Gastric, pancreatic, and biliary responses to meals in hyperthyroidism

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SUMMARY
Upper gastrointestinal function in response to a mixed nutrient meal was evaluated in hyperthyroid patients, both before and after therapy, and in healthy controls. Gastric secretion, gastric emptying, and pancreatic secretion were all normal and normally integrated postprandially in the hyperthyroid patients. Bile acid output was reduced (p < 0.05) in this group of patients relative to healthy controls. Duodenal bile acid concentrations, however, were above the critical micellar concentration in most of the hyperthyroid patients, and the bile acid output and concentration remained unchanged in all patients three months after treatment. After radioactive iodine therapy, when gastrointestinal symptoms were returning toward normal, a small but statistically significant increase in gastric secretion was observed. However, gastric emptying and pancreatic secretion, like biliary secretion, remained unchanged. Abnormalities responsible for the diarrhoea and steatorrhoea in hyperthyroidism appear to reside primarily distal to the duodenum. However, reduced bile acid output may be a contributory factor in some patients.

Although hyperthyroidism is commonly accompanied by gastrointestinal symptoms, which may be severe or even the sole presenting manifestation, their pathophysiology is incompletely understood.1,2 Among the most obvious manifestations are diarrhoea and malabsorption, which have been attributed to hypermotility.3,4 However, studies of gastric emptying and intestinal transit in hyperthyroid man have been almost exclusively limited to the radiographic observation of transit of an inert barium suspension. Also, although most of these studies have demonstrated increased rate of gastric emptying and shortened bowel transit times, both of which return toward normal after treatment,5,6 some even demonstrate slowed gastric emptying.7 There is only one recent study8 which evaluated gastric emptying of a more physiological meal, whose nutrients can be expected to stimulate release of gut hormones and intrinsic regulators of digestion. This study8 found normal gastric emptying of meal marker; however, it did not evaluate gastric secretion or volumes emptied.

Other data on upper gastrointestinal function in hyperthyroidism are also incomplete or controversial. These studies have been reviewed by Middleton in 1971 and Miller et al. in 1978.1,3 Gastric acid secretion has been reported to be decreased, normal, and increased in studies using different secretory stimuli, different sampling techniques, and non-uniform selection of patients. Also, little data exist relating to postprandial pancreatic or biliary secretion in hyperthyroid man.

Therefore, we have studied gastric, pancreatic, and biliary responses to a mixed nutrient meal in hyperthyroid patients with Graves' disease. Our technique9,10 quantifies these functions concurrently, permitting demonstration of abnormalities as well as any incoordination of events that may occur. Because the time course of any abnormalities in gastric, pancreatic, and biliary functions in hyperthyroid man is not known, results were compared with results from a group of healthy controls and with results from repeated studies in the same patients three months after receiving radioactive iodine therapy.
Table: Characterisation of gastrointestinal symptoms and thyroid function of hyperthyroid patients at times of study

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Study date</th>
<th>T(μg/dl)†</th>
<th>Wt change (lb)</th>
<th>Stool freq/24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>7 April</td>
<td>52.0</td>
<td>Dec 31</td>
<td>2-3</td>
</tr>
<tr>
<td>F</td>
<td>12 April</td>
<td>42.3</td>
<td>Dec 36</td>
<td>1</td>
</tr>
<tr>
<td>36</td>
<td>19 May</td>
<td>27.8</td>
<td>Dec 15</td>
<td>5-6</td>
</tr>
<tr>
<td>50</td>
<td>28 June</td>
<td>18.8</td>
<td>Dec 10</td>
<td>1</td>
</tr>
<tr>
<td>M 49*</td>
<td>7 Sept</td>
<td>30.2</td>
<td>Dec 10</td>
<td>8-10</td>
</tr>
</tbody>
</table>

*21 g faecal fat/24 h on 100 g fat diet.
†Normal: 5-13-5 μg/dl.

Methods

Patients and Controls

Five hyperthyroid patients with Graves' disease (three women and two men, mean age ±SE of 41 ±7 years) were studied before therapy. All patients gave written informed consent. They were all treated successfully, the first patient with thyroidectomy and the other four with radioactive iodine. The four patients treated with radioactive iodine agreed to undergo repeat study approximately three months after therapy. Details of thyroid function and gastrointestinal symptoms at times of study are listed in the Table. Age-matched healthy volunteers (two women and three men, mean age 40 ±7 years) participated in identical studies as controls after giving written informed consent. The protocol for these studies was reviewed and approved by the Mayo Clinic Human Studies Committee.

Meal

The meal consisted of tenderloin steak, salt, bread, butter, ice cream, and chocolate syrup. It was blended with the addition of 240 ml water and a non-absorbable marker, PEG 4000, to produce a 400 ml volume with pH 6.0 and osmolality 540 mosm/l. Caloric content was 458 calories distributed as 40% carbohydrate, 40% lipid, and 20% protein, similar to the usual American diet.

Procedure

Our methods for quantification of postprandial gastric, pancreatic, and biliary secretion, intragastric volume, and gastric emptying of meal and secretions have been validated and reported in detail. In summary, after an overnight fast, subjects swallow duodenal and gastric tubes, which are positioned fluoroscopically. The duodenal tube contains a lumen for continuous perfusion (2 ml/min) of a non-absorbable marker (14C-PEG, specific activity 0.5 μCi/mg) in normal saline at the ampulla of Vater, and a lumen 20 cm distal to this (mixing segment) for continuous sampling of duodenal contents. A gastric sump tube is placed in the antrum for instillation of the meal containing a second non-absorbable marker, PEG 4000, and gastric sampling. We have previously excluded any effect of transpyloric intubation on the gastric secretory and emptying response elicited by a similar meal.

The study is performed with the subject seated in an upright position. Basal gastric and duodenal collections are performed for 30 minutes, after a 30 minute equilibration period. Subsequently, the meal is instilled intragastrically over an eight minute period, and serial gastric and duodenal samples are taken each 10 minutes thereafter until the meal has emptied completely. Determinations of pH (Fisher 520 Digital pH/ion meter) are performed immediately on gastric and duodenal samples. Marker concentrations are also measured in all samples; hydrogen ion concentration is measured by titration in gastric samples, and bile acid and trypsin concentrations are measured in duodenal samples.

Peripheral venous blood samples are obtained
during the basal period 30 and 10 minutes before the meal and 15, 35, 65, 95, 125, and 185 minutes after the meal. Samples are allowed to clot, and they are immediately centrifuged at 4°C; serum is separated and frozen at -20°C until gastrin can be determined by radioimmunoassay.12

**Statistical Analysis**
Differences between data derived from individual patients while hyperthyroid and then after therapy were tested using the paired t test.13 Hyperthyroid data were also compared with normal data by Student's t test or the rank sum test.13 Differences were considered to be significant at p<0.05.

**Results**

**Gastric Secretion**
The meal elicited an acid secretory response in the hyperthyroid patients similar to that elicited in the normal controls (Fig. 1). After radioactive iodine therapy, however, the acid output of the patients increased (p<0.05) (Fig. 1). This was true for the patients who were mildly hypothyroid as well as for those who were euthyroid at the time of repeat study. In spite of differences in acid output, there were no significant differences in gastric pH between any of the three groups (p>0.05) (Fig. 2).

Concentrations of fasting serum gastrin were normal in the hyperthyroid patients studied while hypermetabolic (77±25 pg/ml, mean±SE) and repeated after therapy (69±11 pg/ml). Also, the three hour postprandial integrated gastrin responses were similar before (9.6±3.0 ng-min/ml) and after therapy (8.2±1.7 ng-min/ml) (p>0.05).

**Gastric Emptying**
Nutrient delivery from the stomach to the duodenum was normal in the hyperthyroid patients (Fig. 3) and did not change after radioactive iodine therapy (Fig. 3) (p>0.05). Emptied volumes of gastric contents (meal and gastric secretions) were similar in the normal controls (667±159 ml/3 h, mean±SD) and the hyperthyroid patients before (563±71) (p>0.05) and after therapy (664±173) (p>0.05).

Intragastric volume was expanded by the meal (Fig. 4) and then gradually decreased in patients and normal controls. However, treated hyperthyroid patients tended to have a greater intragastric volume (significantly so (p<0.05) at 100, 110, and 120 minutes) than they had before therapy.
698 patients before (p greater for and oupalt for hyperthyroid at 100 health)' controls. The meal elicited

\[
\begin{align*}
\text{Fig. 5} & \quad \text{Cumulative three-hour postprandial trypsin output for hyperthyroid patients before and after therapy and for healthy controls. No differences exist.}
\end{align*}
\]

\[
\text{Fig. 6} & \quad \text{Cumulative three-hour postprandial bile acid output for hyperthyroid patients before and after therapy and for healthy controls. The hyperthyroid patients have decreased bile acid output relative to the healthy controls (p<0.05). This persists unchanged three months after therapy. The hyperthyroid patient with very low bile acid output was patient no. 2 in the Table.}
\]

Bile acid output was less in the hyperthyroid patients than normal controls (p<0.05) (Fig. 6). This output was unchanged after radioactive iodine therapy (p>0.05). Despite the low bile acid output, luminal bile acid concentrations remained above the critical micellar concentration (2 mmol/l) in all except one hyperthyroid patient. Mean bile acid concentrations during the postprandial period in the hyperthyroid patients (before therapy: \(3.7 \pm 0.9 \text{ mmol/l}\); after therapy: \(3.8 \pm 0.7 \text{ mmol/l}\) were approximately half that found in health (6.6±0.6 mmol/l). The patient with the very low bile acid concentration and output was patient number 2 in the Table, a 54 year old woman with no gastrointestinal symptoms. Patient number 5 in the Table, who had the most severe gastrointestinal symptoms, had the second highest bile acid outputs.

Duodenal pH was not different in the hyperthyroid patients and healthy controls or in the patients pre- and post-therapy (data not shown). The pH did not fall into the range that is suspected to inactivate trypsin or precipitate bile acids.

Discussion

Gastric and pancreatic responses to a mixed nutrient meal were quantitatively normal and normally coordinated in hyperthyroid patients, including those with marked and severe gastro-
Hyperthyroid gastrointestinal function

intestinal symptoms. Although bile acid output was decreased in this group, concentrations were above the critical micellar concentration in all except one patient and they could not be correlated with clinical abnormalities. These findings do not support the hypothesis that abnormalities in upper gut function are responsible for the gastrointestinal symptoms in hyperthyroidism.

The previous studies which reported rapid gastric emptying in hyperthyroidism used metabolically inert meals—barium suspensions that were followed radiographically.5,6 Such an experimental design evaluates gastric emptying independent of the nutrient-stimulated intrinsic regulators of gastric function. The present study quantifies the delivery to the duodenum of gastric contents (gastric secretions plus meal) as well as meal nutrients—both are normal after this mixed nutrient meal in hyperthyroidism, confirming and extending the observation of Wiley et al.8 who found normal meal marker emptying after a nutrient meal. One patient in our series had eight to 10 stools with 21 g faecal fat per 24 hours while hyperthyroid and only one stool daily after radioactive iodine therapy, yet nutrient delivery to the bowel was identical during the initial and repeat studies.

Unlike Wiley et al.,8 we found normal trypsin output in hyperthyroid patients. This was normal both when compared with healthy controls and when compared with the patients themselves after treatment. The methodology differs in that Wiley et al. measured trypsin concentration in chyme aspirated 55 cm distal to the ligament of Treitz, the site of aspiration in our study. Our data, however, clearly show that the secretion of trypsin is normal and that the delivery of this enzyme, at least as far as the ligament of Treitz, is normal. The difference might represent inactivation of trypsin along the lumen of the bowel, but this will require additional study. We found normal intraluminal pH at the level of the ligament of Treitz, thereby eliminating one possible mechanism of trypsin inactivation.

The significance of the reduced bile acid output demonstrated in the hyperthyroid patients is unclear. The combination of low bile acid output and the qualitative abnormality of bile acid composition reported in hyperthyroidism, in which there is a relative rise in chenodeoxycholic acid and decrease in cholic acid,14 could produce an abnormality in micellar formation in some patients. We feel that it probably is not important in most patients for the following reasons. Luminal bile acid concentration is well above the critical micellar concentration in all patients except one, suggesting adequate digestive function. That patient with very low bile acid output and luminal concentration had no gastrointestinal symptoms. The patient with the most severe diarrhoea had the second highest bile acid output. Finally, there were no differences in bile acid output or concentration after treatment, at a time when dramatic improvement in symptoms had occurred in some patients. A possible mechanism for these bile acid data is bile acid malabsorption with a decreased bile acid pool size. This will require further evaluation.

There are two reports of hypergastrinaemia in hyperthyroidism.15,16 However, data on our group of patients do not confirm that finding. It has been suggested that the metabolism of other peptide hormones may be abnormal in hyperthyroidism.2 Gastrointestinal peptide hormones are believed to be important in coordinating postprandial gastric, pancreatic, and biliary functions.37 Even if levels of other peptide hormones are abnormal in hyperthyroidism, our results show that the net effect is still a normally integrated upper gastrointestinal function.

There were differences in postprandial gastric secretion and intragastric volume, however, between the studies performed while the patients were hyperthyroid and those performed after radioactive iodine therapy when the patients were euthyroid or hypothyroid. After therapy, patients secrete more acid and maintain greater intragastric volumes, but this trend away from normal values was associated with normalisation of digestive symptoms. In fact, our patients continued to maintain normal nutrient and volume delivery to the bowel, even though gastric secretion increased. It is not clear why these differences occur. Basal gastrin concentrations and postprandial integrated gastrin responses were similar before and after treatment. Patients who were euthyroid at the repeat study responded similarly to those who were hypothyroid. Perhaps the differences in gastric secretion and emptying were an effect of the radioactive iodine, known to be concentrated in the gastric mucosa as well as in the thyroid.8 Also, the time course of these changes after therapy is unknown.

This characterisation of upper gastrointestinal function in response to a mixed nutrient meal in hyperthyroidism suggests that the site of abnormalities responsible for gastrointestinal symptoms in these patients resides distal to the duodenum. It will be important to evaluate postprandial small bowel and colon function in hyperthyroid man.

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References

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