Effects of L-Thyroxine on Gastric Motility and Ghrelin in Subclinical Hypothyroidism: A Prospective Study

Asena Gökçay Canpolat, Taylan Kav, Bülent Sivri, and Bülent Okan Yildiz

Department of Internal Medicine (A.G.C.), Department of Internal Medicine, Division of Gastroenterology (T.K., B.S.), Department of Internal Medicine, Division of Endocrinology and Metabolism (B.O.Y.), Hacettepe University School of Medicine, Hacettepe 06100 Ankara, Turkey

Introduction: Overt hypothyroidism affects the gastrointestinal system. Limited data are available regarding gastric motility in subclinical hypothyroidism (SCH).

Objective: The aim of this study was to assess gastric motility–related gastric symptoms and levels of ghrelin in patients with SCH compared with those in healthy control subjects and to evaluate the potential effects of L-thyroxine replacement therapy.

Methods: Twenty premenopausal women with SCH and 20 age- and body mass index–matched healthy control women were enrolled in the study. The gastroparesis cardinal severity index questionnaire was used to reveal gastrointestinal motility changes, and electrogastrographic activities were measured. Fasting and postprandial ghrelin levels at 30, 60, and 120 minutes were determined during a mixed meal test. All tests were repeated after 6 months when patients were in the euthyroid state.

Results: The gastroparesis cardinal severity index score, fasting tachygastria ratio, and postprandial/fasting bradygastria ratio in electrogastrography were higher in patients with SCH compared with control subjects ($P = .03$, $P = .04$, and $P = .04$, respectively). All 3 parameters significantly improved after L-thyroxine replacement therapy ($P < .001$, $P = .005$, and $P = .02$ respectively) reaching levels similar to those of control subjects. Baseline and area under the curve for ghrelin during mixed meal tests did not show a difference between patients with SCH and control subjects and before and after L-thyroxine replacement in SCH.

Conclusion: Gastric dysmotility and the resultant upper gastrointestinal symptoms can be observed in SCH, and symptomatology related to dysmotility and parameters appear to be improved with thyroid hormone replacement. Our results also suggest that ghrelin levels in response to a meal are similar between women with SCH and healthy women and that normalization of thyroid function by L-thyroxine does not modulate these levels. **(*J Clin Endocrinol Metab* 98: E1775–E1779, 2013)**

Subclinical hypothyroidism (SCH) is defined as an elevated serum TSH concentration associated with serum free T4 (fT_4) and T_3 levels within their normal reference ranges (1). It is already well known that overt thyroid disease affects gastrointestinal (GI) system and its motility, but data regarding gastric motility in SCH are scarce. Although most studies investigating the effects of thyroid hormones on the GI system focus on intestinal motility, only limited studies of thyroid disorders that have evaluated gastric motility using the technique of myoelectrical activity are available.

Electrogastrography (EGG) is a technique for recording gastric myoelectrical activity using cutaneous electrodes. The frequency of normal gastric slow waves is approximately 3 cpm; lower or higher deviations from baseline frequencies are defined as bradygastria and tachy-

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Abbreviations: $AUC_{ghrelin}$, area under the curve value for ghrelin; BMI, body mass index; DF, dominant frequency; GCSI, gastroparesis cardinal symptom index; EGG, electrogastrography; GI, gastrointestinal; SCH, subclinical hypothyroidism.

gastria, respectively. The exhibition of normal-frequency activity of EGG recording time less than 70% is defined as gastric dysrhythmia, usually correlated with gastric motility and emptying abnormalities (2). Gunsar et al (3) reported that preprandial tachygastria was increased in patients with overt hypothyroidism compared with that in control subjects and found a decrease after therapy in the euthyroid state. Gastric electrical activity might not always be correlated with gastric motility, and any abnormality may not represent a motility disorder (4). However, some of the studies comparing results obtained with scintigraphy and EGG have shown a correlation (5, 6). Previous studies reported conflicting results concerning the association between symptom scores, gastric myoelectrical activity, and gastric emptying, but EGG abnormalities were more often observed in patients with dyspeptic symptoms and delayed gastric emptying (7).

Thyroid disorders are also associated with changes in appetite, food intake, and energy balance. Ghrelin is an orexigenic, gut-derived peptide that regulates appetite and energy expenditure. Ghrelin increases gastric emptying rate (8–10). Parenteral ghrelin administration induces gastric phase III contractions of the migrating motor complex and accelerates gastric emptying (11). Slowed gastric emptying is hypothesized to be associated with reduced active ghrelin concentrations (12). There are conflicting data regarding ghrelin levels in overt hypothyroidism in that levels have been reported to be not affected (13–15), increased (16, 17), or decreased (18). The ghrelin response to a meal along with gastric motility in SCH has not been studied so far.

In the current study, we aimed to determine (1) whether gastric motility with related symptomatology and ghrelin in response to a meal are altered in SCH and (2) whether L-thyroxine replacement has an effect on these parameters.

Materials and Methods

Study population

Premenopausal women with untreated SCH and age- and body mass index (BMI)-matched premenopausal healthy subjects were enrolled consecutively between September 2010 and October 2011. Patients with comorbidities, GI diseases, and illnesses interfering with GI motility were excluded. All participants were nonsmokers and had not taken any medications affecting GI motility for at least 3 months before enrollment in the study.

Informed consent was received from each participant, and the study was approved by the institutional ethics committee.

Study protocol

SCH was determined as an elevated serum TSH level (reference range, 0.27–4.2 μIU/mL) despite a normal level of fT_4 (reference range, 12–22 pmol/L). Anthropometric parameters and thyroid hormones were measured. All participants were asked to complete a validated gastroparesis cardinal symptom index (GCSI) questionnaire at the beginning of the study (19). The questionnaire was developed and validated for the evaluation of symptom severity and treatment responsiveness in upper GI disorders. The GCSI total score equals the sum of the nausea/vomiting and bloating and fullness/early satiety subscales, divided by 3. A scale ranging from 0 (none) to 5 (very severe) was used to rate the severity of each symptom, higher scores reflecting greater symptom severity. The scores are used for evaluation of specific diseases or for comparing patients after some medical interventions so the reference point is the patient himself or herself for the comparison of the effect of an intervention. We set the cutoff point for the total GSCI score as 10, which was reported to have sensitivity of 87% for detecting gastroparesis (20). An EGG recording was also performed as described previously (2). All the measurements were repeated in patients 6 months after therapy in the euthyroid state. The median dose of L-thyroxine given to patients with SCH was 50 μg (25–75 μg).

EGG assessment

EGG data were assessed using an EGG recorder (Synectics Medical Inc.). The EGG signal was analyzed using a fast Fourier running spectral analysis. EGG data was analyzed by 2 authors (T.K. and B.S.). Percentages of dominant frequency (DF) in normal (2.0–4.0 cpm), bradygastric (0.5–2.0 cpm), and tachygastric (4.0–9.0 cpm) frequency ranges and the ratio of DF both preprandially and postprandially were evaluated. The ratio of DF reflects the alteration in gastric contractions, and it is generally accepted that a ratio >1 indicates an increase in contractility due to intervention (2).

Meal-mediated hormone response

The subjects were examined between 8:30 and 11:30 AM after an overnight fast of 10 to 14 hours. After 1 hour of the fasting EGG record, a standardized 612-kcal test meal consisting of a sandwich with cheese and fruit juice (46% carbohydrate, 32% protein, and 22% fat) was served (2). Blood samples for ghrelin were collected through an IV cannula in the fasting state and 30, 60, and 120 minutes after consumption of the test meal.

Assay methods

Blood samples were centrifuged immediately, and the serum was stored at −20°C until assayed. TSH levels were measured by a sandwich chemiluminescence immunoassay (Roche Diagnostics). Serum fT_4 levels were measured by electrochemiluminescence immunoassay (Modular Analytics E170). A RIA kit (Phoenix Pharmaceuticals, Inc) was used to determine the serum ghrelin levels. The intra- and interassay coefficients of variation for ghrelin were 13.6% and 8.7%, respectively.

Statistical analysis

The Student *t* test was used to compare normally distributed measurements; Wilcoxon and Mann-Whitney *U* tests were used to compare non-normally distributed variables. Repeated-measures analysis was used where appropriate. Correlations were tested for significance by the Spearman and Pearson rank tests. Statistical analyses were performed using SPSS statistical software (version 16.0; SPSS Inc). A value of $P < .05$ was considered statistically significant.

Table 1. Percentage of Time Spent Preprandially − Postprandially and Thyroid Hormone Status of the Groups

	SCH Group Before Treatment (A)	SCH Group After Treatment (B)	Control Group (C)	*P* Value	
				A − B	A − C
Percentage of time spent					
Normal (2−4 cpm)					
Preprandial	17.4 ± 6.3	8.25 (2–52.2)	15.2 ± 5.2	NS	NS
Postprandial	18.9 (6.7–82.6)	19.2 (0–79)	37.3 ± 9	NS	NS
Postprandial/preprandial	2.1 (0.2–11)	1.75 (0–16.3)	2.8 (0.7–99)	NS	NS
Bradygastria (0.5–2.0 cpm)					
Preprandial	75.56 ± 6.3	88.7 (47–95)	84.8 (52–100)	.01	NS
Postprandial	74.5 (17–89)	70 ± 9	57 ± 10	NS	NS
Postprandial/preprandial	0.9 ± 0.3	0.8 (0.3–1.1)	0.7 (0.5–1.1)	NS	.01
Tachygastria (4.0–9.0 cpm)					
Preprandial	6.7 ± 2.3	1.8 (0–10)	2.8 (0–15)	.005	.04
Postprandial	2.1 (0–10)	2 (0–18.4)	5.3 ± 2.2	NS	NS
Free T3, pg/mL	2.7 (2.5–3.3)	2.75 (2.6–3.6)	2.9 (2.6–3.4)	NS	NS
Free T4, pmol/L	15.1 ± 2	15.9 ± 1.9	15.1 ± 2.3	NS	NS
TSH, mIU/L	7.38 ± 1.8	2.67 ± 0.9	1.91 ± 0.93	<.001	<.001

Abbreviation: NS, nonsignificant. Data are means ± SD or median (range).

Results

Twenty premenopausal women with SCH (mean age, 35.4 ± 10.8 years; BMI, 26.1 kg/m^2 [range, 19.1–41.5 kg/m^2]) and 20 age- and BMI-matched healthy control women (mean age, 38.3 ± 11.0 years; BMI, 24.4 kg/m^2 [19.9–32 kg/m^2]) were enrolled. There was a significant difference between the SCH and control groups in terms of serum TSH levels (7.38 ± 1.8 and 1.91 ± 0.93 μIU/mL, $P < .001$) and GCSI scores (9.5 ± 3.6 and 5.9 ± 2.7, respectively, $P = .03$). After L-thyroxine therapy, a significant difference was observed in BMI (27 ± 6.2 and 26.2 ± 5.8 kg/m^2, $P < .001$) and the GCSI scores (9.5 ± 3.6 and 7.1 ± 3.2, $P < .001$) in the SCH group. At baseline, 10 patients in the SCH group and 5 women in the control group had scores >10, suggesting impaired gastric emptying, whereas only 5 patients in the SCH group had scores >10 after reaching euthyroid status.

EGG in hypothyroid patients

EGG recordings of women with untreated SCH showed 25% normal and 75% dysrhythmic results. The SCH group had a higher percentage of preprandial tachygastria and a higher postprandial/preprandial bradygastria ratio compared with controls ($P = .04$ and $P = .01$ respectively). The percentage of both preprandial tachygastria and the postprandial/preprandial bradygastria ratio were reduced in the euthyroid state ($P = .005$). These 2 parameters also did not differ from those in control women after achieving the euthyroid state ($P = .2$ and $P = .1$, respectively). There was no difference for the other EGG parameters between control women and patients before or after treatment (Table 1). In addition, there was no correlation between symptom scores and percentage of time in abnormal EGG rhythm.

Mixed meal test results: ghrelin responses to mixed meal

Fasting ghrelin concentrations and area under the curve values for ghrelin ($AUC_{ghrelin}$) were similar between control patients with patients with SCH both before ($P = .55$) and after ($P = .64$) treatment. $AUC_{ghrelin}$ after achieving euthyroidism was not significantly higher than $AUC_{ghrelin}$ in patients with untreated SCH ($P = .46$) and when adjusted for BMI ($P = .07$) (Figure 1).

Correlations

Initial TSH levels correlated positively with the GCSI score ($r = 0.5$, $P = .001$), preprandial tachygastria ratio ($r = 0.4$, $P = .009$), and postprandial/preprandial bradygastria ratio ($r = 0.31$, $P = .04$). The Δ change in TSH levels before and after treatment did not show a correlation with changes in GCSI scores or EGG parameters ($P > .05$). There was no correlation between symptom scores and percentage of time

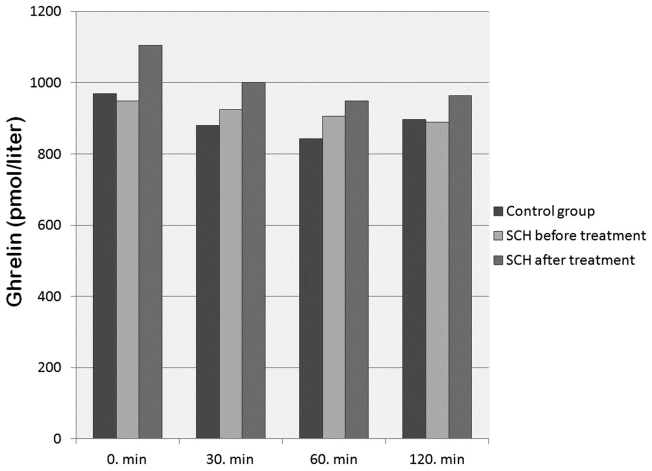

Figure 1. Ghrelin-time curves of SCH and control group patients.

in abnormal EGG rhythm. The initial fT4 levels correlated negatively with the ghrelin levels of women with untreated SCH ($r = -0.36$, $P = .02$). Ghrelin levels in women with SCH after achievement of the euthyroid state correlated positively with the preprandial tachygastria ratio ($r = 0.44$, $P = .045$). There was no correlation between fT4 levels with ghrelin in control subjects or women with SCH after achievement of euthyroidism.

Discussion

We report here that gastric dysmotility and the resultant upper GI symptoms can be observed in SCH, and symptoms of dysmotility might be improved with thyroid hormone replacement. We also show that ghrelin levels in response to a meal are similar between women with SCH and healthy women and that normalization of thyroid function by L-thyroxine does not affect these levels. To the best of our knowledge, this is the first study of SCH in the literature evaluating gastric motility and time-dependent changes of ghrelin during a mixed meal test.

EGG reflects the electrical activity of the stomach and provides a thorough measure of gastric motility. Hypothyroidism may cause delays in gastric emptying that may not be correlated with the abnormalities detected by EGG. Moreover, symptoms of dyspepsia may be improved by hormone replacement in hypothyroid patients. The total GSCI score was found to correlate well with delayed gastric emptying, especially at 2 hours postprandially (20). EGG abnormalities were more often observed in patients with dyspeptic symptoms and delayed gastric emptying (7). We found in our study that achievement of euthyroidism resulted in a significant decrease in dyspeptic symptoms and GCSI scores. Even though there was an improvement in symptoms suggestive of gastroparesis, symptom scores did not show any correlation with percentage of time in abnormal EGG rhythm. This could be either a result of low sensitivity of GCSI for detecting gastroparesis or the complex interaction between the gastric myoelectric activity and contraction, which could not be assessed in electrogastrographic studies.

Diminished motility of stomach and delayed gastric emptying was shown in overt hypothyroidism (19, 20). The only gastric myoelectrical study in overt hypothyroidism, led by Gunsar et al (3), showed increased preprandial tachygastria compared with that in healthy subjects and a nonsignificant decrease after L-thyroxine therapy. It was not clearly determined by gastric myoelectrical activity whether gastric motility is affected in SCH. We found increased preprandial tachygastria and postprandial/preprandial bradygastria ratios in patients with SCH similar to that in patients with overt hypothyroidism that were significantly decreased after thyroxine replacement.

A significant change in GCSI scores was observed after hormone replacement, suggesting an improvement in gastric emptying. Our data indicate that gastric motility dysfunction and symptoms of disordered gastric motility are apparent in the SCH state and could be improved with L-thyroxine therapy. Hence, we can propose that screening dyspeptic symptoms of patients with SCH could yield a large number of patients with gastric dysmotility, which in turn could be detected with EGG abnormalities of gastric contractility.

Previous studies assessing ghrelin levels in individuals with overt hypothyroidism indicate conflicting results in that both similar (17–19) and decreased (20) levels of ghrelin have been reported compared with those of healthy individuals. Potential time-dependent changes of ghrelin in patients with SCH during a meal were not evaluated before. In our study, ghrelin levels in patients with SCH both before and after L-thyroxine treatment did not show a significant difference compared with those in control subjects.

We have failed to find a significant correlation between motility parameters and ghrelin levels in the control group. However, we found a positive correlation in patients with SCH after treatment between ghrelin concentrations and preprandial tachygastria ratios, which was one of the parameters found different between patients with SCH and control subjects. Why this observation did not apply to healthy control subjects who were also euthyroid remains unknown. Nevertheless, the correlation in the SCH group may be attributed to the ghrelin increase in the preprandial period and the decrease shortly after feeding or its acceleration effect on gastric emptying. This finding suggests that a potential interaction between thyroid status and motility and exogenous L-thyroxine therapy could contribute to the improvement in gastric dysmotility.

Small sample size and lack of evaluation of gastric motility by other techniques, such as antral motility testing are limitations of our study. Inclusion of only premenopausal women precludes generalization of our findings to the overall population. In addition, not being blinded to L-thyroxine treatment for the patient group could have had an influence on their GCSI scores.

In conclusion, gastric dysmotility may be observed in SCH, and thyroid hormone replacement may improve motility parameters and symptoms. Ghrelin levels at baseline and in response to a meal in SCH are similar to those levels in healthy control subjects. Achievement of euthyroid state by L-thyroxine replacement in women with SCH does not seem to alter baseline or stimulated levels.

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Address all correspondence and requests for reprints to: Bülent Okan Yildiz, Hacettepe University Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology and Metabolism, 06100 Ankara, Turkey. E-mail: yildizbo@yahoo.com.

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