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Received: 12 December, 2023

Accepted: 17 April, 2024

Published: 24 June, 2024

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CITATION

Ceylan S. Comparison of gastric emptying before and after treatment for subclinical hypothyroidism. Atlantic J Med Sci Res. 2024;4(2):32-6.

DOI: 10.5455/atjmed.2023.12.055

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INTRODUCTION

While serum free thyroid hormone levels are within normal values, high thyroid stimulating hormone (TSH) levels are defined as subclinical hypothyroidism (SH). SH is observed at a rate of 3-8% in the general population. Its prevalence increases with age and is more common in women (1,2). In overt hypothyroidism, gastrointestinal functions are negatively affected due to decreased metabolic rate, edema, inflammation and similar mechanisms.

Comparison of gastric emptying before and after treatment for subclinical hypothyroidism

Abstract

Aim: The aim of this study was to evaluate the effect of levothyroxine treatment on dyspeptic symptoms and gastric emptying time in patients with subclinical hypothyroidism.

Materials and Methods: Liquid gastric emptying scintigraphy was performed to detect the presence of gastroparesis in patients with dyspeptic complaints who were followed up with a diagnosis of subclinical hypothyroidism in the thyroid outpatient clinic. Those with specific hypothyroidism symptoms during their follow-up were treated with low dose (25 mg) levothyroxine for at least 6 months. Liquid gastric emptying scintigraphy test was performed again after treatment for those who continued to have dyspeptic complaints. Patients whose gastric emptying time was calculated using a liquid gastric emptying scintigraphy test before and after levothyroxine treatment were retrospectively examined. For testing, 18.5-37 MBq (0.5-1 mCi) 99m-Tc nanocolloid was added to 300 ml of water. Late images were acquired at 30 minutes and one hour. The time activity curve was obtained.

Results: Gastric emptying was normal in 13 (23.6%) patients in the liquid gastric emptying scintigraphy test performed before treatment. After treatment, gastric emptying half-time was normalized in 34 (81%) of 42 (76.4%) patients with a long gastric emptying half-time before treatment. In total, 47 patients had normal gastric emptying half-time values after treatment, and gastric emptying half-time was calculated to be long in 8 patients (14.5%).

Conclusion: In our study, gastric emptying time was prolonged in 76.4% of patients with subclinical hypothyroidism, and in 81% of these patients, gastric emptying time was calculated within normal limits after LT4 treatment. Detection of prolongation of gastric emptying time due to the presence of gastroparesis in subclinical hypothyroidism cases followed up without treatment may be a guide in the prescription of treatment.

Keywords: Subclinical hypothyroidism, levothyroxine, radionuclide imaging, gastric emptying time, gastroparesis

The cause of recurrent dyspeptic complaints in patients followed for SH may be due to gastroparesis. The presence of gastroparesis in patients with dyspepsia can be evaluated with gastric emptying scintigraphy. Liquid gastric emptying scintigraphy (LGES) is a test that is easy to administer and evaluate and has very good patient compliance. In these patients, levothyroxine (LT4) treatment can be started when TSH reaches a certain level or in the presence of recurrent hypothyroidism symptoms (3,4).

This study aims to evaluate whether there is a normalization of gastric emptying after 25 mg of levothyroxine treatment in subclinical hypothyroidism cases with dyspepsia and to contribute to the literature on this issue.

MATERIALS AND METHODS

55 adult patients were included in this retrospective study. LGES test was performed to detect the presence of gastroparesis in patients with dyspeptic complaints who were followed up with a diagnosis of SH in the thyroid outpatient clinic. Those who had specific hypothyroidism symptoms during follow-up were treated with low dose (25 mg) LT4 for at least 6 months. LGES test was performed again after the treatment for those whose dyspeptic complaints continued. Patients whose (gastric emptying half-time) GEHT was calculated by performing LGES test before and after LT4 treatment were examined retrospectively. Thyroid function tests (TFT) and thyroid USG were performed in all patients. While fT3 and fT4 values were normal in at least one year of follow-up, TSH levels were high. Thyroid volume was higher than normal in neck USG in 20 of the patients. LGES test was performed due to the complaints of indigestion in the patients who were followed up with SH without treatment. Patients with a thyroid volume greater than 40 ml, very thin or obese patients, chronic disease, prokinetic drug use, chronic drug use, diabetes mellitus, smoking, presence of stomach or bowel disease, history of operation, hiatal hernia, gastroesophageal reflux were excluded from the study.

A fasting state of four to six hours was maintained prior to scintigraphy. Imaging was performed in the early morning hours when gastric emptying was faster. Those with blood sugar levels <40mg/dl or >275 mg/dl were not included in the study. For the test, 18.5-37 MBq (0.5-1 mCi) 99m-TC nanocolloid was added to 300 ml of water and the patient was asked to swallow immediately. Scintigraphic images of the patients were recorded with a Siemens E-cam gamma camera. A low-energy multipurpose collimator was used in a 128x128 matrix. The patient was seated at an angle of 30 to 45 degrees. Imaging started immediately after the patient drank the fluid. Late images were acquired at 30 minutes and one hour. To reduce physical activity between images, the patient was kept in a sitting position. ROIs (regions of interest) including the antrum and fundus were plotted from the anterior images and the time activity curve was obtained. The LGES half-time

was accepted as 23±3 normal gastric emptying time (5). Our patients with dyspepsia and high TSH levels were given 25 mg of levothyroxine treatment for at least 6 months. Patients who had control scintigraphy after treatment were included in this retrospective study. LGES test was repeated after treatment. The patients took this medicine in the morning, fasting. TFT was repeated for the controls. Our study was retrospective and informed consent was obtained from patients. Our retrospective study was approved by Gaziosmanpaşa Training and Research Hospital Ethics Committee with 28 numbers on 01.03.2023.

Statistical Analysis

For statistical analysis, SPSS version 21 software was used. Variables were expressed as the number and percentage of cases for categorical variables and as the median (minimum-maximum) for continuous variables. Wilcoxon test was used for non-normally distributed continuous variables and the Mc-Nemar test was used for categorical variables in the comparison of pre- and post-treatment variables. Mann-Witney U test was used for non-normally distributed continuous variables and the Chi-square test was used for categorical variables in the comparison of cases whose gastric emptying time improved with treatment and did not. The independent variables that determined the normalization of gastric emptying time with treatment were calculated by logistic regression analysis. $p < 0.05$ was considered statistically significant as two-sided.

RESULTS

The mean age of the patients was 60 (55-67). Of these, 41 (74.5%) were women. LGES test was performed on 55 patients with dyspeptic complaints before and after treatment. TSH levels were higher than normal in all of our patients. In our patients, the TSH value was measured as 7.33 (7.12-7.47) mIU/L before treatment and 3.57 (3.44-3.69) mIU/L after treatment. Gastric emptying was normal in 13 (23.6%) patients in the LGES test performed before treatment. After treatment, GEHT was normalized in 34 (81%) of 42 (76.4%) patients with a long GEHT before treatment. In total, 47 patients had normal GEHT values after treatment, and GEHT was calculated to be long in 8 patients (14.5%). The rate of normalization is higher in female patients after treatment. As age increases, the normalization rate after treatment in GEHT decreases. The results are summarized in Tables 1-3.

Table 1. Data of patients with gastric emptying time calculated before and after LT4 treatment

	Those whose gastric emptying is normalized after treatment	Those whose gastric emptying is still prolonged after treatment	p
Gender (female/male) (% in gender)	28 (90.3) / 6 (54.5)	3 (9.7) / 5 (45.5)	0.02
Age	59.79 (55-67)	64.5 (61-67)	0.01

Table 2. Data of patients whose gastric emptying half-time is calculated to be long after treatment

Patients	Age	Gender	TSH (mIU/L) (pre-treatment)	TSH (mIU/L) (post-treatment)	The volume of the thyroid gland
1	67	Male	7.28	3.64	Normal
2	65	Male	7.37	3.49	Goiter
3	62	Male	7.31	3.63	Goiter
4	61	Male	7.38	3.55	Goiter
5	67	Male	7.47	3.61	Goiter
6	67	Female	7.12	3.47	Goiter
7	64	Female	7.15	3.55	Goiter
8	63	Female	7.35	3.57	Goiter

Table 3. The significance of age and gender in terms of response to treatment in patients with prolonged gastric emptying

	Confidence interval	Odds	p
Age	0.434-0.897	0.624	0.11
Gender (female compared to man)	1.402-137.24	13.87	0.25

DISCUSSION

In this study, GEHT returned to normal after treatment in 34 (81%) of 42 (76.4%) patients who had long GEHT before treatment. While GEHT values returned to normal after treatment in a total of 47 patients, GEHT was calculated to be prolonged in 8 patients (14.5%). SH is highly prevalent in the general population. The association between overt hypothyroidism and gastroparesis is well-established (6,7). Thyroid hormones play a crucial role in metabolic regulation (6). Gastroparesis, a condition characterized by delayed gastric emptying without mechanical obstruction, significantly impacts the quality of life (8,9). LT4 tablets are successfully utilized in treating overt hypothyroidism. However, for patients with SH, LT4 is selectively prescribed (10). Approximately 10 percent of patients undergoing LT4 therapy remain euthyroid. Initiation of treatment in these cases is prompted by recurrent hypothyroidism symptoms (11).

In our study, 42 out of the 55 patients exhibited prolonged GEHT in the LGES test. This extension in GEHT might be attributed to a relative hypothyroid state in these SH patients. After at least 6 months of treatment with a 25 mg LT4 tablet, GEHT was normalized in 36 patients, leading to a decrease in dyspeptic complaints frequency. In patients with SH, LT4 therapy may be administered to safeguard the thyroid gland from TSH effects. Notably, significant recurrent hypothyroid symptoms may necessitate treatment initiation, including extreme fatigue, resistant obesity despite a low-calorie diet, hypercholesterolemia,

treatment-resistant depression, infertility, and goiter growth over time (12).

The prolongation of GEHT before LT4 treatment in the study participants may be attributed to the patients' relative hypothyroid state. The presence of intracellular hypothyroidism or changes in LT4 transfer due to insufficient production of peripheral LT3 may have contributed to the prolongation of GEHT in patients with SH (13).

Goiter is typically asymptomatic until the thyroid volume reaches 40 ml or more (14). In 85 percent of asymptomatic goiter cases, there is compression on the trachea or esophagus in 30 percent (14). The volume of goiter in the patients included in our study ranged from 20 to 30 ml. Notably, in patients with goiter, the normalization of GEHT after treatment was lower than in those without goiter.

In 8 patients with long GEHT before treatment, there was no post-treatment normalization. Seven of these eight patients had a goiter. Most of these patients were male. Some large-scale studies show a decrease in the volume of goiter after LT4-iodide treatment (7). The protective effect of LT4 on the thyroid gland is quite significant. None of our patients had received radioactive iodine therapy before the study. More care should be taken in starting LT4 therapy in elderly patients. TSH suppression may pose the risk of atrial fibrillation and metabolic bone disorder. Our patients, for whom we were prescribed LT4 treatment, were kept under follow-up and regularly checked out.

Thyroid disease is usually seen more frequently in women (6). In our study, the female gender was also higher in number. Some male patients were excluded because of smoking, which is more common in males in the country of study. Solid gastric emptying scintigraphy can also be performed to evaluate gastroparesis. The Solid Gastric Emptying Scintigraphy (SGES) test, due to its length and complexity, may pose challenges in the elderly population. However, results from LGES and SGES are generally correlated (15). LGES, conversely, is remarkably easy to administer and elicits cooperation, especially in elderly patients. Delayed imaging in the SGES test can take up to 4 hours and is difficult in the elderly population due to long hospital stays and the presence of medications that must be taken orally. SGES test is completed within 1 hour, which is very advantageous for the patient. In our study, it was evaluated using the GEHT LGES test. Previous research indicates a weak relationship between GEHT and dyspeptic complaints (15). In our study, GEHT was within normal limits for 13 patients with dyspeptic complaints. According to the results of our study, the normalization rate is higher in female patients after treatment. As age increases, the rate of normalization after treatment in GEHT decreases. Nevertheless, scintigraphic GEHT calculations may not fully capture the digestive process and gastrointestinal neuroendocrine events (16).

Unlike solid gastric emptying scintigraphy, LGES is an easy and short-term test. Solid food is broken down into smaller pieces by enzymes and gastric juice. Solid food needs to be broken down to pass through the pyloric sphincter, while liquids pass directly. The scintigraphic calculation of GEHT is superior to barium tests because LGES is a physiological test (17).

The prevalence of gastroparesis in diabetic patients was reported to be 64 percent (18). Some studies involving diabetic patients have reported a relationship between dyspeptic complaints and prolonged GEHT. In addition, acute changes in blood sugar affect gastric emptying (17). Diabetic patients were not included in this study; The included patients did not have hypoglycemia or hyperglycemia.

Rapid gastric emptying may also be a result of autonomic dysfunction (18). There was no evidence of rapid gastric emptying in the observed patients of this study. Since the radiation dose required for LGES imaging is very low and the test time is short, it has fulfilled a practical test requirement. Many chronic diseases such as diabetes, neuromuscular disorders, and endocrine disorders may be accompanied by indigestion complaints. However, with appropriate precautions, dyspeptic complaints can be prevented. In cases of SH, minor changes in thyroid hormone levels can delay gastric emptying.

Study Limitations

The weakness of our study is that it is retrospective. Solid gastric emptying scintigraphy and intestinal transit time calculation were not performed on the patients.

CONCLUSION

The clinical and biochemical follow-up of SH cases is very important. When LT4 is prescribed in these patients, some symptoms that they feel uncomfortable in their daily lives can be improved. Detection of prolongation of gastric emptying time due to the presence of gastroparesis in SH cases followed without treatment may guide the treatment prescription. Close follow-up is required after treatment. There is a need for prospective studies on this subject.

Conflict of Interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical Approval

Our retrospective study was approved by Gaziosmanpaşa Training and Research Hospital Ethics Committee with 28 numbers on 01.03.2023.

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