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Research Article

THE EFFECT OF RIFAXIMIN TREATMENT FOR SMALL INTESTINAL BACTERIAL OVERGROWTH ON THYROID DISORDERS

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Abstract- Introduction. Clinical findings indicate frequent coexistence of small intestinal bacterial overgrowth (SIBO) and autoimmune thyroiditis. However, the causal relationship of these diseases has not been confirmed. The aim of the study was to assess the effect of rifaximin treatment of SIBO on thyroid function. **Material and methods.** The study included 146 patients, aged 25-68 years, with diagnosed SIBO on the basis of lactulose hydrogen breath test (LHBT). Furthermore, in 62 patients the levels of free triiodothyronine and thyroxine (FT3, FT4) or thyroid-stimulating hormone (TSH) and anti-thyroid peroxidase antibodies (ATPO) deviated from the accepted laboratory standards. From this group 32 patient with predominant diarrhea (group I) and 30 patients with predominant constipation (group II) were admitted for further evaluation. Rifaximin at 3x 400 mg was used for 7 days and this cycle was repeated 3 times every 28 days. Results were assessed after 3 months. **Results.** After 3 months the result of LHBT decreased in group I by 72,1% and in group II by 76,3%. A positive correlation between the results of LHTB and the level of ATPO was observed, partially in II group. After the treatment the level of ATPO decreased in group I from 31.9 ± 23.4 to 19.4 ± 19.7 ± 13.4 IU/ml ($p < 0,05$) and in group II from 94.1 ± 56.3 to 23.4 ± 13.3 IU/ml ($p < 0,01$). In group II the level of TSH also decreased from 5.1 ± 0.9 to 3.7 ± 1.8 mU/L ($p < 0,01$). **Conclusion**. Rifaximin treatment of small intestinal bacterial overgrowth improves thyroid disorders.

Keywords- small intestinal bacterial overgrowth, rifaximin, thyroid disorders.

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Introduction

Small Intestinal Bacterial Overgrowth (SIBO) is a common cause of abdominal pain, bloating and diarrhea or constipation [1-4]. The variability of the clinical picture may depend on the intensity of the colonization of the bacterial species and their biological activity [5-7]. Allergy and food intolerance and coexistence of other diseases including thyroid disease are considered after excluding non-specific inflammatory diseases of the digestive tract. Constipation is usually observed in hypothyroidism, whereas diarrhea is more common in hyperthyroidism [8-10]. However, diarrhea also occurs in hypothyroidism [11]. Impaired intestinal micro-flora may coexist in such cases [12,13]. Bacterial overgrowth in the small intestine changes its secretory, digestive and immune functions [14,15]. The weakening of the intestinal epithelial barrier contributes to the release of bacterial and food antigens into the bloodstream and can trigger or exacerbate immune and inflammatory processes in other organs [16,17]. The cases of coexistence of intestinal bacterial overgrowth and immune-mediated diseases, including Hashimoto's disease are the indication of that [18,19]. Own previous studies in SIBO patients revealed increased levels of antibodies against thyroid peroxidase [20]. The obtained results did not allow conclusions to be drawn about the casual relationship of these changes. Thus, studies have been undertaken to evaluate thyroid function indices after rifaximin treatment of small intestinal bacterial overgrowth.

Material and methods

The study included 146 patients, aged 25-68 years (mean age 42.6 ±21.1), 97 women and 49 men, with chronic abdominal pain, bloating and diarrhea or constipation. Diagnostic and therapeutic procedures were performed at the Department of Clinical Nutrition and Gastroenterological Diagnostics and at the Department of Gastroenterology of the Medical University of Lodz.

Diagnostic procedures

In the first stage, the lactulose hydrogen breath test (LHBT) and the breath-hydrogen analyzer (Gastrolyzer, Bedfont Scientific Ltd) were used to identify or exclude small intestinal bacterial overgrowth. The test result was considered positive when an increase in the concentration of hydrogen in the expired air exceeded 20 ppm above the baseline following ingestion of 25 ml lactulose according to generally accepted criteria [21]. Routine laboratory tests were also performed: complete blood count, glucose, urea, creatinine, lipase, amylase, bilirubin, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, cholesterol, triglycerides, acute phase proteins and fecal calprotectin. Furthermore, serum levels of thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4) were determined by immunochemical method (ELFA) and anti-thyroid peroxidase antibodies (ATPO) by immunoenzymatic method.

In 62 patients the results of the study indicated the possibility of SIBO coexistence with immune-mediated thyroiditis. Taking into account the nature of the complaints two groups of patients were distinguished (open trial).

Group I (n=32) patients with predominant diarrhea

Group II (n=30) patients with predominant constipation

In the differential diagnosis the patients with documented allergy and food intolerance, celiac disease, inflammatory bowel diseases and other organic,

metabolic and mental diseases were excluded from the study.

Therapeutic procedures

Both groups were assigned to take rifaximin at the dose 3x400 mg for 7 days. This 7-day cycle was repeated twice every 28 days. The patients were also recommended to follow the same balanced diet. At the end of the third month, after completion of the treatment program, the patients' clinical status was evaluated, hydrogen breath test was repeated and the levels of TSH, FT3, FT4 and ATPO were determined.

Ethical procedures

The patients' written consent and the approval of the Bioethics Committee of the Medical University of Lodz were obtained. The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice (GCP).

Statistical analysis

Comparisons between groups were performed with Wicoxon test and Mann-Whitney rank-sum test. The relationship between LHBT and ATPO was estimated with the Spearman correlation and linear regression equation. The calculations were performed with Statistica 9.1 software.

Results

The results of the hydrogen breath test were similar in both groups whereas the levels of thyroid hormones and thyroglobulin differed significantly [Table-I], p <0.05).

Table-1 *The preliminary results of patients enrolled in this study; group I – patients with predominant diarrhea, group II – patients with predominant constipation,* p < 0.05, **p = 0.01.*

Features	Group I (n=32)	Group II (n = 30)
LHBT (ppm)	66,9 ± 16,9	62,1 ± 15,3
TSH (mU/L)	2,24 ± 0,59	3,79 ± 1,83*
FT3 (pmol/L)	5,13 ± 0,93	3,77 ± 1,06
FT4 (pmol/L)	13,4 ± 2,16	9,47 ± 2,56*
(IU/ml)	31,9 ± 23,4	94,1 ± 56,3**

LHBT – Lactulose Hydrogen Breath Test; TSH – Thyroid-Stimulating Hormone
FT3 - Free Triiodothyronine; FT4 – Free Thyroxine; ATPO – Anti-Thyroid Peroxidase

Group II also demonstrated significantly higher level of ATPO – 31.9± 23.4 iU/ml vs. 94.1 ± 56.3 IU/ml (p< 0.01).

In both groups a positive correlation was found between the results of the hydrogen breath test and the level of ATPO, respectively in group I - r = 0.069, p > 0.05 [Fig-1], in group II – r = 0.854, p< 0.01 [Fig-2].

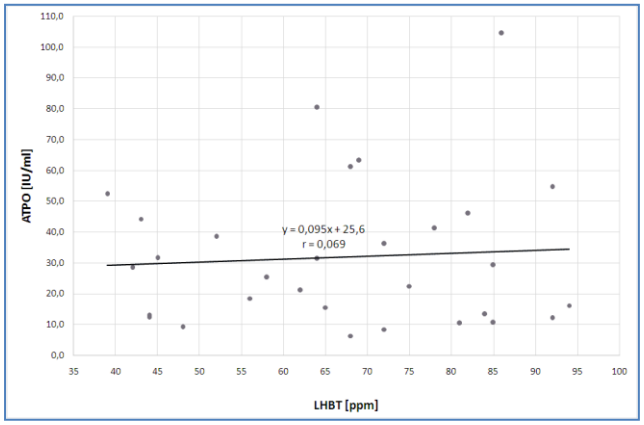

Fig-1 Correlation between the value of lactulose hydrogen breath test (LHBT) and the level of anti-thyroid peroxidase (ATPO) in patients with predominant diarrhea; p > 0.05

After rifaximin treatment the mean value of LHBT decreased in group I from 66.9± 9.6 to 15.6 ± 6.8 ppm, and in group II from 62.1 ± 15.5 to 14.9 ± 7.5 ppm (p< 0,001, [Fig-3].

The mean level of thyroid hormones did not change significantly [Fig-4,5], whereas the level of TSH decreased in group II from 5.1 ± 0.9 to 3.7 ± 1.8 mU/L (p< 0,01, [Fig-6].

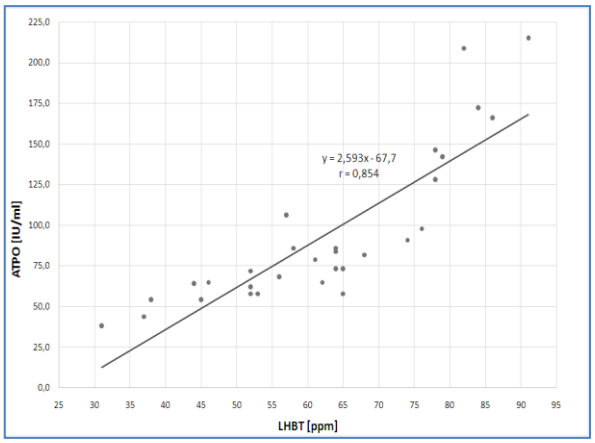

Fig-2 Correlation between the value of lactulose hydrogen breath test (LHBT) and the level of anti-thyroid peroxidase (ATPO) in patients with predominant diarrhea; p < 0,01.

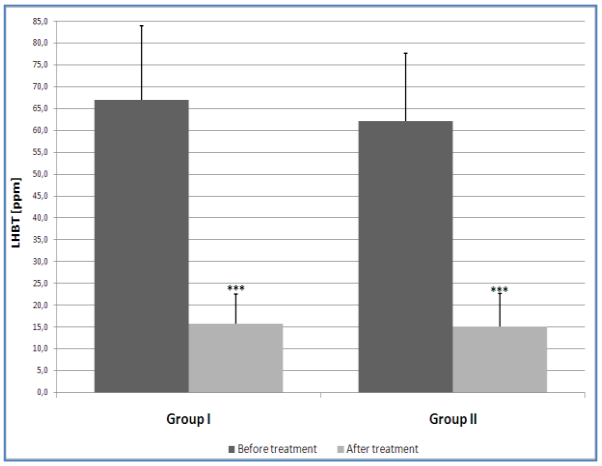

Fig-3 The value of lactulose hydrogen breath test (LHBT) before and after rifaximin treatment in patients with predominant diarrhea group I) and patients with predominant constipation (group II); ***p < 0.001

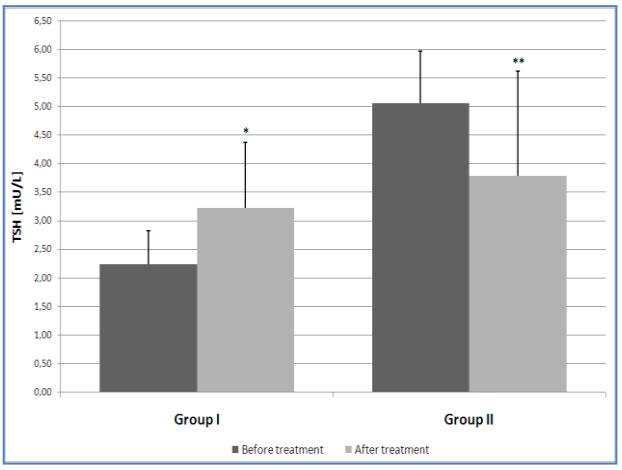

Fig-4 The level of thyroid-stimulating hormone (TSH) before and after rifaximin treatment in patients with predominant diarrhea (group I) and patients with predominant constipation (group II); *p < 0.05, **p < 0.01

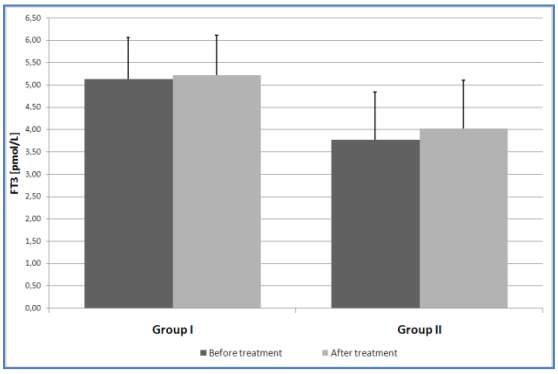

Fig-5 The level of free triiodothyronine (FT3) before and after rifaximin treatment in patients with predominant diarrhea (group I) and patients with predominant constipation (group II); differences no significant.

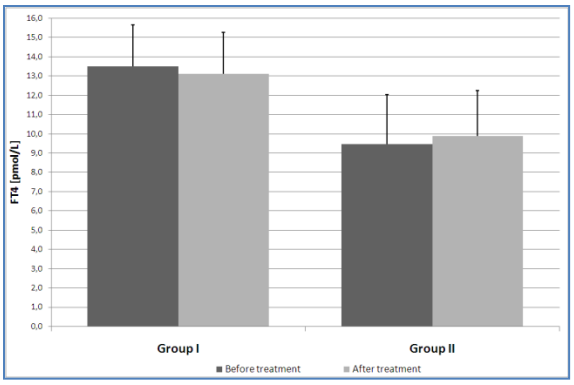

Fig-6 The level of free thyroxine (FT4) before and after rifaximin treatment in patients with predominant diarrhea (group I) and patients with predominant constipation (group II); differences no significant.

After the treatment the level of ATPO decreased significantly in both groups; in group I from 31.9 ± 23.4 to 19.4 ± 13.4 IU/ml ($p<0.05$), in group II from 94.1 ± 56.3 to 22.4 ± 13,9 IU/ml ($p< 0.01$, [Fig-7]. Gastrointestinal symptoms resolved in 26 (81,2%) group I and 18 (60,0%) group II patients ; significant alleviation of complaints was observed in the remaining patients.

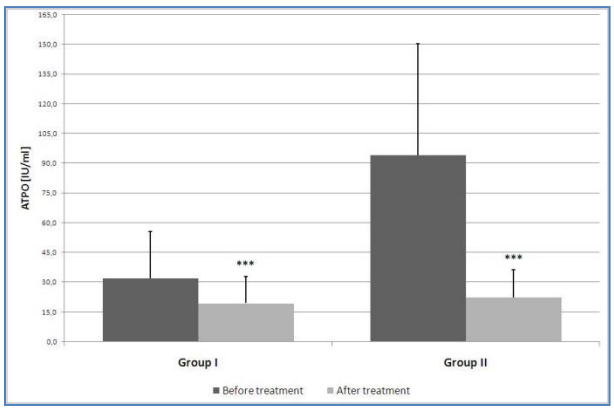

Fig-7 The value of anti-thyroid peroxidase (ATPO) before and after rifaximin treatment in patients with predominant diarrhea (group I) and patients with predominant constipation (group II); ***p < 0.001

Rifaximin was well tolerated, the patients did not report adverse effects in the course of the treatment.

Discussion

The incidence of autoimmune thyroid diseases has increased significantly in recent decades. The reasons for this phenomenon are seen, among others, in changes in dietary patterns and impaired intestinal microflora [22, 23]. The obtained results indicate the possibility of coexistence of thyroid diseases and small intestinal bacterial overgrowth. The evidence of this is the positive correlation between the results of the hydrogen breath test and the level of ATPO as well as the decreased antibody titer after rifaximin treatment. It should be noted that the ATPO level was still above normal range in most patients after 3 months of treatment. This indicates the chronic nature of the immune process, which is a characteristic feature of chronic lymphocytic thyroiditis. In most patients small intestinal bacterial overgrowth is the cause of chronic inflammatory process. Intestinal barrier damage may contribute to homeostatic imbalance of the immune system. The release of bacterial antigens into the bloodstream brings with it adverse effects. Immune complexes that are formed migrate to many organs and can trigger or exacerbate inflammatory processes involving cytokines and oxygen free radicals. These changes can occur simultaneously in the intestinal wall and in the thyroid gland [24-26]. Bacterial antigens activate helper lymphocytes (CD4+) directed against thyroid antigens. These in turn activate cytotoxic lymphocytes (CD8 +) and B lymphocytes, initiating a further step of the immune cascade. In the next stage, there comes to the cumulation of macrophages and dendritic cells in the parenchyma of thyroid gland [27]. As a result, the secretion of anti-thyroid peroxidase (ATPO) and anti-thyroglobulin (ATG) antibodies increases. These antibodies bind to specific receptors on thyroid follicular cells [28]. The release of proinflammatory cytokines and prostaglandin E, leading to the destruction of thyroid follicles and apoptosis of thyrocytes is the last stage of the pathogenesis of lymphocytic thyroiditis [29]. These changes are manifested as hypoechogenic lesions on ultrasound imaging. Laboratory tests show increased titers of ATPO and ATG and decreased production of thyroid hormones.

In the examined material, a significant decrease in ATPO level after rifaximin treatment draws attention. The increased production of these antibodies is probably related to the immune response to bacterial antigens. If these factors are long-lasting they can lead to functional and destructive disorders in the thyroid gland.

The obtained results do not prejudge the exclusive involvement of intestinal bacteria in the pathogenesis of lymphocytic thyroiditis. In these cases, the simultaneous effect of nutritional factors should be considered [30]. Gier D. [31] found specific anti-gliadin IgG antibodies in as many as 92.0% of patients with Hashimoto's thyroiditis. Celiac disease and non-celiac gluten sensitivity were equally observed [32,33]. Own study excluded individuals with specific IgE and IgG antibodies against most common foods, which does not exclude food intolerance of enzymatic origin. Heckl et al. [34] observed fructose and lactose intolerance in 73.3 patients with Hashimoto's disease. Esposito et al. [35] reported that 83.3% of patients with high ATPO levels had lactase deficiency and following a strict dairy-free diet, lowered this antibody level and improved clinical status. Similarly, Asik et al. [36] found that 75.9% of patients with Hashimoto's thyroiditis had lactose intolerance and showed that introduction of a restrictive diet led to the decreased levels of TSH.

Immune and enzymatic disorders and changes in the small intestine bacterial flora cause impairment of digestion and absorption and may therefore lead to nutritional deficiencies [37,38]. Vitamin B12 deficiency is suggested to be one of the factors inducing the development of Hashimoto's thyroiditis [39].

A crucial role is attributed to vitamin D, which has immunoregulatory properties and inhibits the production of proinflammatory cytokines. The results of many studies indicate its deficit in subjects with autoimmune thyroiditis [40-45]. Absorption disorders can also be the cause of mineral deficiencies (phosphorus, magnesium, iron) and microelements such as iodine, selenium, zinc, chromium [46-49].

Selenium plays a crucial role in maintenance of thyroid homeostasis. It is a component of iodothyronine deiodinase and is responsible for the conversion of thyroxine to triiodothyronine [50,51]. In the form of selenocysteine it is present in other enzymes protecting the thyroid gland against oxidative damage [52]. The level of selenium in patients with Hashimoto's thyroiditis is lower than in healthy subjects, which is an indication for its supplementation [53].

Zinc ions also demonstrate immunomodulatory and anti-inflammatory properties and their deficiency may impair the synthesis and metabolism of thyroid hormones [54].

The importance of these factors in the pathogenesis of thyroid diseases has been confirmed by the results of the research on the effects of their supplementation. Mazokopalis et al. [55] reported decreased TSH levels and ATPO titers after several-month supplementation with vitamin D (dose ranging from 1200 to 4000 IU/ daily). Nacamulli et al. [56], after 12-month selenium supplementation (80ug /daily) achieved a decrease in ATPO level in 28.5% of patients; Balzacs C [57] under similar conditions - in 60.3% of patients using selenium daily dosage of 2x100 µg.

The above observations show that patients with small intestinal bacterial overgrowth and thyroid diseases require a balanced diet suitable for individual needs, elimination of some products or supplementation with many nutrients. Such management aims at getting rid of the effects of a complex process of malabsorption. The removal of the causes of these disorders requires antibacterial treatment. Various antibiotics have been used for this purpose, but many years of clinical experience have shown that rifaximin is the most effective and safest antibiotic [58,59]. Rifaximin acts on many pathogenic bacteria but does not decrease beneficial bacterial species. Moreover, it exhibits cyto-protective properties, improves epithelial barrier stability, prevents bacterial translocation, inhibits the secretion of pro-inflammatory cytokines and regulates local and systemic immunity [60]. However, the therapeutic dose and the duration of the treatment remain controversial. Most frequently the 7-day treatment is recommended, dosage 800 - 1200 mg/day with indication of several repetitions in subsequent months [61]. The therapy was also conducted continuously for many weeks [62, 63] and even months [64]. In own study, such therapy was repeated three times in anticipation of diminished intestinal immunological and inflammatory changes, the improvement of digestion and absorption and regression of symptoms. This effect was obtained in most patients with simultaneous improvement of thyroid disorders. This confirms the view that small intestinal bacterial overgrowth can adversely affect thyroid function. On the other hand, it indicates that patients with thyroid diseases should undergo examinations of the intestinal bacterial flora, particularly in the case of coexistence of chronic gastrointestinal symptoms.

Conclusion

Rifaximin treatment of small intestinal bacterial overgrowth improves thyroid disorders.

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Conflict of interest: The authors declare no conflict of interest

Author statement: All authors read, reviewed, agree and approved the final manuscript

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Research Category: Medical Research

Abbreviations:

LHBT – Lactulose Hydrogen Breath Test
TSH – Thyroid-Stimulating Hormone
FT3 - Free Triiodothyronine
FT4 – Free Thyroxine
ATPO – Anti-Thyroid Peroxidase

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