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EDITORIAL

Consequences of dysthyroidism on the digestive tract and viscera

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Abstract

Thyroid hormones define basal metabolism throughout the body, particularly in the intestine and viscera. Gastrointestinal manifestations of dysthyroidism are numerous and involve all portions of the tract. Thyroid hormone action on motility has been widely studied, but more complex pathophysiologic mechanisms have been indicated by some studies although these are not fully understood. Both thyroid hormone excess and deficiency can have similar digestive manifestations, such as diarrhea, although the mechanism is different in each situation. The liver is the most affected organ in both hypo- and hyperthyroidism. Specific digestive diseases may be associated with autoimmune thyroid processes, such as Hashimoto's thyroiditis and Grave's disease. Among them, celiac sprue and primary biliary cirrhosis are the most frequent although a clear common mechanism has never been proven. Overall, thyroid-related digestive manifestations were described decades ago but studies are still needed in order to confirm old concepts or elucidate undiscovered mechanisms. All practitioners must be aware of digestive symptoms due to dysthyroidism in order to avoid misdiagnosis of rare but potentially lethal situations.

Key words: Hypothyroidism; Hyperthyroidism; Gastrointestinal motility; Intestine; Liver; Viscera

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INTRODUCTION

Thyroid hormones act on almost all organs throughout the body and regulate the basal metabolism of the organism[1]. The gut and viscera are not spared, and disturbances in thyroid function have numerous gastrointestinal manifestations, the true incidence of which is unknown[2]. Digestive symptoms or signs may also reveal clues to thyroid disease and, when ignored or underestimated, diagnosis may be delayed and serious consequences may occur[3-5]. Additionally, patients with dysthyroidism are at an increased risk of developing specific pathologies in the digestive system, whether due to thyroid hormone disturbances or associated with a particular thyroid disease[6-17].

Thyroid interactions with the gastrointestinal system have been widely reported but the literature lacks an exhaustive report on different consequences of dysthyroidism. Gastrointestinal motor dysfunction has been widely accepted as the main cause of symptoms but many complex phenomena have not yet been completely elucidated[4,11,18-21]. This review aims to gather up-to-date knowledge about the effects of dysthyroidism on the gut and viscera.

HYPERTHYROIDISM

As thyroid hormones act on almost all organs within the gastrointestinal tract (gut and viscera), hyperthyroidism induces several symptoms and signs, and causes different biologic and metabolic derangements. Digestive symptoms may represent the only manifestations of hyperthyroidism. A lack of cardinal features of the disease and the presence of persistent abdominal pain, intractable vomiting, weight loss and altered bowel habits are designated as apathetic hyperthyroidism[22].

Esophagus and stomach

Dysphagia is a rare manifestation of hyperthyroidism and can have an acute or chronic pattern[3]. It may be related to direct compression from goiter or to altered neurohormonal regulation[23,24]. Excess thyroid hormone may cause myopathy which involves striated muscles of the pharynx and the upper third of the esophagus[23]. Subsequently, the oropharyngeal phase of deglutition is predominantly impaired and patients are predisposed to nasal regurgitation and aspiration pneumonia. Correction of the endocrine disorder is believed to reverse dysphagia[3,23,24].

In the esophagus, thyroid hormone excess increases the propagation velocity of contractions[25]. Thyrotoxic patients may frequently complain of chronic dyspeptic symptoms such as epigastric pain, fullness and eructation[2]. Tachygastria has been incriminated in upper gastrointestinal symptoms but the true mechanism is not yet fully understood[19,20]. Vomiting is rarely intractable and may involve neurohormonal mediators along with direct action[26]. Studies have yielded variable, even contradictory results concerning gastric emptying in thyrotoxicosis[18,19,27,28]. A significant increase in the dominant electrical frequency and dysrhythmia was shown through a myoelectrical activity study[19,20] but lack of correlation between electrogastrography (EGG) findings and gastric emptying by scintigraphy may be the result of intervening factors such as a smooth muscle disorder, electro-mechanical dissociation, pylorospasm or incoordination of the antrum and duodenum[20,29]. Hypergastrinemia found in hyperthyroidism may also influence gastric and intestinal motility[30].

Intestine and colon

Appetite increase is common but may not be adequate to maintain weight in severe disease[31]. Up to 25% of patients with hyperthyroidism have mild-to-moderate diarrhea with frequent bowel movements[22,32]. Some degree of fat malabsorption is usually present and may reach 35 g/d[33]. Intestinal hypermotility in thyrotoxicosis reduces small bowel transit time, especially when diarrhea is present[18]. Increased appetite and excessive fat-rich food intake may contribute to excessive fecal fat[34]. Moreover, diarrhea may be related to a hypersecretory state within the intestinal mucosa[22,35]. The adrenergic system may contribute to diarrhea as suggested by correction of transit in hyperthyroid patients treated with the β-adrenergic antagonist propranolol[36]. A reduction in mixing of food with digestive secretions may also contribute to decreased fat absorption. Alterations in intestinal absorptive function are still a matter of debate, as absorption may be increased for glucose[34,37] but decreased for calcium[38]. Anorectal physiology is impaired in hyperthyroidism; when compared to controls, mean anal resting and squeeze pressures are lower as is the rectal threshold of sensation[39].

Liver

Increases in aspartate aminotransferase and alanine aminotransferase in 27% and 37%, respectively, of hyperthyroid patients have been reported[40]. These disturbances are attributed to a hypoxic state with disproportionately increased liver activity compared to blood flow[41]. Mild elevation of alkaline phosphatase is encountered in up to 64% of patients with hyperthyroidism[42-44]. This elevation is not specific to the liver since a high turnover in bones may contribute. Elevations of γ-glutamyl transferase and bilirubin do not exceed 20% of normal values[44]. Increases in liver enzymes and hepatic injury related to anti-thyroid therapy is well documented[45]. Mild histological changes are common[46], but cases of fulminant hepatic failure with centrizonal necrosis have been described[46,47]. Long term untreated hyperthyroidism can ultimately lead to cirrhosis[48]. Quantitative 99mTc-HIDA cholescintigraphy in hyperthyroid rats without a gallbladder showed accelerated bile flow to the duodenum[21].

Hyperthyroidism and associated gastrointestinal diseases

Ch'ng *et al*[6] found that patients with Grave's disease were at a 5-fold added risk of developing celiac disease when compared to sex- and age-matched controls. In such cases, celiac disease may contribute to diarrhea and malabsorption. Thyrotoxicosis has been reported in 3.8% of patients with ulcerative colitis while the incidence of ulcerative colitis in hyperthyroid patients varies around 1%[17]. Thyroid disease may exacerbate ulcerative colitis symptoms or alter the response to therapy. Moreover, a positive correlation between Grave's disease and ulcerative colitis has been reported[12], but a common autoimmune origin could not be proven[11]. Isolated instances of an association between Grave's disease and Crohn's disease have been reported, but a common pathogenesis is still to be identified[16]. Primary biliary cirrhosis in association with hyperthyroidism is extremely rare and has only described as isolated case reports[8]. One study showed a prevalence of pernicious anemia of 5% in thyrotoxic patients, mainly resulting from Grave's disease[49], but parietal cell antibodies have been found in up to 30% of patients[50].

HYPOTHYROIDISM

Hypothyroidism occurs mostly secondary to an autoimmune disease or as a consequence of therapy for hyperthyroidism. It manifests throughout the body with decreased metabolic functions. It is biochemically characterized by the accumulation of glycosaminoglycans, mainly hyaluronic acid, in soft tissues[51]. Interstitial edema predominating in the skin and muscles (including the heart and intestinal muscular layer) will follow. Clinical presentation of the disease is related to the severity of the disease (biochemical derangement) but harbors significant individual variation[52]. Gastrointestinal manifestations are not rare and involve different digestive organs.

Esophagus and stomach

Severe hypothyroidism may lead to disturbances in esophageal peristalsis. When the proximal portion is involved, myxedema causes oropharyngeal dysphagia[53] while esophagitis and hiatal hernia occur when the

distal esophagus is altered[22,54]. Esophageal motility disorders, reduced velocity and amplitude of esophageal peristalsis and a decrease in lower sphincter pressure all contribute to dysphagia[55]. Although it represents an extremely rare cause of dyspepsia, hypothyroidism should be investigated when all exploratory methods are negative[56]. A gastric myoelectrical study led by Gunsar *et al*[19] showed a positive correlation between dyspepsia and hypothyroid scores. Additionally, gastric dysmotility is significantly more frequent in hypothyroid patients and is a result of muscle edema and altered myoelectrical activity[57]. Despite a few contradictory results[58], the hypothyroid state seems to delay gastric emptying[19,59]. Phytobezoar due to hypothyroidism has also been reported[60]. Achlorhydria in hypothyroidism may be related to subnormal serum gastrin[61]. Finally, hypothyroidism is associated with a decrease in duodenal basal electrical rhythm[62].

Intestine and colon

Appetite is usually reduced, but weight gain may reach 10% because of fluid retention[31]. Vague abdominal discomfort and bloating may be erroneously attributed to functional bowel disease[2]. The effect of hypothyroidism on the gastrointestinal tract seems to be multifactorial with possible alterations in hormone receptors, neuromuscular disorders and myopathy caused by infiltration of the intestinal wall. Reduction of peristalsis in hypothyroidism is the main pathophysiologic process[62], and constipation remains the most frequent gastrointestinal complaint[22]. Up to 15% of patients have fewer than 3 bowel movements weekly[2]. Moreover, thyroid hormone deficiency may influence transepithelial flux transport by inhibiting Cl^-/HCO^{3-} anion exchange with a subsequent effect on intestinal motility[35]. Although rare, severe cases of hypothyroidism lead to ileus and colonic pseudo-obstruction with fecal impaction and megacolon[63,64]. Inadvertent surgery in these situations is harmful and may be lethal[5]. Absorption of specific substances may be decreased but the total quantity absorbed is usually normal or increased due to an extended time in bowel transit[31,65]. Diarrhea in the hypothyroid state is mainly the result of increased bacterial growth secondary to bowel hypomotility[66,67]. Exceptionally, hypothyroidism may be the cause of gastrointestinal bleeding refractory to usual treatments[68], most probably by means of acquired coagulopathy[69]. Deen *et al*[39] found that the anorectal physiology is altered in hypothyroid states. While maximal anal resting and squeeze pressures are normal, the threshold for rectal sensation is higher and the maximal tolerable volume is diminished when compared to controls.

Liver

Liver function tests are mildly disturbed in almost 50% of patients with hypothyroidism despite normal histological findings[22]. Decreased hepatic metabolism in hypothyroidism is reflected by reduced oxygen consumption[70] and causes a significant decrease in gluconeogenesis[71] and urea nitrogen production[72]. Myxedema ascites in hypothyroidism is rare and may be a long-standing overlooked and/or isolated sign of the disease[73]. The serum-to-ascites albumin gradient is usually > 1.1 g/dL with a high protein content[4,73]. Although considered to be the result of hypothyroidism-related chronic right-heart failure[74,75], it is mainly attributed to increased permeability of vascular endothelium[4,76]. Patients with a common bile duct stone and gallbladder stone have, respectively, 7-fold and 3-fold increases in the frequency of hypothyroidism[77]. This may be related to the triad: hypercholesterolemia, hypotonia of the gallbladder and reduced bilirubin excretion. Experiments in rats confirmed a thyroxine effect on bile composition[78,79], decreased hepatocytic bile salt excretion in hypothyroid state[80] and relaxation of the sphincter of Oddi[81]. Moreover, Laukkarinen *et al*[21] confirmed that bile flow to the duodenum was reduced in hypothyroid rats.

Hypothyroidism and associated gastrointestinal diseases

Compared to the general population, patients with autoimmune thyroiditis have an almost 5-fold increased risk of developing celiac disease[14,15,82,83]. Valentino *et al*[7] showed that as many as 43% of patients with Hashimoto's thyroiditis carry cellular markers for celiac disease. The prevalence of thyroid antibodies is extremely high in patients with pernicious anemia (57%)[13], and the prevalence of overt pernicious anemia among patients with primary hypothyroidism is 12%[31]. An association between hypothyroidism and primary biliary cirrhosis is well documented and ranges from 5% to 20%[9,10,84]. Among patients with primary biliary cirrhosis, antithyroid antibodies were present in 20%[10]. The coexistence of Hashimoto's thyroiditis and Crohn's disease is rare and the etiological background remains to be elucidated[16,85].

CONCLUSION

Dysthyroidism, whether in excess or deficiency, has clinical manifestations within different portions of the digestive tract and viscera. Whether these are related to hormone level disturbances alone or are associated with a specific thyroid disease, the underlying pathophysiology is often complex and not yet fully elucidated in current studies. Although most frequent manifestations are well known, some situations are often underdiagnosed, leading to serious illness and death.

Digestive diseases related to thyroid hormone abnormalities or associated with particular thyroid diseases must be recognized by most, if not all practitioners. Much research requires to be performed in order to add to our understanding of the scientific background of the older empirical works.

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