Role of Helicobacter Pylori Infection in the Thyroid Diseases

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Helicobacter pylori (*H. pylori*) is a Gram negative bacterium, which colonizes the stomach and affects gastric physiology, especially gastric acid secretion. When *H. pylori* infection is confined to the antrum, i.e. antral gastritis, an increased acid production occurs which may cause either duodenal ulcer or dyspeptic symptoms. On the contrary, when it spreads to the fundus, i.e. pangastritis, the gastric acid production is reduced, and this condition is associated with an increased risk of both gastric ulcer and cancer [1].

Due to its importance as a global pathogen with significant morbidity and mortality, accurate tests are important to diagnose the infection, to target antibiotic therapy, and to verify bacterial eradication. Several tools have been proposed, including both invasive (endoscopy) [2, 3], and noninvasive methods [4] and it is firmly recommended to eradicate the infection with either triple therapy for 7-14 days in those geographic areas with low primary clarithromycin resistance rate, or bismuth quadruple therapy for 10-14 days or sequential therapy [5] where there is a high (>15-20%) clarithromycin resistance rate [6]. Although the causal link between the infection and peptic (duodenal and gastric) ulcer is well known as well as the link between long-term colonization of the pathogen and the development of gastric adenocarcinoma and mucosal associated lymphoid tissue lymphoma (MALT) [7, 8], there is still controversy regarding the benefit of *H. pylori* eradication in other clinical conditions, such as non-ulcer dyspepsia, gastro-esophageal reflux disease (GORD), and patients taking chronic non-steroidal anti-inflammatory drugs (NSAIDs) [9]. *H. pylori* infection can involve some extragastric diseases, such as respiratory (COPD, bronchiectasis and asthma), cardiovascular (atherosclerosis, myocardial infarction), and immune-mediated allergic diseases. However, to date, convincing data exist only for the role of *H. pylori* in the idiopathic thrombocytopenic purpura and idiopathic sideropenic anemia.

H. pylori has also been suggested as a causal agent of drug malabsorption. In particular, malabsorption of thyroxin has been described in patients with *H. pylori* infection or treated with drugs that can modify an acid environment.

The relationship between *H. pylori* infection and the daily thyroxin dose in patients with thyroid diseases has been demonstrated in several studies [10-12]. The mechanism of thyroxin absorption involves the intestinal mucosa at the level of the jejunum and ileum, and the range is from 62% to 82% of the ingested dose, with a peak between the first and third hour [13, 14]. The intestinal modulation of thyroxin absorption is determinant for the effectiveness of therapy and it is influenced by several factors, including the patient's age, adherence to therapy, dietary habits, absorption kinetics, malabsorption, and interference of other drugs [15 -17]. It has been speculated that the acid environment might have a role in thyroxin absorption [18]. The normally acid environment of the stomach becomes altered in patients with *H. pylori*-related gastritis, atrophic gastritis of the gastric body, or both, as well as in patients who are receiving long-term treatment with PPI [19]. The concomitant presence of such gastric disorders with thyroid diseases may lead to uncertainty about the daily dose of thyroxin. Recently, the dose of thyroxin that is required to lower levels of thyrotropine in patients with goiter having impaired secretion of gastric acid has been evaluated [20]. Data found confirmed that normal gastric acid secretion is important for the subsequent intestinal absorption of thyroxin: an increased requirement of oral thyroxin was observed in patients with

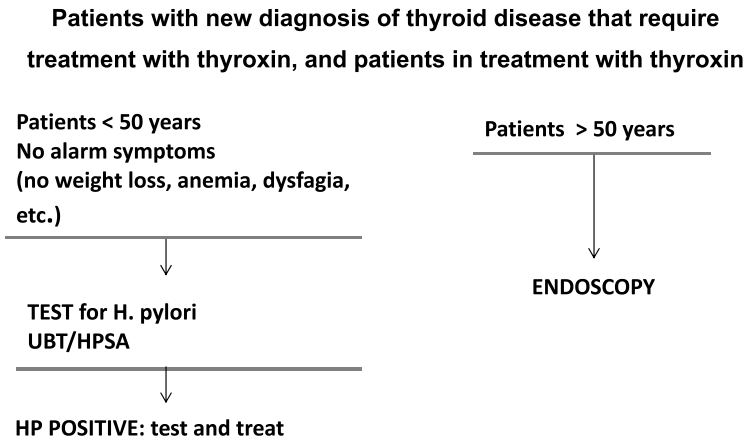

Fig.1. Algorithm for investigating the patients with thyroid diseases.
UBT: urea breath test; HPSA: *H. pylori* stool antigen

atrophic gastritis and concomitant *H. pylori* infection. Another study investigated the thyroid function changes following *H. pylori* eradication in those patients who failed to respond to high thyroxin doses. In cured patients, the TSH decreased and factitious thyrotoxicosis developed in 21% [21]. These data pointed out that *H. pylori* gastritis may be responsible for an inadequate response to hormone treatment, and that the patients receiving high doses of thyroxin are at risk to develop thyrotoxicosis. A recent systematic review evaluated absorption of different drugs in *H. pylori* infected patients. An impaired absorption of l-dopa, thyroxin and delavirdine was observed; in addition, thyroxin requirement was higher in hypochlorhydric goitre subjects with *H. pylori*-gastritis and thyrotropine levels decreased by 94% after treatment [22]. However, other studies provided conflicting results, with significant differences between patients with *H. pylori* infection and controls being observed at univariate but not multivariate analysis [23].

In summary, *H. pylori* has been suggested as a causal agent of thyroxin malabsorption by ammonia production in the stomach and/or development of atrophic gastritis. The severe hypochlorhydria associated with *H. pylori*-related pangastritis may cause an increased need for thyroxin. Although the exact mechanism by which intestinal absorption of thyroxin is impaired in patients with hypochlorhydria is still unknown, it has been speculated that since oral thyroxin is administered as a sodium salt, it is less lipophilic than the native hormone, which enters target cells both through passive diffusion and in a carrier-mediated way [24, 25]. Moreover, achlorhydria may alter the ionization status and the conformational characteristics of the thyroxin molecule and, consequently, its intestinal absorption. Drugs that decrease (e.g. calcium carbonate) or inhibit gastric acid secretion (in particular PPIs) can also diminish the absorption of levothyroxine. A plausible explanation for this is the decrease in the speed of dissolution of the tablet in a gastric environment with higher pH [26]. Therefore the drug reaches the duodenum still largely un-dissolved and the proportion of levothyroxine available for absorption will be lower than normally observed. With an oral solution, this effect of pH on the dissolution and hence absorption does not occur, since dissolution is no longer required. It seems realistic to assume that in patients with insufficient gastric acid secretion, administration of levothyroxine as an oral solution results in better absorption compared to that observed with tablets.

Conflicts of interest: None.

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