS and ThyTSQ questionnaire

* FODMAP = A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

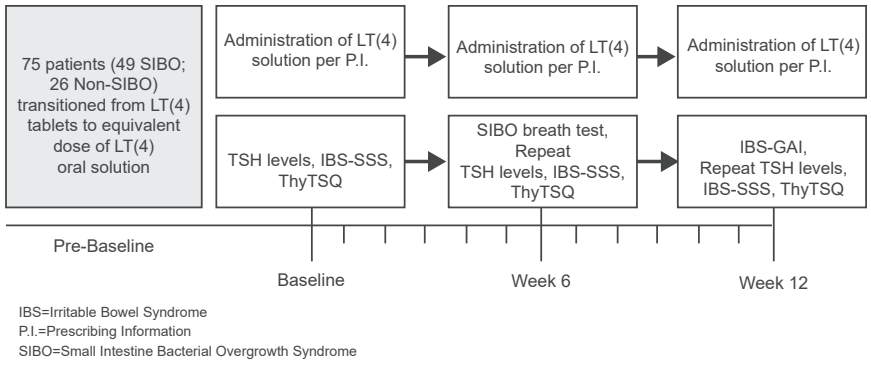

Fig. 1. Study flow chart.

assessments. Patients were also administered the IBS global assessment of improvement scale (IBS-GAI) after taking 12 weeks of liquid T4 therapy (details of all questionnaires can be found in the Supplementary File). Patients were asked to self-record all daily bowel movements and quantify frequency and stool appearance according to the BSCS. At the 12-week mark after completing the questionnaires, SIBO results were revealed and discussed with patients. Positive patients were treated for SIBO as per standard of care at the study's conclusion (Fig. 1).

Sample Size

We hypothesized a large effect size of $d = 0.8$ for purposes of statistical power. Using a 2-tailed hypothesis, the effect size of d = 0.8, an alpha value of 0.05, a beta value of 0.20 (1-beta = power), an attrition rate of 10%, and a 3:1 allocation ratio of SIBO to non-SIBO, we determined a total of $n = 75$ participants ($n = 18$ in the Non-SIBO group and $n = 57$ in the SIBO group). The 3:1 allocation ratio comes from a published incidence value of 54% for SIBO in the overall hypothyroid population,[6] and an increase to 75% based on screening patients for symptoms such as bowel frequency and BSC abnormalities.

Data Collection and Management

The study was under IRB approval and under study supervision by the IRB (WIRB, WCG Clinical, Inc). Data were kept as a password-protected Excel file on a security-protected and password-protected clinical computer. Consent forms were scanned to a secure drive on the computer and hard copies kept in a locked location. All serious adverse events (SAEs) were reported to the Study Sponsor in a timely and efficient manner according to standard protocol.

Statistical Methods

Frequency and descriptive statistics were used to describe the demographic and clinical characteristics of the sample. Fisher's Exact Test or Chi-square analysis were used for categorical parameters. For continuous parameters, the assumption of normality was checked using Shapiro– Wilk tests. The assumption of homogeneity of variance was also tested, using Levene's Test of Equality of Variances. Appropriate statistical analyses, including *t* tests or nonparametric Mann–Whitney U tests, were performed. Within-subjects analyses of binary, categorical outcomes were analyzed using McNemar's test. Cross-tabulation tables were analyzed for the McNemar's test. Cochran's Q test was performed when there were more than 2 within-subject observations of a binary, categorical outcome. Posthoc analyses were performed when a significant main effect was detected using Cochran's Q test. Wilcoxon Signed Ranks tests were performed for within-subject analyses of ordinal outcomes and continuous outcomes that violated statistical assumptions. Medians and interquartile ranges (IQRs) were reported for the repeated observations. Friedman's ANOVA was used to test for significant changes in ordinal or non-normal continuous outcomes across 3 observations. When a significant main effect was detected, posthoc tests were performed using Dunn's test. All analyses were performed using SPSS Version 29 (Armonk, NIY: IBM Corp) and statistical significance was assumed at an alpha value of 0.05. A professional statistician assisted with analysis of the data in preparation for the manuscript submission of findings.

Results

Patient Recruitment and Demographics

A total of 75 patients were recruited for study involvement. All patients presented with primary hypothyroidism on LT4-only tablets and self-reported GI issues, including abnormal BSCS, abnormal frequency including constipation or diarrhea, and abdominal pain or bloating, consistent with IBS. Rome IV Diagnostic Criteria screening was used to identify patients with IBS.[8] No patients had inflammatory bowel disease (IBD), celiac disease, gastroparesis or prior gastric bypass surgery. Patient demographics reflected the demographics of the community where the study took place (Table 1).

Prevalence of SIBO

All 75 patients had hypothyroidism and IBS. Forty-nine (49) of the patients (65.3%) had SIBO based on the gold standard lactulose SIBO breath test. A majority of those with SIBO had both methane and hydrogen gas elevation on breath testing (57.1%), with 20.41% and 22.45% having hydrogen-only or methane-only SIBO, respectively.

Primary Outcome Measure

The baseline TSH level in the SIBO group was significantly higher (2.51 uIU/ml (median) (25%-75% CI 1.63-4.73)) than the non-SIBO group (1.57 uIU/ml (median) (25%-75% CI 0.566-2.90)), despite equivalent baseline mcg/kg dosing ($P = .047$, Mann–Whitney):

Upon transitioning from tablet to liquid LT4 at equivalent dosing, there was a significant improvement in SIBO patients reaching TSH goal (0.4-4.0 uIU/ml) by Week 6 (57.14% at baseline vs 77.55% by Week 6) ($P = .021$, McNemar Test/Binomial Distribution, $P = .032$ Cochran's Q Test); 71.43% remained in range by week 12.

For those with TSH over 4 uIU/ml at Baseline, suggesting malabsorption of the LT4 tablet, TSH significantly improved in the SIBO group from 5.96 uIU/ml to 4.00 uIU/ml ($P < .001$) after

Table 1
Baseline Patient Characteristics

Patient characteristics	No SIBO (n = 26 patients)	SIBO (n = 49 patients)	P-value
Female Gender	96.2%	93.9%	NS
Age (mean ± stddev)	47.5 ± 12.2	41.76 ± 15.06	NS
Dose Prior to Enrollment (mcg/kg/d; mean ± stddev)	1.17 ± 0.49	0.96 ± 0.429	P = .06
Ethnicity (White %)	100%	95.9%	NS
BMI (median ± stddev)	27.1 (25-75% CI 22.93-39.22)	28.98 (25-75% IQR 25.16-32.96)	NS
Formulation prior to enrollment	Levothyroxine: 57.7% Synthroid: 42.3%	Levothyroxine: 57.1% Synthroid 36.7% Unithroid 4.1% Levoxyl: 2.0%	NS

FODMAP = A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

switching to an equivalent dose of the oral LT4 solution (Fig. 2). There was also improvement in TSH among those without SIBO, though $n = 4$ was too low to reach statistical significance ($P = .47$).

Secondary Outcome Measures

LT4 Tablet to Solution Improves Absorption in SIBO. The dose of LT4 did not significantly change from Baseline and Week 6 (the dose was equivalent per study design) vs Week 12 among those with SIBO: baseline mcg/kg tablet and 6-week mcg/kg SOL were as follows: 0.96 mcg/kg ± 0.43 mcg/kg; and 12-week mcg/kg SOL was 0.97 mcg/kg ± 0.46 mcg/kg (P = NS). This demonstrates that there was significant improvement in the percentage of SIBO patients optimized within the TSH reference range at Weeks 6 and 12, despite similar mcg/kg dosing of tablet vs liquid, consistent with enhanced absorption of the oral LT4 solution.

LT4 Tablet to Solution Improves Thyroid Symptoms. Upon recruitment, patients filled out the ThyTSQ questionnaire, a clinically-validated questionnaire for thyroid-related symptoms. Baseline scores in both SIBO and non-SIBO groups were consistent with uncontrolled hypothyroid symptoms. After 6 weeks of treatment with the oral solution, ThyTSQ significantly improved in both groups (P = .001 and P = .017, respectively). This significant improvement persisted at Week 12 after transition from the tablet to the oral LT4 solution (P < .001 and P = .005, respectively). There was no significant difference in ThyTSQ scores between Weeks 6 and 12 (P = 1.0) (Fig. 3). Patients in both groups had significant improvements in Questions (Q) 1, 2, 6, and 7 and SIBO patients had additional improvements in Q4 and Q5 (see Supplementary File). For all patients with IBS, despite SIBO status, switching from LT4 tablet to liquid T4 significantly improved daily thyroid symptoms as assessed by the clinically-validated ThyTSQ.

LT4 Tablet to Solution Improves SIBO and IBS Symptoms, Significantly Improving Quality of Life. Mean IBS-SSS Scores (a clinically-validated IBS questionnaire) significantly improved in both groups after transition from LT4 tablets to liquid, regardless of SIBO status. The transition significantly improved IBS symptoms in SIBO patients from moderate to mild. Over 12 weeks there was significant improvement in GI behavior as reported by the IBS-SSS validated questionnaire in both SIBO and non-SIBO patients after transition from tablet to solution (Fig. 4).

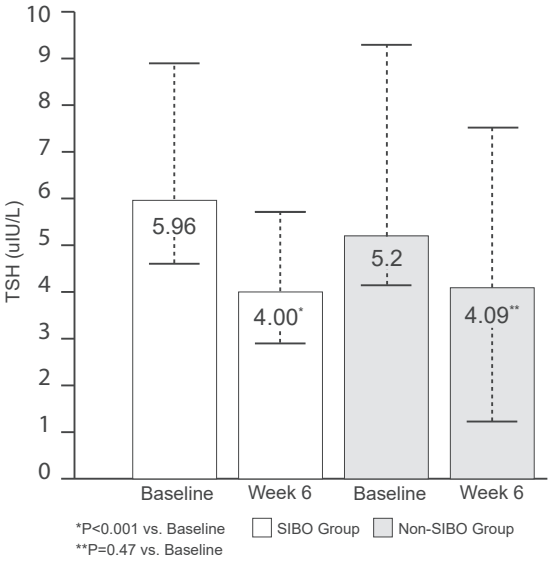

Fig. 2. Improvement in TSH in patients with baseline TSH >4 uIU/ml. In patients with SIBO and baseline TSH >4 uIU/ml, suggesting malabsorption of LT4 tablet, there was a significant improvement in TSH from baseline to Week 6: 5.96 uIU/ml, (25%-75% 4.83-8.98) to 4.00 uIU/ml, (25%-75% CI 2.91-5.77) (n = 16, P < .001; Wilcoxon Signed Ranks Test). There was an improvement in TSH among non-SIBO patients as well, but the group was underpowered to show significance: TSH at Baseline: 5.2 uIU/ml, (25%-75% CI 4.16-9.32) vs TSH at 6 weeks: 4.09 uIU/ml, (25%-75% CI 1.20-7.53) (n = 4 patients, P = .47 NS; Wilcoxon Signed Ranks Test).

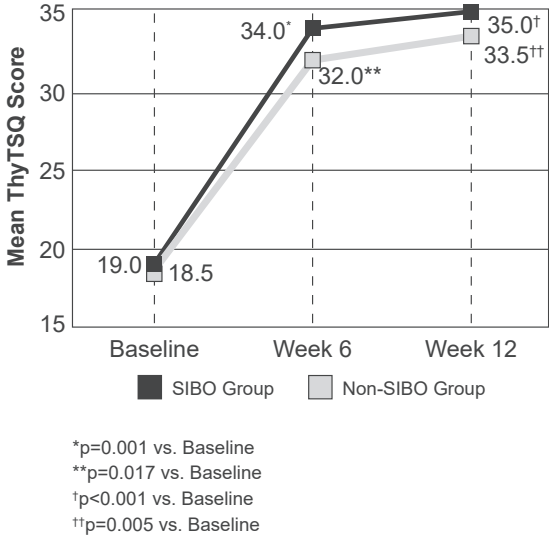

Fig. 3. Improvement in mean ThyTSQ scores after transition from tablet to LT4 solution. The mean baseline ThyTSQ scores among SIBO and non-SIBO patients were 19.0 (14.0-24.0), median (IQR) and 18.5 (17.0-26.0), respectively (P = NS, P = .27; 2 sided t test). After 6 weeks of treatment with the oral solution, ThyTSQ significantly improved in both groups to 34.0 (29-37) (SIBO) (P = .001) and 32.0 (26.0-37.0) (non-SIBO), (P = .017). This significant improvement persisted at Week 12 after transition from the tablet to the oral solution 35.0 (IQR 31.0-38.0) (SIBO) (P < .001) and 33.5 (27.0-38.0) (non-SIBO) (P = .005). There was no significant difference in ThyTSQ scores between Weeks 6 and 12 (P = 1.0).

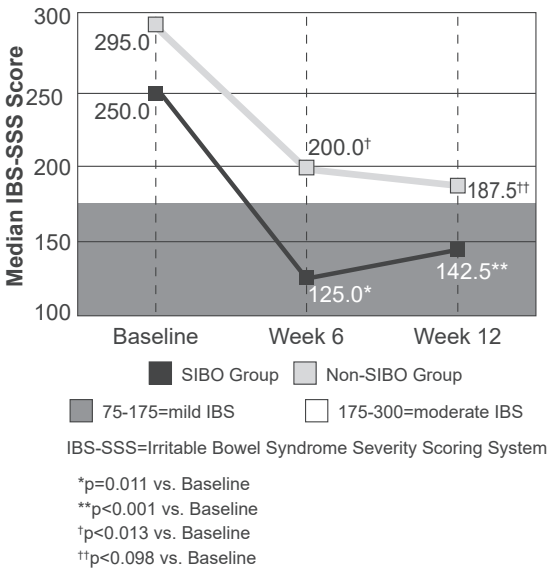

Fig. 4. Improvement in IBS-SSS scores after transition from tablet to LT4 solution. Both groups of patients had a significant improvement across time in IBS-SSS scores after transition from LT4 tablet to LT4 solution (SIBO $P < .001$, non-SIBO $P = .012$). Patients with SIBO reported improved IBS symptoms from moderate to mild. Specifically, the SIBO IBS-SSS Score at baseline was 250 (195.0-325.0) (median, IQR 25%-75%), consistent with moderate IBS. This score improved at Week 6 to 125 (75.0-225.0) (median, IQR 25%-75%) ($P = .011$) and 142.5 (75.0-225.0) (median) at Week 12, consistent with mild IBS ($P < .001$). There was improvement in score among those in the non-SIBO group with Baseline Score: 295 (200-325) (median, IQR) improving to 200 (110-250) (median, IQR) at Week 6 ($P = .013$) and 187.5 (110-322.5) (median, IQR) ($P = .098$) at Week 12.

All 5 questions had significant improvement in scores after the transition, with the most significant improvement in quality of life (QOL) (SIBO + non-SIBO $P = 7.33$ E-0.7, and for SIBO only $P = 5.33$ E-05); 71.4% of SIBO patients and 72% of non-SIBO patients experienced a clinically meaningful improvement in IBS (as defined by a $\geq$ 50 point decrease in score from baseline) by Week 6. This improvement from baseline persisted until the conclusion of the study with meaningful improvement in 67.5% and 70% at Week 12, in the 2 groups, respectively (Fig. 5 *A*).

Transition from LT4 tablet to liquid completely resolved IBS symptoms (as measured by the IBS-SSS questionnaire) in 32.7% of SIBO patients by Week 6 ($P < .001$ vs Baseline), with persistent resolution of IBS symptoms in 15% of SIBO patients by Week 12, ($P = .096$) even before antibiotic treatment of SIBO (Baseline negative IBS-SSS 2.0%) (Cochran's Q test significant change across time $P < .001$) (Fig. 5 *B*). This finding was independent from improvement in TSH. Similar findings were observed in the non-SIBO group, with complete resolution of IBS symptoms in 20% and 15% of patients by Weeks 6 and 12, respectively (Baseline negative IBS-SSS 3.8%), though power was not high enough to meet statistical significance ($P = .17$, $n = 26$). This finding was also independent from improvement in TSH.

Evaluation of IBS symptoms showed improvement on an equally-validated IBS questionnaire, the IBS-GAI: 25% of patients in the SIBO group were classified as "responders" after transition to the oral solution. Among those in the non-SIBO group, 21% were "responders", with improvement of IBS symptoms after 12 weeks of LT4 sodium oral solution. This finding was also independent from improvement in TSH. On average, 1 in 5 patients with hypothyroidism and IBS (20.53%) obtained complete remission of IBS symptoms simply by transitioning from LT4 tablets to the oral solution, independent of improvement in TSH or treatment of underlying SIBO.

In addition to validated questionnaires, we also asked patients to objectively record and document daily BSCS and frequency as objective measures of improvement in bowel habits (see Supplementary File). Among all patients, there was improvement in those with BSCS 3 to 4 (normal) after transition to the oral solution, offering objective demonstration of a positive effect of LT4 solution on gut secretion and behavior (Fig. 6 *A*). Among patients with SIBO, bowel frequency significantly changed from 1.57 ± 0.97 bowel movements per day at Week 6 to 1.23 ± 0.76 bowel movements per day at Week 12 ($P = .027$) (Fig. 6 *B*). There was no change in frequency among those in the non-SIBO group, which is consistent with a significant effect on bowel motility by liquid LT4 among those with SIBO.

Adverse Events

There were no reported Grade 3 or 4 adverse or safety events throughout the duration of the study. The most commonly-reported adverse event was fatigue (12.67%; see Supplementary File).

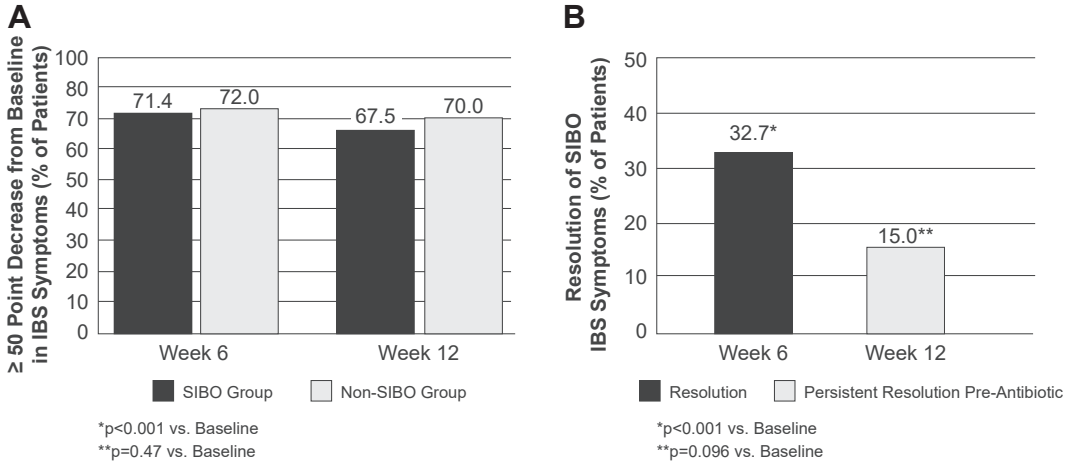

Fig. 5. *A*, Sustained improvement from baseline in IBS symptoms. Approximately 70% of patients had a significant improvement in IBS symptoms after transition from LT4 tablet to solution, regardless of SIBO status. *B*, Resolution of IBS symptoms. In the SIBO group ($n = 49$), 32.7% of patients had complete resolution of SIBO symptoms by Week 6 and 15% of them maintained symptom resolution by Week 12, prior to antibiotic treatment of SIBO.

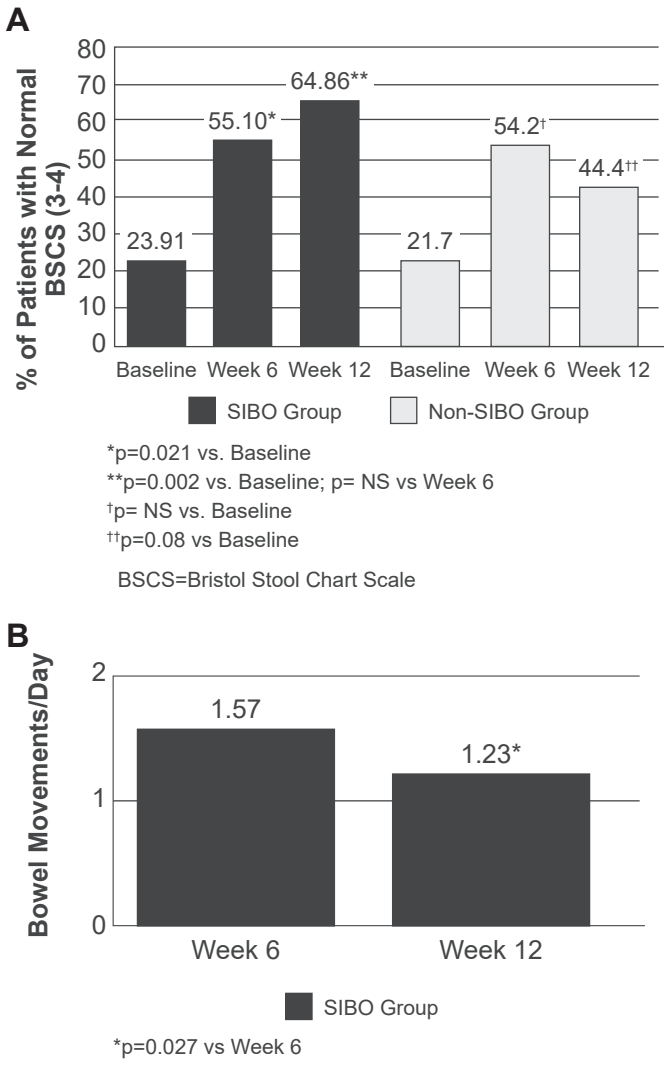

Fig. 6. Objective measures of GI improvement after transition from tablet to LT4 solution. There was a significant improvement in stool appearance and frequency in patients with SIBO after transition from LT4 tablet to solution. There was a trend towards significant improvement in BSCS among non-SIBO patients, though this group was underpowered. *A*, Normalization of Bristol Stool Chart Scores. Among all patients, there was improvement in those with BSCS 3 to 4 (normal) after transition to the oral solution, offering objective demonstration of a positive effect of LT4 solution on gut secretion and behavior. *B*, Significant effect on stool frequency. Among patients with SIBO, bowel frequency significantly changed from 1.57 ± 0.97 bowel movements per day at Week 6 to 1.23 ± 0.76 bowel movements per day at Week 12 ($P = .027$). There was no change in frequency among those in the non-SIBO group, though this group was likely underpowered. This may suggest that, among those with SIBO, transition to liquid LT4 did have a significant effect on bowel motility.

Discussion

Prevalence of SIBO in Patients With Hypothyroidism and IBS Symptoms

In our study, 65.3% of patients with hypothyroidism and IBS symptoms had SIBO. Our results are consistent with published data that the prevalence of SIBO is greater than 50% in patients with hypothyroidism.[3,7,8] In comparing 50 patients with hypothyroidism with 40 healthy volunteers, investigators found that 27/50 (54%) patients with a history of hypothyroidism were positive for SIBO. This study identified prior hypothyroidism as a risk factor for SIBO and suggested that once SIBO develops in a hypothyroid state, restoring normal thyroid status may not be enough to clear bacterial overgrowth.[7] A retrospective cohort study of 1809 patients having various risks factors for SIBO found hypothyroidism and LT4 therapy to be associated with 2.6 and 3.0 times increased risk for SIBO, respectively.[10] Our study and past studies suggest that patients with hypothyroidism presenting with chronic GI symptoms should be considered for the evaluation of SIBO.[3]

In part, the increased incidence of SIBO in hypothyroidism likely correlates with slowed gastric and intestinal motility, allowing for overgrowth of bacteria in the small intestines. Overgrowth of bacteria in the small intestines not only contributes to GI symptoms but also likely significantly affects LT4 absorption and processing in the duodenum, jejunum, and ileum.

Administration of LT4 medication itself has been shown to affect the diversity and balance of the gut microbiome, potentially increasing the risk for SIBO. A 2017 retrospective cohort study by Brechmann et al[10] found that not only hypothyroidism but also levothyroxine use were among the strongest contributors to the development of SIBO. This finding may potentially be due to the fact that many tablet forms of levothyroxine have excipients, including forms of glucose, that have a known effect on production of methane and hydrogen gas and proliferation of SIBO-specific bacteria. In contrast, LT4 sodium oral solution does not have glucose or any other excipient known to potentiate SIBO (contains water, glycerol and T4 only), and does not require a gastric phase of dissolution prior to absorption.

SIBO and Malabsorption of LT4

The efficacy and absorption of LT4 tablet formulations may be affected by the following: GI comorbidities, allergies to tablet excipients, prescription or OTC medications, and dietary supplements, among others.[4] The large number of LT4 dose changes, the unanticipated requirement for high doses, and the inability of LT4 to control hypothyroid symptoms associated with tablets, moreover, have been shown to correlate with the presence of GI comorbidities, such as SIBO.[1,11]

Our study showed that SIBO patients were able to normalize TSH levels after switching from LT4 tablet to equivalent dosing of the oral solution by Week 6. This normalization of TSH was maintained over the 12-week duration of the study, suggesting that liquid levothyroxine may be more consistently absorbed in this population over time. For those with SIBO and malabsorption of the tablet (TSH >4 uIU/ml), transition from tablet to liquid also significantly improved TSH by Week 6. A systematic review and meta-analysis confirmed that patients having suboptimal TSH levels when treated with tablet LT4 significantly improved TSH when switched to a liquid LT4 formulation at an unchanged dose, primarily because of malabsorption associated with a variety of factors.[12]

It is unknown why some people with SIBO malabsorb more than others. This likely has to do with the degree of overgrowth of bacteria and the composition of bacterial strains that have overgrown in the gut.

Studies have shown that the gut microbiome affects the enterohepatic cycling of thyroid hormones and the bioavailability of liquid LT4.[13] Among other actions, the bacteria in the human gut wall may directly inhibit type 2 deiodinase, reducing T4 activation and indirectly contributing to elevations in serum TSH.[14-16] Studies have also demonstrated that gut bacteria may be able to absorb thyroxine in its deconjugated form (a form that is unable to be absorbed by the human gut wall), thereby serving as a reservoir for thyroid hormone and a competitor for orally-administered LT4.[14,16] Bargiel and colleagues recently published a 2021 review, noting

that microbiome composition is altered by some GI disorders, which contributes to an increased requirement for oral LT4.[17]

SIBO patients may do better with absorption of liquid levothyroxine for several reasons: the oral solution does not rely on gastric pH or dissolution of solid dose forms, and the pharmacokinetics show a quicker time to peak serum levels. This may allow a higher concentration of drug to reach the small intestine, resulting in improved intestinal absorption, possibly circumventing inactivation of the drug by bacteria.[18,19]

Liquid LT4 has been shown to be more readily absorbed and more effective than tablet formulations in patients with hypothyroidism both with and without gastric disorders or malabsorption.[13,20-22] In a retrospective study of 11,000 patients treated with liquid LT4, the presence of PPIs significantly increased serum TSH compared to baseline.[23] Liquid LT4 can bypass the malabsorption associated with an increased gastric pH seen in elderly patients with achlorhydria, PPI use, and *H. pylori* infection.[24]

Improvement in Hypothyroid Symptoms With Transition to LT4 Solution

Hypothyroid symptoms improved in all patient groups upon transition from tablet to liquid as assessed by the ThyTSQ. Past studies have shown that this is true based on patient satisfaction with improved QoL. In one study using the ThyTSQ, there were significant improvements in Q1, 3, and 7. In that study, the investigators assessed changes in the QoL of 418 patients with hypothyroidism who were dissatisfied with their LT4 tablet therapy and were switched from tablets to liquid at the same dosing. The switch to LT4 liquid improved QoL in the majority of patients, without affecting thyroid function.[25] Our study showed improvement in Q1, 2, 4, 5, 6, 7 after switching from tablets to the oral solution. The improvement in thyroid-related symptoms is likely in part due to the normalization of TSH and more consistent administration of levothyroxine to the small intestine for absorption.

Bornikowska et al evaluated the QoL impact and efficacy of LT4 oral solution in 76 euthyroid patients with primary (PH, $n = 46$) and central hypothyroidism (CH, $n = 30$). The investigators compared the results to retrospective data for equivalent doses of LT4 tablets. Using the ThyPRO questionnaire, following 8 weeks of treatment with liquid LT4, a significant improvement in QoL was reported in both PH and CH patients. TSH levels were unchanged in PH patients. Free hormone levels (fT4 and fT3) were found to increase in all patients, with the exception of fT3 in the CH cohort. The investigators concluded that LT4 oral solution provided a better thyroid hormone profile and greater improvement in QoL than LT4 tablets, possibly attributable to its more favorable PK profile enhancing absorption, as suggested by the increased levels of free thyroid.[26] Our findings are consistent with improvement in hypothyroid symptoms in all patients, regardless of SIBO status, upon transition to liquid LT4. Improvement was independent of changes in thyroid levels. This suggests that transition from LT4 tablet to liquid may have hypothyroid benefits independent of TSH normalization, potentially due to more consistent and local absorption in the small intestine.

Improvement in GI Symptoms With Transition to LT4 Solution

Subjective Measures

Abnormal GI behavior, including constipation and delayed bowel motility, is a known symptom of hypothyroidism. Multiple published studies have shown a direct effect of thyroid hormone on GI system motility, transport, and secretory function.[27-34] In our study, GI symptoms significantly improved in both the SIBO and non-SIBO groups after transition from LT4 tablets to liquid, as assessed by the IBS-SSS, a clinically-validated questionnaire evaluating IBS symptoms, including abdominal pain, frequency of abdominal pain, severity of abdominal distention, dissatisfaction with bowel habits, and interference in quality of life (QoL).

On average, 70% of patients, regardless of SIBO status, had a positive GI response after transition from LT4 tablets to the oral solution. Further, 1 in every 5 patients with hypothyroidism had complete resolution of IBS symptoms confirmed by 2 separate clinically-validated questionnaires (IBS-SSS and IBS-GAI) after transitioning, independent of changes in TSH or diagnosis of SIBO and prior to any antibiotic treatment.

These improvements may have occurred due to more consistent LT4 local administration to the small intestine and the direct effect of liquid LT4 on motility and/or the gut microbiome.

Improvement may also be due to delivery of a purer formulation of thyroid medicine, free of excipients such as glucose, that are known to promote small intestinal gas production. Further research is needed.

Objective Measures

Change from LT4 tablets to the oral solution significantly improved stool appearance, as measured by the BSCS in all groups, and significantly altered bowel frequency among those with SIBO. Objective measures of bowel health such as stool appearance and frequency of bowel movements should theoretically also correlate with patient self-reported improvement in IBS symptoms. Stool appearance improved among all groups after transition to LT4 sodium oral solution, regardless of TSH or SIBO diagnosis, suggesting improvement in bowel wall secretory function and stool formation. Bowel movement frequency also significantly changed throughout the 12 weeks of treatment, suggesting that there may be a direct effect of the solution on bowel motility. Because bowel motility is a key factor in the development of SIBO, it is possible that LT4 solution may also be beneficial in the prevention of recurrent SIBO in patients with hypothyroidism.

Study Limitations

The study would have been strengthened with 2 additional control groups: one with IBS remaining on tablet and one without IBS remaining on tablet. It is possible that the participants were more adherent during the study or had closer follow-up and standardized dose adjustments that helped improve symptoms (though baseline and week 6 doses were the same). The broad improvement in gastrointestinal (GI) symptoms does not prohibit a type of placebo effect, in particular with subjective (albeit validated) questionnaires, though the significant change in objective measures of stool form and frequency does support our conclusions. Future follow-up controlled studies are recommended.

Conclusions

Malabsorption of LT4 is often seen in patients with Hashimoto's disease-related hypothyroidism and comorbid GI conditions, such as IBS and SIBO. Our study of adult patients with hypothyroidism and SIBO confirms published data that the prevalence of SIBO is greater than 50% in patients with hypothyroidism. In this difficult-to-treat patient population, LT4 tablets were inefficiently absorbed, leading to suboptimal control of hypothyroid symptoms; however, transitioning from LT4 tablets to liquid significantly improved key hypothyroid symptoms, normalized TSH, and significantly improved IBS symptoms, stool appearance, and bowel motility regardless of SIBO status. In our study, GI symptoms significantly improved in both the SIBO and non-SIBO groups after transition from LT4 tablets to liquid, as assessed by the IBS-SSS, a clinically-validated questionnaire evaluating IBS symptoms, including

abdominal pain, frequency of abdominal pain, severity of abdominal distention, dissatisfaction with bowel habits, and interference in QoL. Additionally, 70% of IBS patients had a positive GI response after transition to liquid levothyroxine and 1 in 5 patients with IBS and hypothyroidism had complete resolution of GI symptoms after simply switching from tablet to solution, independent of changes in TSH. The improvement in thyroid-related symptoms is likely in part due to the normalization of TSH, as well as improvement in TSH in cases of malabsorption, and more consistent administration of levothyroxine to the small intestine for absorption. Because bowel motility is a key factor in the development of SIBO, it is possible that LT4 solution may also be beneficial in the prevention of recurrent SIBO in hypothyroid patients.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

No AI technologies were utilized in the development of this manuscript.

Disclosure

Brittany Bohinc Henderson serves on the Speakers Bureau of IBSA, Amgen and Eisai. The project was an investigator-initiated study funded in part by IBSA. Dr Henderson's personal time in study design, interpretation, data analysis, and manuscript submission were unpaid.

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