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DOES GRAVES' DISEASE AFFECT ESOPHAGEAL MOTILITY?

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Abstract

Context. The gastrointestinal tract is one of the most affected systems in hyperthyroidism. Although thyrotoxicosis is thought to be associated with gastrointestinal dysmotility, there are limited studies focused on motility disorders in hyperthyroidism.

Objectives. We aimed to investigate the manometric measurements to determine if esophageal motility is affected in Graves' disease.

Materials and Methods. Thirty patients with Graves' disease (18 female and 12 male) and 30, age and sex matched, healthy controls (22 female and 8 male) were recruited to the study between 2015 and 2016. Esophageal manometry was performed using MMS (Medical Measurement Systems bv. The Netherlands) Solar GI – Air Charged Intelligent Gastrointestinal Conventional Manometry.

Results. The mean lower esophageal sphincter pressure (LESP) was 16.9 ± 5.3 mmHg in hyperthyroid patients and 20.1 ± 8.8 mmHg in the control group and there was no significant difference ($p>0.05$). It was observed that the duration of contraction was 3.9 ± 0.7 s in healthy subjects and, significantly shorter 3.2 ± 0.5 s in hyperthyroid patients ($p<0.001$). Duration of contraction was negatively correlated with TSH receptor Ab titer in patients ($p=0.006$, $r= -0.48$). Also, it was observed that the duration of relaxation was negatively correlated with fT4 levels in the patient group ($p<0.05$, $r= -0.46$).

Conclusion. In this study, we observed that esophageal motility can be affected via shortened duration of contraction in Graves' disease. The gastrointestinal symptoms due to possible motility dysfunctions should be considered in the evaluation of hyperthyroid patients.

Key words: Graves' disease, esophagus, motility, manometry.

INTRODUCTION

The gastrointestinal tract is one of the most affected systems in hyperthyroidism. The symptoms related to the gastrointestinal system were reported to be frequent varying between 30% to 50% of hyperthyroid patients (1, 2). Diarrhea, bloating, dysphagia, and vomiting are not uncommon (3-6). Although thyrotoxicosis is thought to be associated with gastrointestinal dysmotility, there are limited studies focused on this issue (7). Mainly, gastric myoelectrical activity and emptying were studied in the upper gastrointestinal tract. Increased gastric emptying and dysrhythmia were reported in hyperthyroid patients (8). Meshkinpour *et al.* studied esophagus motor function and they reported an increased velocity of esophageal contractions in a study with 10 Graves' patients (9). However, esophageal motility in hyperthyroidism is still a controversial issue.

Esophageal manometry is the gold standard for the investigation of its motor functions. It is the most useful technique to measure the amplitudes and timing of the pressure alterations which describe the strength and duration of smooth muscle contraction and relaxation. It is an essential procedure in the diagnosis of esophageal motility disorders such as achalasia and diffuse esophageal spasm. Manometric measurements may also clarify the pathophysiological mechanisms of gastrointestinal motility disorders in endocrine diseases (10-12). In a previous study, we observed that hypothyroidism could impair esophageal motility via shortened duration of and reduced percentage of relaxation (13). In this study, we aimed to investigate the manometric measurements to determine if esophageal motility is affected in Graves' disease.

MATERIAL AND METHODS

Thirty patients with Graves' disease (18 female and 12 male) and 30, age and sex matched, healthy controls (22 female and 8 male) were recruited. The mean ages were 34.3 ± 11.4 years in the hyperthyroid patients and 39.5 ± 14.6 years in the healthy controls. All patients with Graves' disease were newly diagnosed and had no gastrointestinal symptoms such as dyspepsia,

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reflux, dysphagia, nausea or vomiting. The disease was diagnosed by the combination of clinical findings and laboratory tests showing hyperthyroidism, supported by thyroid antibodies and high radioiodine uptake. TSH receptor antibody (TRAb) was measured in all subjects. The reference ranges were as follows: TSH: 0.35-4.94 mIU/L, fT4: 9-19 pmol/L, fT3: 2.62-5.7 pmol/L, anti-TG: 0-4.11 IU/mL, anti-TPO: 0-5.61 IU/mL TRAb: <1.0 IU/L.

The patients having a history of gastrointestinal system diseases that could affect gastrointestinal system motility (diabetes mellitus, connective tissue diseases, etc.) and chronic systemic disorders (infections, malignancies, etc.) were excluded from the study. The patients taking any medications known to influence gastrointestinal motility, smoking or drinking alcohol were also excluded.

The parameters of esophageal manometry were evaluated by using MMS (Medical Measurement Systems, Netherlands) Solar GI — Air Charged Intelligent Gastrointestinal Conventional Manometry. The measurements were obtained by the methodology previously published (11, 13). The wave amplitude from the average intraesophageal baseline to the peak of the wave was competed. The duration between the onset of the major upstroke and the end of the wave was based on the measurement of duration of contractions. Peristaltic percentage was defined according to 10 consecutive wave forms.

This study was approved by the local ethics committee of our institution, and informed consent was obtained from all participants.

Statistical analysis

SPSS software was used to perform statistical analyses (version 20.0 for windows, SPSS Inc., Chicago, IL, USA). The means of two groups were compared by Student's t test. Pearson's correlation was used to calculate the relationship between two variables. Statistical significance was set at $p<0.05$. The variables are expressed as mean ± standard deviation.

RESULTS

Table 1 shows the characteristics of the patients and control subjects. Age, gender and body mass index (BMI) were similar. Mean TSH levels were 0.01 ± 0.004 mIU/L and 1.7 ± 0.9 mIU/L in patients and controls, respectively. In hyperthyroid patients, mean fT4 levels were 32.1 ± 11.4 pmol/L and fT3 levels were 21.5 ± 12.7 pmol/L. Mean fT4 levels and fT3 levels were 13.3 ± 1.7 pmol/L and 4.6 ± 0.8 pmol/L in the control group, respectively. Thyroid antibodies including Anti-TPO, Anti-TG and TSH receptor Ab were increased in patients and in normal range in healthy subjects. Mean Anti- TPO, anti-TG and TSH receptor antibody levels were 944.8 ± 1796.1 IU/mL, 133.9 ± 237.4 IU/mL and 14.7 ± 11.5 IU/L in the patient group, respectively.

The mean lower esophageal sphincter pressure (LESP) was 16.9 ± 5.3 mmHg in hyperthyroid patients and 20.1 ± 8.8 mmHg in the control group and the difference was not significant. It was observed that the duration of contraction was 3.2 ± 0.5 s in hyperthyroid patients and 3.9 ± 0.7 s in healthy subjects. It was significantly shorter in hyperthyroid patients compared to controls ($p<0.001$). Percentage of relaxation was 66.1 ± 11.3 % in hyperthyroid patients and 66.4 ± 16.8% in the control group, respectively ($p>0.05$). Duration of relaxation and maximum upstroke were similar in both groups.

Table 1. Characteristics of patients and control group

	Hyperthyroid Patients	Control Group	P
Age (y)	34.3 ± 11.4	39.5 ± 14.6	NS
Gender (Female/Male)	18/12	22/8	NS
BMI (kg/m^2)	23.03 ± 3.3	24.6 ± 5.2	NS
TSH (mIU/L)	0.01 ± 0.004	1.7 ± 0.9	<0.001
fT4 (pmol/L)	32.1 ± 11.4	13.3 ± 1.7	<0.001
fT3 (pmol/L)	21.5 ± 12.7	4.6 ± 0.8	<0.001
Anti-TPO (IU/mL)	944.8 ± 1796.1	3,2 ± 1,1	
Anti-TG (IU/mL)	133.9 ± 237.4	2,9 ± 0,6	
TRAb (IU/L)	14.7 ± 11.5	NA	
LESP (mmHg)	16.9 ± 5.3	20.1 ± 8.8	NS
Percentage of Relaxation (%)	66.1 ± 11.3	66.4 ± 16.8	NS
Duration of Relaxation (s)	4.8 ± 1.9	5.5 ± 2.2	NS
Duration of Contraction (s)	3.2 ± 0.5	3.9 ± 0.7	<0.001
Maximum upstroke (mmHg)	72.0 ± 21.2	74.2 ± 26.1	NS

Data are mean ± standard deviation. BMI body mass index, TSH thyroid-stimulating hormone, Anti-TG anti-thyroglobulin antibody, Anti-TPO anti-thyroid peroxidase antibody, TRAb: TSH Receptor Antibody,LESP: lower esophageal sphincter pressure.

Duration of contraction was negatively correlated with TSH receptor Ab in patients (p=0.006, r=-0.48). Additionally, it was observed that the duration of relaxation was negatively correlated with fT4 levels in the patient group (p<0.05, r= -0.46) (Fig. 1). No other correlation was found between manometric measurements, thyroid hormone levels and thyroid antibodies in patients and healthy groups.

DISCUSSION

In the present study, we observed that the duration of contraction was significantly shortened in hyperthyroid patients. The pathophysiological mechanisms underlying esophagus dysmotility in hyperthyroidism are complex and poorly understood. Regardless of the mechanism by which thyroid hormones influence the functions of the esophagus, it seems that thyroid disorders influence the smooth muscle of the distal esophagus and reversibility of this effect suggests a physiologic dysregulation (9). Although the autonomic dysfunction is a possible candidate to explain motility dysfunction in hyperthyroidism, induced hyperthyroidism increased the gastrointestinal motility regardless of whether the vagal nerve was intact in an experimental study (14). In the previous studies, motility disorders were evaluated generally using scintigraphic and electrogastrographic methods. It has been shown that gastric emptying is not significantly different in hyperthyroid patients compared to the healthy subjects in 3 prospective studies (15-17). In contrast, patients with hyperthyroidism had liquid phase gastric emptying studies that were significantly accelerated from those of a control group in another study (18). Additionally, Gunasar *et al.* found the existence of a significantly higher percentage of postprandial tachygastria and higher preprandial and postprandial dominant electrical frequency on a study of gastric myoelectrical activity (8). In addition to the dysregulated myoelectrical activity, other possible mechanisms include nitric oxide dependent pathways, smooth muscle disorders such as alteration of the composition of myosin chains, electromechanical dissociation and altered local gastrointestinal hormones (e.g. ghrelin or gastrin) that may play a role in the regulation of gastroesophageal motility (19-22).

Previously, we showed that hypothyroidism could affect esophageal motility via shortened duration of relaxation and reduced percentage of relaxation (13). In the present study, we found a significantly shortened duration of contraction in hyperthyroid patients. Meshkinpour *et al.* showed a significant increase in velocity of contractions in a small study with 10 Graves' patients as compared to controls (9). Additionally, basic electrical rhythm or slow wave activity of the intestine were found to be increased, which indicated more frequent contractions in hyperthyroidism (23). All these findings suggested that hyperthyroidism could affect esophageal motility via impaired contractions of the distal esophagus. It was previously shown that the excessive production of thyroid hormones can lead to muscle weakness and dysfunction of bulbar muscles, which may result in oropharyngeal or esophageal dysmotility (24). However, the association between the gastrointestinal system motility and serum levels of thyroid hormones is controversial. Serum levels of thyroid hormones were not correlated with electrogastrography parameters in hyperthyroid patients who had frequent tachygastria and significantly delayed gastric emptying compared to healthy subjects in a previous study (25). Contradictory to this study, a negative correlation between serum levels of fT3 and postprandial normogastria and a positive correlation between postprandial tachygastria and serum levels of fT4 had been reported in another study (8).

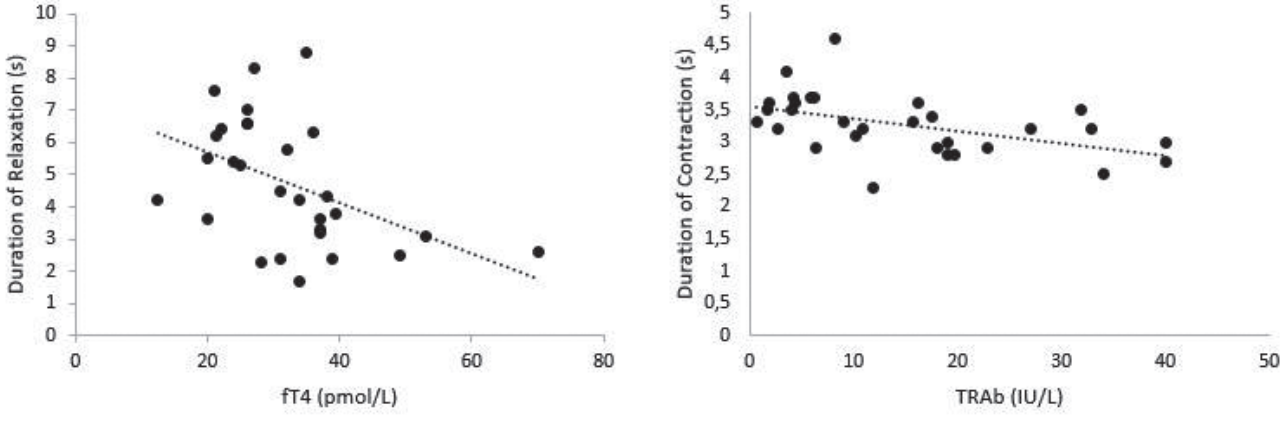

Figure 1. Correlation between fT4 and duration of relaxation (p<0.05, r= -0.46); TRAb and duration of contraction (p=0.006, r= -0.48) in patients.

Wegener *et al.* observed a negative correlation between mouth to cecum transit time and serum T3 levels (16). While in our previous study, duration of contraction had been negatively correlated with fT4 levels in hypothyroidism, in the present study we found that the duration of relaxation was negatively correlated with fT4 levels in hyperthyroid patients. These findings suggest that thyroid hormones can be among the factors involved in the control of the contractions and relaxations of esophageal smooth muscle.

The relationship between TRAb and esophagus dysmotility was an interesting finding in the present study. We observed a negative correlation between TSH receptor antibodies (TRAb) and duration of contraction in manometric measurements. Although thyroid autoimmunity was associated with many gastrointestinal diseases (e.g., atrophic gastritis, celiac disease) (26-29), motility disorders were generally not linked to thyroid antibodies. A previous study demonstrated that various antibodies including skeletal muscle, GAD65, thyroid or gastric parietal cell can be more prevalent in patients with gastrointestinal motility disorders (30). The possible relationship between TRAb and "autoimmune gastrointestinal dysmotility" should be examined in larger samples.

There is growing evidence that ghrelin can play a role in the regulation of gastrointestinal motility via specific receptors located on vagal, myenteric and central neurons (31). Ghrelin increases gastric emptying, activates phase 3 of the migrating motor neurons, acts on vago-vagal reflex and induces central pathways. In hyperthyroidism, it has been found that increased levels of gastric mucosal ghrelin are more associated with the gastrointestinal dysmotility than plasma ghrelin levels (32, 33). Despite a contradictory report, experimental studies indicate that ghrelin has a contractile activity on the esophagus and gastrointestinal tract (34-36). In light of this evidence, it can be postulated that in hyperthyroidism, ghrelin mediated pathways can play a crucial role in esophagus dysmotility. However, future studies are warranted to explain the mechanisms involved in the pathogenesis of esophagus dysmotility in hyperthyroidism.

In conclusion, we observed that esophageal motility can be affected via shortened duration of contraction in Graves' disease. The gastrointestinal symptoms due to possible motility dysfunctions should be considered in the evaluation of hyperthyroid patients. Future clinical and experimental studies are needed to clarify the effect of thyroid hormones on esophageal motility.

Conflict of interest

The authors declare that they have no conflict of interest related to the study.

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