



Radionuclide Esophageal Transit Scintigraphy in Primary Hypothyroidism

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Background/Aims

Esophageal dysmotility is associated with gastrointestinal dysmotility in various systemic and neuroregulatory disorders. Hypothyroidism has been reported to be associated with impaired motor function in esophagus due to accumulation of glycosaminoglycan hyaluronic acid in its soft tissues, leading to changes in various contraction and relaxation parameters of esophagus, particularly in the lower esophageal sphincter. In this study we evaluated esophageal transit times in patients of primary hypothyroidism using the technique of radionuclide esophageal transit scintigraphy.

Methods

Thirty-one patients of primary hypothyroidism and 15 euthyroid healthy controls were evaluated for esophageal transit time using 15-20 MBq of Technetium-99m sulfur colloid diluted in 10-15 mL of drinking water. Time activity curve was generated for each study and esophageal transit time was calculated as time taken for clearance of 90% radioactive bolus from the region of interest encompassing the esophagus. Esophageal transit time of more than 10 seconds was considered as prolonged.

Results

Patients of primary hypothyroidism had a significantly increased mean esophageal transit time of 19.35 ± 20.02 seconds in comparison to the mean time of 8.25 ± 1.71 seconds in healthy controls ($P < 0.05$). Esophageal transit time improved and in some patients even normalized after treatment with thyroxine. A positive correlation ($r = 0.39$, $P < 0.05$) albeit weak existed between the serum thyroid stimulating hormone and the observed esophageal transit time.

Conclusions

A significant number of patients with primary hypothyroidism may have subclinical esophageal dysmotility with prolonged esophageal transit time which can be reversible by thyroxine treatment. Prolonged esophageal transit time in primary hypothyroidism may correlate with serum thyroid stimulating hormone levels.

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Key Words

Esophageal dysmotility; Hypothyroidism; Technetium; Thyroid stimulating hormone; Thyroxine

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Introduction

In the backdrop of overwhelming cardiovascular, metabolic and musculoskeletal symptoms associated with thyroid hormonal imbalance the gastrointestinal symptoms get unnoticed and often ignored. Nevertheless, the gastrointestinal symptoms in hyperthyroidism or hypothyroidism have variable presentations from subtle to substantial and can be disturbing to patient's body and mind. The gastrointestinal symptoms in hypothyroidism range from mild constipation to frank paralytic ileus and sometimes colonic pseudo-obstruction.¹ The precise mechanisms responsible for causing symptoms in hypothyroidism continue to be discussed and debated. Various theories proposed to explain the changes in gastrointestinal tract (GIT) motility in hypothyroidism include autonomic neuropathy, altered impulse transmission at myoneural junction, interstitial ischemia, and intestinal myopathy. There is enough published data supporting the view that accumulation of glycosaminoglycans, notably hyaluronic acid within the soft tissues of GIT in hypothyroidism, results in interstitial edema causing impaired GIT motility.²⁻⁵ Decrease in the electrical and motor activity of the esophagus, stomach, small intestine, and colon has been demonstrated in hypothyroid humans and dogs.⁵ Decrease in the percentage of relaxation in lower esophageal sphincter pressure (LESP) and shortened duration of relaxation in the LESP has been reported in patients with hypothyroidism.⁵ The abnormalities of esophageal motility in hypothyroidism often correct with thyroid hormone replacement.⁶ Conventionally esophageal manometry has been used profoundly to study the motility disorders of esophagus, and this technique continues to be the gold standard.^{7,8} Kazem⁹ originally described the technique of radionuclide esophageal transit time measurement in his seminal work published in 1972. The useful technique of radionuclide esophageal transit scintigraphy (RETS) is substantially reported in literature for evaluating esophageal motility disorders like achalasia, diffuse esophageal spasm, and nutcracker esophagus.¹⁰⁻¹⁵ In patients of symptomatic dysphagia and a normal endoscopy, RETS is a noninvasive, safe, and reproducible technique for quantification of global and segmental esophageal transit time.^{14,15} In this study we aim to study the esophageal motility in primary hypothyroidism by quantification of esophageal transit time of a radioactive liquid bolus in patients of hypothyroidism.

Materials and Methods

Patients

The study cleared by the institute ethical committee included 31 (males 7 and females 24) primary hypothyroidism diagnosed patients with serum thyroid stimulating hormone (TSH) values greater than 10 $\mu\text{IU/mL}$ (normal: 0.5-6.5 $\mu\text{IU/mL}$). The mean age of patients was 36.03 ± 8.84 years (range 20-50 years). After a written and informed consent a clinical history and examination was recorded for all patients. None of the patients gave a history of dysphagia, esophageal motility disorders like achalasia, diffuse esophageal spasm, and myasthenia gravis. No patient suffered from systemic diseases like multiple sclerosis, dermatomyositis, polymyositis, and diabetes mellitus. No patient gave a history of consuming drugs modifying GIT motility, proton pump inhibitors, or alcohol intake and smoking.

Controls

After a written and informed consent, 15 (males 10 and females 5) healthy euthyroid volunteers with a mean age of 30.86 ± 14.61 years (range 22-58 years) were recruited as the control group. Their mean serum TSH was $3.09 \pm 0.66 \mu\text{IU/mL}$. None gave a history of consuming drugs modifying GIT motility, alcohol intake, or smoking.

Radionuclide Esophageal Transit Scintigraphy

Patients and controls underwent RETS after 6-8 hours of fasting. Patients and controls were placed in a supine position under a large field view gamma camera fitted with low energy, all-purpose, parallel collimator interfaced to a processing work station. Fifteen to twenty megabecquerels (405-540 μCi) of Technetium-99m sulfur colloid diluted in 10-15 mL of drinking water was aspirated into the mouth through a plastic straw. Patients were asked to retain the radioactive bolus in their mouth for a few seconds and then swallow the entire bolus in one go, followed by dry swallows every 15 seconds. Continuous data acquisition was done in 2 phases. In the first phase (2 minutes), 120 frames of 1 second duration in a matrix of 128×128 were acquired. In the second phase (10 minutes), 40 frames of 15 seconds duration were acquired. For quantitative analysis, region of interest (ROI) was drawn on the esophagus excluding the stomach fundus (Fig. 1). From the time activity curve generated for the acquired data the esophageal transit time (ETT) was calculated as the time taken for clearance of 90% of radioactiv-

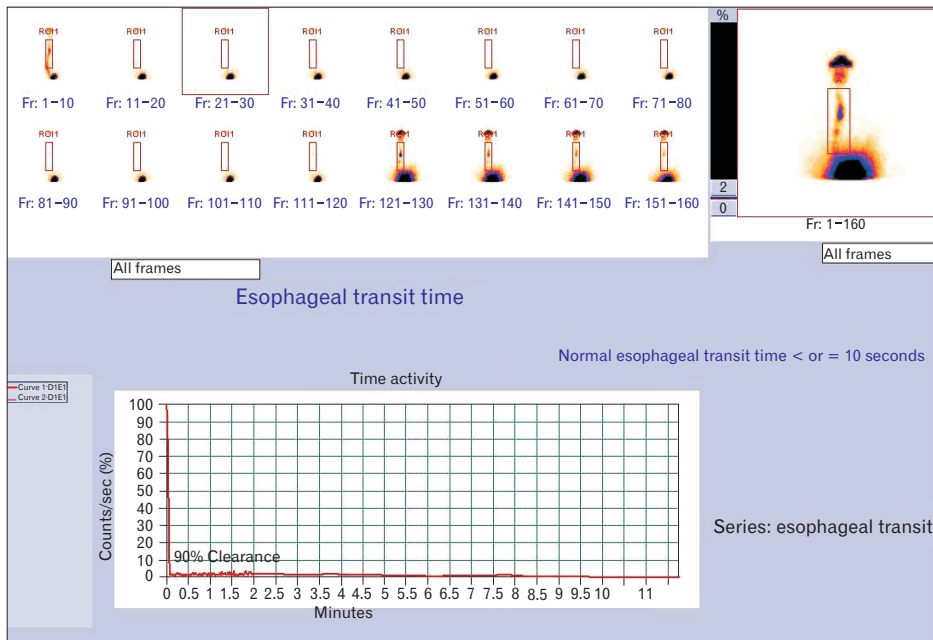


Figure 1. An illustrative image showing the plot of time activity curve for the esophageal region of interest.

Table 1. Esophageal Transit Time and Other Parameters

	Patients (n = 31)	Controls (n = 15)	P-value
Age (yr)	38.03 ± 8.84	30.86 ± 14.61	> 0.05
Sex			
Male	7	10	
Female	24	5	
Mean TSH (μIU/mL)	41.83 ± 38.42	3.09 ± 0.66	< 0.05
Mean ETT (sec)	19.35 ± 20.02	8.25 ± 1.71	< 0.05

TSH, thyroid stimulating hormone; ETT, esophageal transit time. Values expressed as mean ± SD.

ity from the esophageal ROI. Time of up to 10 seconds for 90% clearance of radioactivity from the ROI was considered normal.¹⁶

Statistical Methods

The data were analyzed using SPSS 20.0 version software. The values were expressed as mean ± SD. Unpaired and paired *t* tests were used for comparing the means between the study group and controls and within the study group (before and after treatment). Chi-square test was used for comparing the categorical variables. Pearson's correlation co-efficient was used to assess the relationship between serum TSH values and ETT. A *P*-value of less than 0.05 at 95% confidence interval was considered statistically significant.

Results

The overall mean esophageal transit time in the 31 patients with primary hypothyroidism was 19.35 ± 20.02 seconds which was significantly higher (*P* < 0.05) than ETT of 8.25 ± 1.71 seconds among the 15 healthy controls (Table 1). On detailed analysis ETT in the 31 patients of hypothyroidism was found to be increased in 20 (64.5%) patients with a mean ETT of 25.90 ± 22.70 seconds (range, 10.5 to 102 seconds). In 11 (34.5%) patients ETT was normal (Table 2) with a mean ETT of 7.30 ± 1.70 (range, of 5.1 to 10 seconds) this difference in the ETT was significant (*P* < 0.05). The 20 patients with prolonged ETT were put on thyroxine and asked to report for repeat RETS 3 months after documenting euthyroid status with serum TSH levels within 0.50-6.50 μIU/mL.

Table 2. Esophageal Transit Time and Thyroid Stimulating Hormone in Patients (n = 31)

	Patients with prolonged ETT (n = 20)	Patients with normal ETT (n = 11)	P-value
Mean ETT (sec)	25.90 ± 22.70	7.30 ± 1.70	< 0.05
Mean TSH (μIU/mL)	54.60 ± 42.50	18.10 ± 8.10	< 0.05

ETT, esophageal transit time; TSH, thyroid stimulating hormone.
Values expressed as mean ± SD.

Table 3. Mean Esophageal Transit Time in Patients Before and After Treatment with Thyroxine

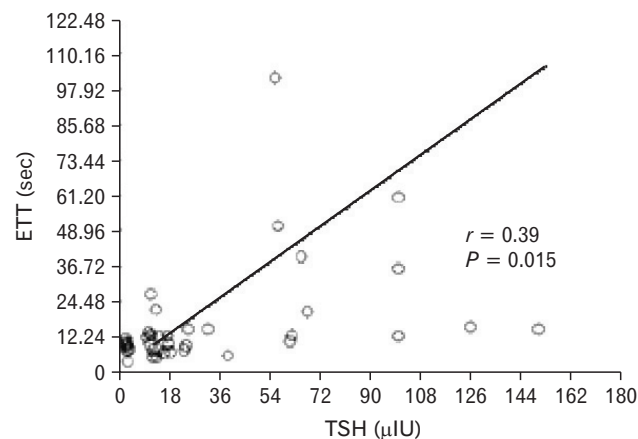
	Before treatment (sec)	After treatment (sec)	P-value
Mean ETT (n = 12) ^a	26.80 ± 26.40	15.08 ± 12.60	< 0.05
Mean ETT (n = 4) ^b	18.30 ± 11.80	7.80 ± 1.60	> 0.05
Mean ETT (n = 8) ^c	31.00 ± 31.00	19.80 ± 14.00	> 0.05

^aGroup including all patients.

^bSubgroup of patients with normalized esophageal transit time (ETT).

^cSubgroup of patients with decreased ETT.

Values expressed as mean ± SD.

**Figure 2.** Scatter plot for serum thyroid stimulating hormone (TSH) and esophageal transit time (ETT).

Out of these 20 patients only 12 patients reported for post treatment repeat RETS at 3 months in a euthyroid state. The pretreatment ETT of 26.80 ± 26.40 seconds in these patients decreased significantly ($P < 0.05$) to 15.08 ± 12.60 seconds (Table 3). In 4 patients (Table 3) the ETT decreased from a pretreatment mean ETT of 18.30 ± 11.80 seconds to post treatment mean ETT of 7.80 ± 1.60 seconds ($P > 0.05$). In 8 patients (Table 3) the ETT decreased from a mean pretreatment of 31.00 ± 31.00 seconds to 19.80 ± 14.00 seconds ($P > 0.05$) however in both cases the decrease was not statistically significant. A significant ($r = 0.39$, $P < 0.05$) positive correlation was seen between serum TSH and ETT values (Fig. 2).

Discussion

The gastrointestinal symptoms in hypothyroidism are often insidious to begin with but do assume significance in severe hypothyroidism when abdominal pain, abdominal distention may mimic intestinal obstruction, paralytic ileus, and atony.¹ Esophageal motility disorders sometimes manifesting as dysphagia are not uncommon in hypothyroidism. Various theories have been proposed to explain the motility disorders associated with hypothyroidism with an underlying process at the cellular level being attributed to accumulation of polysaccharide glycosaminoglycans, resulting in interstitial edema. Autonomic neuropathy resulting in altered impulse transmission causing decrease in duration and amplitude of relaxation in the lower esophageal sphincter pressure has been reported in patients with overt hypothyroidism.³⁻⁵ In the majority of patients esophageal dysmotility associated with hypothyroidism is corrected with thyroid hormone replacement because thyroid hormone inhibits glycosaminoglycans accumulation in a dose, time dependent, and reversible manner. This inhibition is apparently due to specific effects on the rate of macromolecular synthesis.¹⁷ Esophageal manometry has been performed in patients suspected to have functional esophageal dysmotility.^{7,8} RETS using a radioactive liquid bolus is convenient, safe, and reproducible technique for quantification of ETT.^{11-15,18} A sensitivity of 97% has been reported with RETS in detecting esophageal motor disorders using esophageal manometry as the gold standard.¹⁵ The whole body effective radiation dose from the RETS procedure is approximately 5 mrad that is comparable to a chest CT scan and most of other nuclear medicine

procedures.¹⁹ The present study was undertaken to evaluate the status of esophageal motility among patients with hypothyroidism. The study group of 31 patients diagnosed to have primary hypothyroidism were evaluated and comparisons made with healthy euthyroid controls. ETT of 8.25 ± 1.71 seconds for clearance of more than 90% radioactivity in controls was in conformity with the published value of 7-10 seconds.¹⁶ To give an extra allowance for swallowing aberrations an ETT of 10 seconds was taken as the cut off value for normal (≤ 10 seconds) and prolonged ETT (> 10 seconds). We observed that 11 (34.48%) patients of primary hypothyroidism had normal ETT values (mean ETT: 7.3 ± 1.7 seconds) and their mean TSH values were 18.15 ± 8.50 μ IU/mL. In comparison 20 (64.51%) patients of primary hypothyroidism had significantly prolonged ETT values (mean ETT: 25.90 ± 22.70 seconds). We inferred that all patients of primary hypothyroidism do not have an esophageal motility disorder reflected in their prolonged ETT, however the possibility of esophageal dysmotility seems to increase with increased absolute value of serum TSH at that point of time. We attempted to study the correlation between prevailing serum TSH values and ETT. A statistically significant ($r = 0.39$, $P < 0.05$) positive correlation, albeit weak, was found between serum TSH and observed ETT. The positive correlation is likely to become statistically more robust on a larger study sample. This study also attempted to find out the impact of treatment with thyroxine on prolonged ETT among patients of hypothyroidism. The mean ETT of 12 patients who reported after thyroxine treatment were significantly reduced from their pretreatment levels (Table 3). The statistical significance of the improvement in ETT after thyroxine replacement is likely to change favorably on a larger study sample and a longer follow-up period. Due to the paucity of published data on RETS in hypothyroidism a comprehensive comparison of our results was not possible.

In the present study we have observed that a significant number of patients with primary hypothyroidism may have subclinical esophageal dysmotility with prolonged ETT which is reversible by thyroxine treatment. Prolonged ETT in primary hypothyroidism may correlate with serum TSH levels. A prospective multi-institutional study based on a larger study sample and spread over longer time is likely to throw more light on esophageal motility in thyroid hormonal imbalance.

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Conflicts of interest: None.

Author contributions: Soukat H Khan conceived and designed the study, built the team for carrying the study, prepared the manuscript with final results, and was involved in carrying the study and results; Madhu Vijay P carried out the procedure of the study, prepared the master chart of all the patients, and retrieved references; Tanveer A Rather actively involved in carrying the technical procedure, analyzed and reported all cases, formatted the manuscript, and submitted the manuscript on behalf of the corresponding author; and Bashir A Laway selected patients of primary hypothyroidism, counseled for written and informal consent, and provided clinical and hormonal profiles.

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