Review Article

The Interaction of *Helicobacter pylori* Infection and Type 2 Diabetes Mellitus

Abstract

Helicobacter pylori is one of the most common human pathogens that can cause gastrointestinal (GI) disorders, including simple gastritis, gastric ulcer, and malignant gastritis. In some cases, such as immunodeficiency and underlying diseases, it can be problematic as opportunistic infections. Diabetes mellitus (type 2) (T2DM) is one of the *H. pylori* underlying diseases. Since GI problems are observed in diabetic patients, it is necessary to treat *H. pylori* infection. In this review, we aimed to evaluate the possible relationship between *H. pylori* and T2DM according to epidemiological surveys of 70 studies retrieved from databases, including Scopus, PubMed, and Google Scholar about the relationship between *H. pylori* and T2DM, and discuss the reported background mechanisms of this correlation. According to the results of our study, the different studies have shown that *H. pylori* is more prevalent in Type 2 diabetic patients than healthy individuals or nondiabetic patients. The reason is development of *H. pylori* infection-induced inflammation and production of inflammatory cytokines as well as different hormonal imbalance by this bacterium, which are associated with diabetes mellitus. On the other hand, by tracing anti-*H. pylori* antibodies in patients with diabetes mellitus and occurrence of symptoms such as digestive problems in >75% of these patients, it can be concluded that there is a relationship between this bacterium and T2DM. Considering the evidence, it is crucially important that the probability of infection with *H. pylori* is evaluated in patients with T2DM so that medical process of the patient is followed with higher cautious.

Keywords: *Diabetes, diabetes mellitus, Helicobacter pylori, Type 2 diabetes*

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Introduction

In 1983, Warren (a biologist) and Marshall (a clinician) described *Helicobacter pylori*.[1] First, they named the bacterium *Campylobacter pyloridis*, and then, it was named *Campylobacter pylori*. Diagnosis and treatment of the upper gastroduodenal disease have been changed dramatically since 20 years ago that *H. pylori* was cultured for the first time.[2-4] Peptic ulcer disease is now approached as an infectious disease.[5] The role of *H. pylori* infection is increasingly recognized in gastric cancers as well as evaluating its role in other gastrointestinal (GI) diseases.[6]

Elevated antibodies level against *H. pylori* also attracted the attention to some extra-gastric diseases, including diabetes mellitus.[7,8]

Among the patients referring to diabetes clinics, as many as 75% of them will report significant GI symptoms.[9,10] The entire GI tract can be affected by diabetes from the oral cavity and esophagus to the large bowel and anorectal region. Thus, the experienced symptom complex may be vary widely.[11] The common complaints can include dysphagia, early satiety, reflux, constipation, abdominal pain, nausea, vomiting, and diarrhea. Many patients remain undiagnosed and undertreated because the GI tract has not been conventionally associated with diabetes and its complications.[12]

Type 2 diabetes mellitus (T2DM) is turning to be pandemic so that it is responsible for death of 3.8 million of the adult population in the world and regarded as a serious risk for public health.[13,14] Increasing blood sugar, which is chronically observed in the patients with diabetes, may cause long-term damage to different organs, especially eyes, kidney, nervous system, heart, and blood vessels. At least 80% of the patients with diabetes will die due to consequences of cardiac complications.[14-16]

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Pathogenic mechanisms of diabetes mellitus include insulin resistance (IR), chronic inflammation, insufficiency of insulin secretion (due to impaired pancreatic beta-cells), glucose toxicity, and lipotoxicity.[14]

Relationship between *Helicobacter pylori* and Type 2 Diabetes Mellitus

Evidence indicates that diabetes may accompany by *H. pylori* infection, which chronic and insulin-resistant inflammation may increase the risk for T2DM. In addition, gastritis resulting from *H. pylori* may potentially affect gut-related hormones and inflammatory cytokines.[14,17]

Although there is no strong evidence for this relationship, some reasons can be considered to discuss it, which are summarized in the following:

First, diabetes causes impairment in the function of the cellular and humoral immunity, which also increases the individual's sensitivity to *H. pylori* infection.[18] Second, it reduces GI movements and secretion of gastric acid, which in turn increases colonization and bacterial infections.[19] Third, changes in glucose metabolism may alter chemical production in the gastric mucosa, which results in colonization of more bacteria.[20] Ultimately, diabetic patients are more likely to be exposed to pathogens than healthy people, due to their more presence in the hospital environment.[21]

There is controversy about the link between *H. pylori* infection and diabetes as some studies indicate a higher prevalence of infection in diabetic patients,[22-24] whereas in the others, no difference has been reported.[25-27] Jeon *et al*. have been reported for the first time that *H. pylori* infection leads to increase the incidence of T2DM using a prospective cohort of 782 Latino individuals older than 60 years.[19] This study showed that people with *H. pylori* infection would more suffer from diabetes in comparison to healthy individuals.

It is found that 84.6% of diabetic patients with *H. pylori* infection had diabetics for >10 years. Besides the glycemic control, diabetes duration is the main risk factor of increasing the risk of chronic diabetes-related complications, which its importance in our study is the autonomic neuropathy and gastropathy that are critical predictors for *H. pylori* infection in diabetics.[12,28]

Bayati *et al*. in a study concluded that 61.5% of those with *H pylori*-positive status had one or more of the chronic diabetic complications. This finding is in agreement with the findings of a study indicating that diabetic patients with a history of retinopathy, nephropathy, or neuropathy should be presupposed to have GI abnormalities until proven otherwise.[29]

Role of Inflammatory Cytokines

At the initial phases of infection, polymorphonuclear cells penetrate into GI mucus. After a while, these cells are replaced by mononuclear cells at chronic phase of infection. Mononuclear cells are specified by the production of inflammatory cytokines, which in addition to local effect can be effective also as released on other tissues and organs. It causes increase in the extraintestinal diseases in people with *H. pylori* infection, such as cardiovascular, neurological, autoimmune, thyroid, liver, and biliary diseases.[30] Therefore, the bacteria cause to develop inflammation and production of different cytokines and impairment in absorption of nutrients and medicines and can lead to the induction and development of various diseases.[31-35] In a study by Zojaji *et al*. on 85 patients referring to a endocrinology clinic of Shahid Beheshti University of Medical Sciences in Tehran, Iran, it concluded that the most important produced inflammatory cytokines include C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α), which contribute to IR and diabetes incidence.[36-41] High levels of CRP (high-sensitive CRP [hsCRP]) are important determinants in diabetes-related research so that the most papers reported strong relationship between CRP level and diabetes risk. Various studies introduced this factor as the connection between *H. pylori* and Type 2 diabetes; as of 11 prospective studies, seven reported a significant positive association between hsCRP levels and diabetes risk[30,42-48] while it found no association in the others.[49-52] Various studies have identified this factor as a bridge between *H. pylori* and Type 2 diabetes as El Hadidy *et al*. reported a significant increase in CRP level and *H. pylori* infection among Type 2 diabetic patients as well as Oshima *et al*. found a significant increase in CRP level in nonsmoker healthy individuals seropositive for *H. pylori* infection. Markus *et al*. found significant association between CRP and *H. pylori* seropositivity.[30,37,53]

A study by Aydemir *et al*. showed higher homeostatic model assessment-estimated IR scores in *H. pylori*-positive individuals.[54] Furthermore, a Japanese study in 2009 conducted on a large population of 1107 asymptomatic individuals showed that *H. pylori* was significantly and independently related to IR.[55] However, Gillum supported that there are no consistent associations between *H. pylori* infection and prevalence of diabetes or syndrome-related variables of the IR in American men of 40–74 years.[56] Furthermore, Park *et al*. reported that metabolic and inflammatory parameters, including blood sugar, lipid profiles, IR, white blood cell count, and CRP levels, were not changed after *H. pylori* eradication. It is worth noting that *H. pylori* infection was not determined in all studies by organisms' histologic detection of mucosal biopsy specimens, which is considered the diagnostic gold standard.[14,57]

Role of Hormones

Helicobacter by induction of gastritis is potentially able to influence the secretion of hormones, such as leptin, ghrelin,

gastrin, and somatostatin, and subsequently increases the diabetes risk. Gastrin increases insulin secretion and somatostatin leads to reduction. *Helicobacter* causes to increase gastrin concentration and lower serum somatostatin concentration through influencing these hormones and thus affects insulin secretion.[58-60]

Reduced insulin secretion is one of the major factors in the incidence of Type 2 diabetes. In the studies by So *et al*., it indicated that *H. pylori* interdependently can predict dysfunction of pancreatic beta-cells in Chinese males.[61]

In addition, Rahman *et al*. found a positive relationship between *H. pylori* infection and defective insulin secretion so that insulin molecules are highly susceptible to damage from oxidative stress and inflammation. Hence, *Helicobacter* inflammation probably causes defection in insulin production.[62]

In addition, in the study by Hsieh *et al*., it reported that patients infected *by H. pylori*, especially at young ages are defective in insulin secretion, which is considered as a risk factor for Type 2 diabetes.[63] In addition, Gen *et al*. proved that elimination of pylori infection considerably reduces insulin level.[64]

Ghrelin causes reduction of energy consumption and increasing the weight, whereas leptin reduces food absorption, on the one hand, and increases energy consumption, on the other hand.[60,65]

It has been shown that *H. pylori* infection impairs ghrelin production and enhances leptin production.[66-68] Low ghrelin levels are associated with elevated fasting insulin concentrations, IR, and T2DM.[69] Leptin has also been implicated in IR development, and elevated levels correlate with IR in lean men and patients with T2DM[70-72] [Figure 1].

Insulin resistance and abnormal insulin secretion are central to the development of Type 2 diabetes mellitus. On the one hand, *Helicobacter pylori* infection brings about chronic low-grade inflammation with upregulation of several cytokines such as C-reactive protein, tumor necrosis factor, and interleukin-1β, which may impact insulin action and pancreatic β-cell secretion. On the other hand, Helicobacter pylori-induced gastritis can potentially affect gastric hormones secretion, including leptin, ghrelin, gastrin, and somatostatin, which could affect insulin sensitivity and glucose homeostasis. In addition, other mechanisms and mediators may be involved in the possible causative relationship between *Helicobacter pylori* infection and Type 2 diabetes mellitus.[73,74]

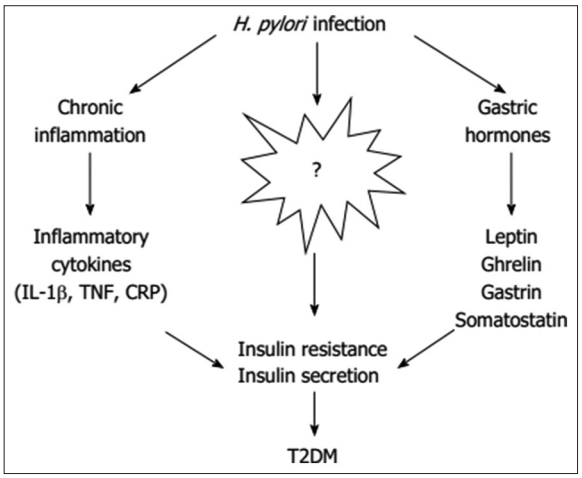

Figure 1: Potential mechanisms for *Helicobacter pylori* contribution to Type 2 diabetes mellitus

Helicobacteria Can also Be Associated with Other Diseases due to Type 2 Diabetes

Diabetic patients are at risk of cardiovascular and thrombo-occlusive cerebral diseases. There is a possible correlation between *H. pylori* infection and cardiovascular or cerebrovascular diseases. Chronic *H. pylori* colonization may be in association with an increased risk of atherosclerosis. It is hypothesized that *H. pylori* infection has atherogenic capacities by activating chronic low grade of homeostasis cascade.[73-75] The association between *H. pylori* and acute cerebrovascular disease may be due to a higher prevalence of virulent *H. pylori* strains in atherosclerotic stroke patients.[76]

El Hadidy *et al*. also found a significant increase in fibrinogen level as one of the risk factors of atherosclerosis in *H. pylori*-positive diabetic patients in comparison to negative patients.[30] The same results were found by Schumacher *et al*. in patients with coronary heart disease.[77] Zito *et al*. reported the increased level of plasma fibrinogen in *H. pylori*-infected patients even after controlling of possible related confounding factors either infection or fibrinogen.[78]

Conclusions

In this regard by studying various studies, we can conclude that:

1. *H. pylori* infection is more common in diabetic patients
2. There is higher frequency of *H. pylori* infection among elderly diabetics
3. *H. pylori* infection enhances the presence of chronic diabetic complications in its different categories
4. There is no significant difference in male-to-female ratio distribution of *H. pylori* infection.

However, as already mentioned, there are opposite results in this regard, though diabetes mellitus is a multifaceted and multistep disease that is improbably resulted from a single cause, as the risk factors that deserve attention include GI infections and the intestinal microbiota composition. Evidence supporting an etiological role of *H. pylori* in T2DM developing would indicate that preventive measures, such as improving hygiene and treatments using

antibiotics and proton-pump inhibitor combinations, should be explored as the target of interventions in high-risk communities.

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Conflicts of interest

There are no conflicts of interest.

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