0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(11):4180–4184

doi: 10.1210/jc.2007-0606

Association between Hypothyroidism and Small Intestinal Bacterial Overgrowth

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Objectives: Small intestinal bacterial overgrowth is defined as an abnormally high bacterial population level in the small intestine. Intestinal motor dysfunction associated with hypothyroidism could predispose to bacterial overgrowth. Luminal bacteria could modulate gastrointestinal symptoms and interfere with levothyroxine absorption. The aims of the present study were to assess the prevalence and clinical pattern of bacterial overgrowth in patients with a history of overt hypothyroidism and the effects of bacterial overgrowth decontamination on thyroid hormone levels.

Methods: A total of 50 consecutive patients with a history of overt hypothyroidism due to autoimmune thyroiditis was enrolled. Diagnosis of bacterial overgrowth was based on positivity to a hydrogen glucose breath test. Bacterial overgrowth positive patients were treated with 1200 mg rifaximin each day for a week. A glucose breath test, gastrointestinal symptoms, and thyroid hormone plasma levels were reassessed 1 month after treatment.

Results: A total of 27 patients with a history of hypothyroidism demonstrated a positive result to the breath test (27 of 50, 54%), compared with two in the control group (two of 40, 5%). The difference was statistically significant ($P < 0.001$). Abdominal discomfort, flatulence, and bloating were significantly more prevalent in the bacterial overgrowth positive group. These symptoms significantly improved after antibiotic decontamination. Thyroid hormone plasma levels were not significantly affected by successful bacterial overgrowth decontamination.

Conclusions: The history of overt hypothyroidism is associated with bacterial overgrowth development. Excess bacteria could influence clinical gastrointestinal manifestations. Bacterial overgrowth decontamination is associated with improved gastrointestinal symptoms. However, fermenting carbohydrate luminal bacteria do not interfere with thyroid hormone levels. **(*J Clin Endocrinol Metab* 92: 4180–4184, 2007)**

SMALL INTESTINAL bacterial overgrowth (SIBO) is a clinical condition, caused by an increased level of microorganisms exceeding the presence of more than 10^6 colony forming units/ml intestinal aspirate or colonic-type bacteria within the small intestine (1).

SIBO is considered a malabsorption syndrome because bacteria can adhere and damage small bowel absorptive surface, and can metabolize carbohydrates, lipids, and proteins normally absorbed in the small bowel (2). Although asymptomatic cases exist, SIBO is clinically characterized by signs and symptoms such as abdominal pain, bloating, flatulence, diarrhea, and weight loss (3).

Antibiotic therapy is the cornerstone of the treatment of SIBO. Several absorbable and nonabsorbable broad-spectrum antibiotics can be used. Rifaximin is a rifamycin derivative with antibacterial activity caused by the inhibition of bacterial synthesis of RNA (4). It is active against gram-positive and gram-negative bacteria, including both aerobes and anaerobes (5). Rifaximin 1200 mg/d is an effective treatment to achieve SIBO decontamination without increasing the incidence of side effects (6).

First Published Online August 14, 2007

Abbreviations: GBT, Glucose breath test; H_2, hydrogen; SIBO, small intestinal bacterial overgrowth.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

In the healthy subject, the main mechanisms restricting the bacterial colonization in the upper gut are the gastric acid barrier, mucosal and systemic immunity, and intestinal clearance. When these mechanisms fail, bacterial overgrowth develops. Failure of the gastric acid barrier can be caused by *Helicobacter pylori*-induced gastritis, drug-induced inhibition of acid secretion, autoimmune disease, malnutrition, and aging (7). Regarding local mucosal and systemic immunity, conditions such as HIV or immunoglobulin deficiencies (IgA deficit) can be linked to SIBO development.

Failure of intestinal clearance can be associated with anatomical abnormalities, such as gastrointestinal surgery, intestinal diverticula or fistula, or with conditions that impair intestinal peristalsis, such as myopathic, neuropathic, autoimmune, inflammatory, metabolic, and endocrine diseases (7).

With regard to endocrine disorders, it is known that thyroid hormones may influence gut motility modulating neurological and smooth muscle function (8, 9). Several studies have shown that hypothyroidism could be associated with decreased frequency of rhythmic colonic activity and slower oro-cecal transit time both in animal (10) and human subjects (11).

These neuromuscular disorders are responsible for diarrhea and constipation observed in patients affected by hyperthyroidism and hypothyroidism, respectively (12, 13).

Patients with hypothyroidism are supplemented with syn-

thetic T_4 hormone (levothyroxine-LT4) in oral doses to achieve physiological thyroid hormone serum levels. Many causes of LT4 malabsorption are known and discussed in literature (14). Common causes are gastrointestinal diseases (15–17) and infections (18), pancreatic and liver diseases (19), gastrointestinal surgical procedures (20, 21), dietary interactions (22), drugs (23, 24), and pregnancy (25). However, causes of malabsorption are sometimes unknown, and increased doses of T_4 are needed for hypothyroidism treatment.

Aims of the present study are to assess: 1) whether a history of overt hypothyroidism is associated with SIBO development, 2) the clinical manifestation of SIBO and the effects of SIBO decontamination in patients with a history of overt hypothyroidism, and 3) whether the presence of SIBO affects thyroid hormone levels.

Patients and Methods

The study was conducted between September 2005 and July 2006 on consecutive outpatients from the Gastroenterology, Endocrinology, and Internal Medicine Departments of the Gemelli Hospital, Catholic University of Rome.

Eligibility criteria

Patients with a history of overt hypothyroidism due to autoimmune thyroiditis were enrolled. The diagnosis was based on standard biochemical and instrumental criteria, which included a biochemical assay of venous blood for thyroid hormones, autoantibodies to thyroid antigens (thyroid peroxidase antibody, antithyroglobulin antibody), and thyroid ultrasound (26, 27). Serum thyroid hormones and thyroid autoantibodies were determined by commercial kits (Roche Elecsys 1010/2010 and Modular Analytics E170 analyzers; Roche Diagnostics, Indianapolis, IN). Free T_3, free T_4, and TSH were determined by immunochemiluminescence assay (normal range 2.3–4.2 pg/ml, 8.5–15.5 pg/ml, and 0.35–2.80 μUI/ml, respectively), and thyroid peroxidase antibody and antithyroglobulin antibody were determined by immunofluorescence assay (normal range $<$ 20.0 U/ml and $<$ 80.0 U/ml, respectively).

Diagnosis of overt hypothyroidism was based on serum TSH levels above 2.8 μUI/ml, and free T_3 and T_4 decreased. Autoimmune origins of hypothyroidism were defined by the presence of thyroid autoantibodies and typical thyroid ultrasound signs, such as reduced echogenicity (26, 27).

All patients were supplemented with synthetic T_4 hormone in oral doses, and they achieved euthyroid condition in the 2–6 months before enrolment.

All patients included in the study gave written informed consent.

The exclusion criteria were: age younger than 18 yr; other causes of hypothyroidism; use of antimicrobial agents within the previous 3 months; hypersensitivity to the antibiotics; pregnancy or breast-feeding; clinical conditions predisposing to SIBO; and evidence of major concomitant diseases, including tumors and hepatic and/or renal insufficiency.

All patients were instructed to maintain their usual diet and oral dose of T_4, and to avoid prokinetics, other antibiotics, and drugs interfering with intestinal motility during the study period.

For each patient, age at hypothyroidism diagnosis, time from diagnosis, and median daily dose of T_4 were recorded.

The control group consisted of healthy subjects, without a history and clinical evidence of thyroid disease and without any well-known clinical conditions predisposing them to SIBO. They were enrolled among the medical staff of our hospital, and were of similar sex and age.

All participants in the study came from Rome and the surrounding area.

Breath hydrogen (H_2) testing

Glucose breath test (GBT) was performed under standard conditions. In the 30 d preceding the test, no patients received antibiotics or laxatives. To minimize basal H_2 excretion, subjects were asked to have a carbohydrate-restricted dinner on the day before the test and to fast for at least 12 h. On the day of testing, patients did a mouthwash with 20 ml chlorhexidine 0.05%. Smoking and physical exercise were not allowed for 30 min before and during the test. End-alveolar breath samples were collected immediately before glucose ingestion. A dose of 50 g glucose in the form of iso-osmotic solution was then administered, and samples were taken every 10 min for 2 h, respectively using a two-bag system. The two-bag system is a device consisting of a mouthpiece, a T valve, and two collapsible bags; the first one collects dead space air, and the second one collects alveolar air. From this bag the breath sample was aspirated into a 20-ml plastic syringe. Samples were analyzed immediately using a model Quintron Gas Chromatograph (Quintron Instrument Co., Milwaukee, WI).

The test was considered as indicative of the presence of SIBO when the peak, *i.e.* the increase over the baseline of H_2 levels, was more than 12 parts per million (28).

The reproducibility of GBTs in our laboratory in patient populations (n = 20) is good, with a κ-statistic of 0.88 and 95% agreement on tests performed 1 wk apart.

Antibiotic treatment

All patients affected by SIBO received rifaximin (Normix 200 mg tablets; Alfa-Wassermann, Woerden, The Netherlands) 1200 mg/d (two tablets three times a day) for 7 d.

A GBT was repeated 1 month after the end of therapy in all treated patients to assess SIBO eradication.

Laboratory parameters

The main hematochemical parameters (total blood cell count, glucose, blood urea nitrogen, creatinine, electrolytes, total protein, albumin, bilirubin, aspartate aminotransferase, alanine aminotransferase, c-glutamyl-transpeptidase, alkaline phosphate, and prothrombin time) were evaluated in all patients at enrolment and 3 d after the end of the antibiotic treatment in patients affected by SIBO.

Thyroid hormone levels were assessed in all patients at enrolment, and 1 month after the end of the antibiotic treatment in patients affected by SIBO and 1 month after the first evaluation in patients without SIBO.

Symptoms assessment

Each patient was asked to complete a questionnaire using a four-point Likert scale (0 = absence, 1 = mild, 2 = moderate, and 3 = severe), including classic gastrointestinal symptoms (abdominal discomfort/pain, bloating, flatulence, constipation, and diarrhea), at enrollment. All symptoms were reevaluated after antibiotic treatment.

"Adverse experiences" occurring during the treatment period were recorded on daily diary cards, with the following grades: 1, mild; 2, moderate; and 3, severe (13). Patient compliance was assessed by a pill count of the drugs boxes returned the day after the last day of therapy administration. Low compliance was defined as more than 20% of pills returned. Side effects were defined as the occurrence of: 1) abnormalities in the main hematochemical parameters considered; and 2) "adverse experiences," considered as clinical findings or patient complaints that were not present in the 24 h immediately before enrollment in the trial.

Data analysis

To detect differences in SIBO prevalence, the χ^2 test was used. Differences according to age at hypothyroidism diagnosis, time from diagnosis, and median daily dose of T_4 between hypothyroid patients with or without SIBO were evaluated by the Levene test. To detect gastrointestinal symptoms, we used a four-point Likert scale (0 = absence, 1 = mild, 2 = moderate, and 3 = severe), but for the purpose of statistical analysis, the prevalence of gastrointestinal symptoms was considered as a binomial variable (1–3 = present/0 = absent). Differences were evaluated by the χ^2 or Fisher exact test, as appropriate. Differences in thyroid hormone levels before and after antibiotic treatment were evaluated by

the Student's *t* test. The statistical analysis was performed using Stata 6.0 (StataCorp, College Station, TX). A *P* value less than 0.05 was considered significant.

Results

Patients characteristics

A total of 50 patients with hypothyroidism and 40 controls were enrolled. Characteristics of the study groups are summarized in Table 1.

GBT positivity in patients and controls

In the patients' group, 27 subjects were found to be positive to GBT (27 of 50, 54%) compared with two in the control group (two of 40, 5%). The difference between groups was statistically significant ($P < 0.001$; odds ratio 22.3, 95% confidence interval 4.8–102.7; Fig. 1).

Clinical parameters of hypothyroidism and SIBO

No significant association was found between the presence of SIBO and age at hypothyroidism diagnosis, time from diagnosis, and median T_4 daily dose (Table 2).

Gastrointestinal symptoms in SIBO-positive and SIBO-negative patients

The prevalence of SIBO-related gastrointestinal symptoms in patients with a history of hypothyroidism are reported in Table 3. Abdominal discomfort, bloating, and flatulence were significantly associated with SIBO ($P < 0.01$). There was no statistically significant correlation between SIBO positivity and bowel habit (constipation or diarrhea).

Decontamination rate and side effects profile

The GBT decontamination rate in SIBO patients was 70.4% (19 of 27) after a 1-wk course with rifaximin 1200 mg/d. No dropouts were recorded.

No abnormalities in the tested laboratory parameters (total blood cell count, liver and kidney function) were observed at the control performed 3 d after the end of the treatment.

Compliance with rifaximin was excellent. More than 95% of patients in all groups took the prescribed number of tablets for the 7-d treatment. The prevalence of adverse events was very low: one patient complained of nausea and one of headache. The adverse events reported were both mild and disappeared rapidly after treatment.

Gastrointestinal symptoms and SIBO decontamination

A significant improvement in abdominal discomfort, bloating, and flatulence was observed in the group of patients decontaminated after rifaximin therapy ($P < 0.01$). No differences were found with regard to constipation and diarrhea after SIBO decontamination (Table 4).

None of the recorded gastrointestinal symptoms significantly improved in the group of treated but nondecontaminated patients (data not shown).

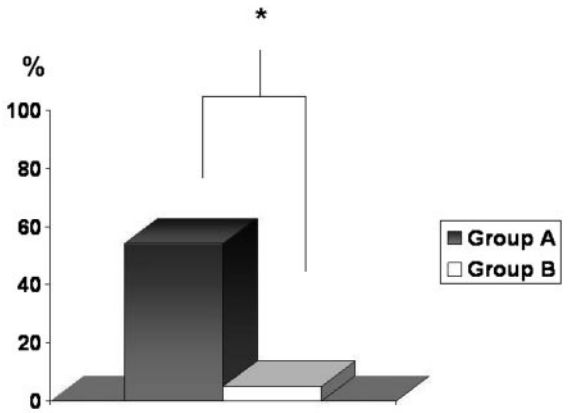

FIG. 1. SIBO prevalence in patients with a history of hypothyroidism (group A) *vs.* control group (group B). *, $P < 0.001$.

Thyroid hormone levels and SIBO decontamination

Median T_4 daily dosage (μg/d; μg/kg) was similar between patients who responded and those who did not respond to the antibiotic treatment (96.54; 1.42 *vs.* 94.89; 1.34).

No statistically significant difference was observed regarding thyroid hormone levels in the 19 SIBO decontaminated patients before and after antibiotic treatment (Table 5).

Thyroid hormone levels were also reassessed in patients without SIBO showing values similar to those of the first evaluation (data not shown).

Discussion

Interdigestive migrating motor complexes play a major role in the clearance of bacteria from the gut (29). In rats, bacterial overgrowth is induced by pharmacological disruption of migrating motor complexes, and restoration of intestinal motility reduces endoluminal bacterial density to normal values (30–32). Several diseases characterized by the disruption of normal motor events are often associated with SIBO: scleroderma (33), idiopathic intestinal pseudo-obstruction, autonomic neuropathy, and radiation enteropathy (34–36). Thyroid hormones may influence gut motility modulating neurological and smooth muscle function, and hypothyroidism could be associated with decreased fre-

TABLE 1. Demographic and clinical characteristics of patients with a history of hypothyroidism and control group

	Patients (n = 50)	Controls (n = 40)	*P* value
No. of males/females	13/37	10/30	ns
Mean age ± SD (yr)	35 ± 9	35 ± 10	ns
Mean BMI ± SD	21 ± 7	22 ± 6	ns

BMI, Body mass index; ns, not significant.

TABLE 2. Age at hypothyroidism diagnosis, time from diagnosis, and median T_4 daily dose in patients with and without SIBO

	SIBO	No.	Median	*P* value
Age at diagnosis (yr)	Positive	27	34.15	ns
	Negative	23	32.91	
Time from diagnosis (months)	Positive	27	6.15	ns
	Negative	23	6.48	
Median T_4 daily dose (μg/d)/(μg/kg)	Positive	27	98.67/1.44	ns
	Negative	23	93.47/1.39	

ns, Not significant.

TABLE 3. Prevalence of gastrointestinal symptoms (%) in patients with a history of hypothyroidism affected by SIBO (group 1) *vs.* patients with history of hypothyroidism without SIBO (group 2)

Gastrointestinal symptoms	Group 1 (%)	Group 2 (%)	*P* value
Abdominal discomfort	66.6	8.7	<0.01
Bloating	74.1	13.0	<0.01
Flatulence	55.5	8.7	<0.01
Constipation	18.0	13.0	ns
Diarrhea	11.1	4.3	ns

ns, Not significant.

quency of rhythmic colonic activity and slower oro-cecal transit time (10, 11). Our study shows that a history of overt hypothyroidism is a risk factor for SIBO development. The pathogenic link could be that intestinal motor dysfunction associated with hypothyroidism reduces the ability of the small bowel to clear luminal bacteria. In our study all enrolled patients had a history of overt hypothyroidism. It could be very interesting to evaluate if differences exist between subclinical and overt hypothyroidism concerning association with SIBO. We can speculate that the prevalence of intestinal overgrowth could be related to the severity of hypothyroidism. On the other hand, intestinal motility could be more heavily altered in overt hypothyroid patients developing SIBO. Intestinal myoelectrical activity, oro-cecal transit time, and intestinal neurohormonal regulation should be studied in future trials to confirm this hypothesis, and elucidate pathophysiological mechanisms behind the association between hypothyroidism and SIBO.

In the present study, all patients were under levothyroxine therapy, achieving euthyroidism at enrollment. It is possible that once SIBO is established during the hypothyroid phase, it does not clear spontaneously, even if made euthyroid.

The prevalence of gastrointestinal symptoms such as abdominal discomfort, bloating, and flatulence is significantly higher in SIBO-positive patients compared with SIBO-negative, and decontamination therapy is associated with statistically significant levels of clinical improvement. These findings suggest that, in patients with hypothyroidism, the presence of gastrointestinal symptoms after reaching a euthyroid condition is related to SIBO persistence. It is well known that, in patients affected by chronic functional disorders, gastrointestinal symptoms respond to placebo in 20–50% of cases. However, two recent randomized double-blind placebo-controlled trials by Pimentel (37) and Sharara (38) *et al.* showed that rifaximin significantly improved gastrointestinal symptoms in patients with chronic functional disorders and that symptom improvement was associated with a reduction in H_2 breath excretion. In addition, in our study, rifaximin is administered only for a short time, with benefits tested after 1 month; the placebo effect could be minimal after this time.

TABLE 4. Prevalence of gastrointestinal symptoms (%) in 19 patients with a history of hypothyroidism affected by SIBO and successfully decontaminated before and after antibiotic treatment

Gastrointestinal symptoms	Pre (%)	Post (%)	*P* value
Abdominal discomfort	73.7	15.8	<0.05
Bloating	84.2	15.8	<0.05
Flatulence	47.4	10.5	<0.05
Constipation	10.5	10.5	ns
Diarrhea	10.5	5.3	ns

ns, Not significant; Pre, before antibiotic treatment; Post, after antibiotic treatment.

TABLE 5. Thyroid hormone plasma levels in patients with a history of hypothyroidism affected by SIBO, eradicated by rifaximin, before and after antibiotic treatment

	No.	Median	SD	*P* value
FT3 (pg/ml) pre	19	3.405	0.403	ns
FT3 (pg/ml) post	19	3.315	0.323	
FT4 (pg/ml) pre	19	11.579	1.389	ns
FT4 (pg/ml) post	19	11.921	1.124	
TSH (μUI/ml) pre	19	1.811	0.428	ns
TSH (μUI/ml) post	19	1.621	0.425	

FT3, free T_3; FT4, free T_4; ns, not significant; pre, before antibiotic treatment; post, after antibiotic treatment.

SIBO-related bacteria excess can also interfere with the absorption of many substances, such as carbohydrates, proteins, and lipids (2). A direct mucosal injury resulting from bacterial adherence and increased production of enterotoxins could affect the activity of brush-border disaccharidases. On the other hand, bacteria can compete with the host for nutrient use (2). In our study the presence of SIBO is not associated with T_4 malabsorption, and SIBO decontamination does not modify thyroid hormone levels. Bacterial population contaminating the upper gut is extremely complex, and metabolic functions are very difficult to investigate (39). In the present study, SIBO diagnosis is based on the H_2 breath test. Its positivity suggests the presence of sugars fermenting bacteria (40), thus producing H_2 and other metabolites. It is possible that this test does not identify bacteria using proteins and amino acids such as T_4 as their prevalent energetic substrates. It could explain why SIBO does not interfere with thyroid hormone levels in our study. On the other hand, the high prevalence of symptoms such as bloating and flatulence could reflect a prevalent "fermentative bacteria" in our population.

In conclusion, a history of overt hypothyroidism is associated with SIBO development and persistence. Excessive bacteria could modulate neuromuscular function and influence clinical manifestations. SIBO decontamination is associated with gastrointestinal symptom improvement. Finally, carbohydrate fermenting bacteria do not interfere with thyroid hormone levels.

Further studies are needed to characterize the bacteria species involved in SIBO, and clarify their metabolic functions and their relationship with intestinal motility.

Acknowledgments

Received March 19, 2007. Accepted August 3, 2007.

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This work was supported by an unrestricted grant provided by Fondazione Ricerca in Medicina, Italy.

Disclosure Statement: The authors have nothing to declare.

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