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The Relationship between *Helicobacter Pylori* and Extra-Gastrointestinal Infections

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ABSTRACT

Helicobacter pylori (*H. pylori*) has been identified as the major agent in human gastric cancer by the International Agency for Research on Cancer (IARC). Infection caused by *H. pylori* plays a leading role in many disorders including duodenal and gastric ulcer, chronic gastritis, lymphoid tissue lymphoma, and gastric adenocarcinoma. In addition, growing evidence suggests that *H. pylori* interferes with many biological processes, causing or affecting the incidence of several extra-gastrointestinal disorders. The bacteria are known to cause iron deficiency anemia (IDA), vitamin B12 deficiency, and immune thrombocytopenic purpura (ITP). Latest studies suggest that H. pylori may contribute in many disorders such as insulin resistance, acute coronary syndrome, neurological diseases among others, which previously was attributed to other factors and conditions. There are several mechanisms proposed for *H. pylori* inducing low-grade chronic inflammation and the incidence of molecular imitation mechanisms. This present study discusses the most critical diseases related with the role of *H. pylori* and related infection (especially extra-gastrointestinal diseases) in these diseases.

Keywords: *Helicobacter pylori*, Gastrointestinal diseases, Extragastric diseases, Pathogenic factors

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Introduction

Helicobacter pylori (*H. pylori*) first discovered by two Australian physicians Robin warren and Barry Marshall in 1982. *H. pylori,* a helical gram-negative bacterium, is known as a significant pathogen causing infection in people, affecting about 4.4 billion people in the world (about 50-60% of the world's population in 2015) **(1 - 5)**. Although the main host for *H. pylori* is stomach, it may reach the distal esophagus or proximal duodenum if gastric metaplasia is presented **(6)**. Unlike many bacteria, *H. pylori* is highly compatible to live in the stomach. Many factors including acidity, peristalsis, nutrient availability, innate and acquired

host immunity, and competition between microbes limit the presence of bacteria in the human stomach. The special characteristics of *H. pylori* enables it to reduce the acidity of the environment it lives in [7, 8]. Many gastrointestinal diseases including gastritis, dyspepsia, peptic and duodenal ulcer, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma are strongly correlated with *H. pylori* infection **(5, 9)**. *H. pylori* has been classified into the first group of carcinogens (meaning causing cancer) of human gastric cancer by IARC in 1994. Chronic infection by *H. pylori* in stomach tissue contribute leads to chronic inflammation or a cancer-prone environment that eventually cause gastric cancer **(1)**. The prevalence of infections caused by this pathogen varies in different countries, for example, in Latin America (75-83%), Japan (39.6), and the United States (17.1) **(9)**. There is a direct correlation between *H. pylori* infection and its transmission with poor socioeconomic status e.g. poor health, water pollution, low quality lifestyle, poor diet, smoking, and lack of physical activity **(1)**.

The association between *H. pylori* and extra-gastrointestinal disorders have also been reported in several studies. The first category of these disorders are unusual metabolic profiles, e.g. diabetes, insulin resistance, hypertension, dyslipidemia, and obesity, all of which are part of metabolic syndrome. As a result, unusual profiles lead to increased risk of cardiovascular disease due to atherosclerosis and vascular disorders. The 2th category of disorders is related to the immune system response, involving atopic diseases, asthma, hives, and autoimmune thyroid diseases (ATDs). The third category of these diseases includes immune thrombocytopenic purpura (ITP), migraine, iron deficiency anemia (IDA), deficiency of vitamin B12, glaucoma, and severe nausea and vomiting [10]. The proposed mechanism for these diseases is that chronic Infection by *H. pylori* causes chronic inflammation caused by the complex response of biological tissue. Inflammatory factors like tumor necrosis factor (TNF) and cytokines interleukin (IL) are specifically due to the chronic-low-grade inflammation, which is common in infectious inflammation pathways in gastritis, diabetes, metabolic syndrome, atherosclerosis, and obesity. The inflammatory factors caused by the mucosa of enflamed stomach are continuously discharged to the bloodstream, thereby affecting the metabolic profile. As a result of cytokine induced by *H. pylori*, low-grade chronic inflammation caused the infection of *H. pylori* my lead to extra-gastrointestinal disorders **(1, 10, 11)**. Recent studies indicate the importance of study on gastrointestinal and extra-gastrointestinal diseases associated with *H. pylori* infections. In this review study, our research team will introduce the most important *H. pylori*-related disorders (especially extra-gastrointestinal diseases) and discuss the role of *H. pylori* in extra-gastrointestinal disorders.

Materials and Methods

The present study aimed to assess the relationship of *H. pylori* with extra-gastrointestinal infections by classifying the subjects researched from 1980 to 2019. This evaluation was conducted in 2020 and databases including PubMed, Medline, Cochran Library, WHO, and Iranmedex were used to obtain the desired articles. Aiming to collect data on the relationship of *H. pylori* with extra-gastrointestinal infections, the keywords such as "gastrointestinal diseases", "*Helicobacter pylori*", "extra-gastrointestinal diseases", and "pathogenic factors" were used. Finally, out of 210 retrieved papers, 51 papers were identified as appropriate and examined in terms of subject, content structure, and relevance.

An Overview of *H. Pylori* Infection and Pathogenic Factors

After entering to the stomach of its host, *H. pylori* uses urease activity to neutralize the acidic conditions of the stomach **(6)**. The bacterium may express inflammatory pathogens associated with inflammation and inflammatory symptoms in infected patients. The main pathogens of *H. pylori* include gamma-glutamyl transpeptidase (GGT), vacuolating cytotoxin A (VacA), and a product of the cytotoxin-associated gene A (CagA), which cause damage to host tissues. The products of these factors are secreted by *H. pylori* into host cells [12]. Studies have shown that CagA may have a leading role in the production of IL-8 and the activation of nuclear factor kappa-B (NF-κβ). In addition, CagA expression induces IL-8 production and NF-β transport in gastric epithelial cells. VacA of *H. pylori* is able to induce intracellular vacuolization in gastric epithelial cells. It is therefore assumed to contribute to damage to the stomach and duodenal mucosa that eventually lead to ulcer. Therefore, pathogenic factors VacA and CagA play a critical role in *H. pylori* pathogenicity and infection [9]. Other factors, including Bab2 adhesion factor, outer inflammatory protein A (OipA), the induced by contact with epithelium antigen (iceA) factor, sialic acid-binding Adhesin (SabA), and duodenal ulcer promoting gene A (dupA) are involved in mucosal colonization. In addition, these factors secrete cytokines to initiate innate immunity and activate neutrophils in the pathogenesis of the gastric epithelial layer, which forms the main link *H. pylori* with the host, leading clinical diseases such as gastritis and ulcers. In short, four steps are required in establishment and pathogenicity of *H. pylori* as follows:

1. Surviving the acidic conditions of stomach
2. Movement to epithelial cells via nodules

3. Connection to host receptors via adhesion factors

Damaging tissues via pathogenic factors (Figure 1) **(9, 12, 13)**.

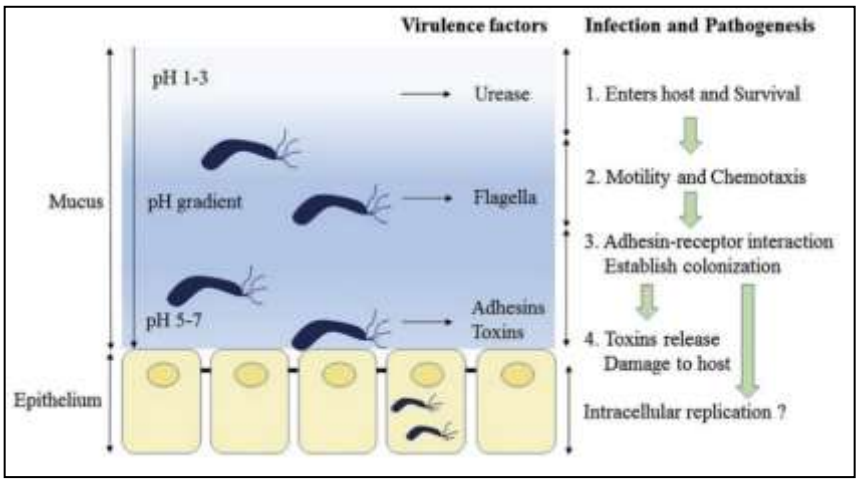

Figure 1. Schematic diagram of pathogenesis and infection of *H. pylori*. **(9)**

Epidemiology and Natural History

A steady decrease has been noticed in the prevalence of *H. pylori* infection and gastric cancer among most populations, especially in affluent Western societies in recent decades. Dominant bacterial genotypes also vary in different societies. Communities with higher risk of gastric cancer have higher pathogenicity strains **(14)**. In some populations, more than one strain with different pathogenicity is located in the gastric mucosa. In these societies, along with the reduction of cancer rates and the spread of infection, great changes have taken place, including economic development; the most important changes include improving the health status of homes, reducing family population, changing eating habits (e.g., consuming less salt and more fresh vegetables and fruits), improving cooling equipment, and controlling infectious diseases. Excessive consumption of antibiotics to deal other infectious disorders may have adverse effects on the prevalence of H. pylori infection **(12, 15)**.

Clinically, *H. pylori* infection has variable course and is affected by the host and microbial agents. The gastritis distribution and pattern is highly correlated with the risk of several clinical disorders including as mucosal atrophy, duodenal and gastric ulcers, gastric lymphoma, and gastric cancer **(16)**. Antral-predominant gastritis is the most prevalent type of *H. pylori* gastritis and patients with this type of gastritis are more prone to duodenal ulcers. However, patients with multifocal atrophic and corpus predominant gastritis are at higher risk to develop ulcers, intestinal metaplasia, gastric atrophy, and eventually gastric cancer. Gastric adenocarcinoma caused by *H. pylori* infection starts with gastritis and results in atrophy followed by intestinal dysplasia, metaplasia, and gastric cancer, respectively. *H. pylori* contributes to most types of gastric and duodenal ulcers. The prevalence of gastric ulcer in a person affected by H. pylori infection varies from 3% in the USA to 25% in Japan. Gastric cancer is considered as the 2th leading reason of death from cancer. The relation of H. pylori with the increased risk of gastric cancer is confirmed in various research, so that in 1994 it was definitively classified as type 1 carcinogen **(8, 12, 15, 17).**

Figure 2. Outbreak of gastric cancer in 2012 **(15)**

Studies have shown that almost all patients with MALT lymphoma are effected by *H. pylori* infection, i.e. *H. pylori* infection significantly elevate the risk of developing MALT lymphoma. Patients who are in the primary stages of the disease are more likely to recover completely with antibiotic treatment, but people with progressed stages of the disease (wounds, submucosal lesion, wall attack, or lymphadenopathy) are more likely in need of lymphoma treatment. Patients with intestinal metaplasia should be tested for H. pylori infection, as intestinal metaplasia is an autonomous risk factor of gastric malignancy. After eradication of the bacterium, the probability of gastric lymphoma (MALT) recurrence is about 70-80% **(5, 8, 12, 15)**.

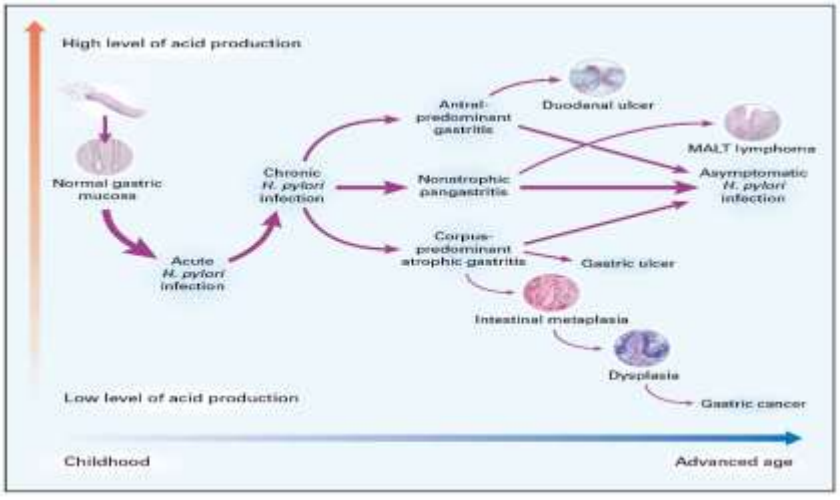

Figure 3. The natural course of *H. pylori* infection **(17).**

It is estimated that about 5% of people with dyspepsia (most of them functional) were due to *H. pylori* infections. Patients with *H. pylori* may have symptoms of dyspepsia without the presence of macroscopic lesions in the gastroduodenal mucosa. This is known as dyspepsia and various pathogenic mechanisms are involved in it. The results of various experiments and data from several extensive studies have noted that eradicating *H. pylori* to improve dyspepsia symptoms is more cost-effective statistically, and has a better effect on the natural history of functional dysplasia compared with placebo. The reasons for the recurrence of dyspeptic symptoms in some patients following elimination of *H. pylori* have not been fully elucidated yet **(12, 15, 18)**.

Gastroesophageal reflux disease (GERD) is referred to a multifactorial disorder which causes the gastric acid to reflux into the esophagus, resulting tissue injury and certain symptoms such as burning and vomiting. Increased prevalence of GERD symptoms indicates decreased prevalence of peptic ulcer and *H. pylori*. The exact link among *H. pylori* infection and GERD seems complex. However, current evidence does not support a definitive conclusion as to whether patients infected by *H. pylori* have the same GRED symptoms as non-infected patients **(19, 20)**. Studies to date have noted that the treating infection caused by *H. pylori* leads to worsening of GERD. According to a theory that suggests an exact link between *H. pylori* infection and GERD, because the induction of

gastric atrophy by bacteria and the resulting lack of stomach acid, the development of GERD in individuals is reduced, which is a potential risk for Barrett's esophagus and esophageal adenocarcinoma. Therefore, the concern is that eradication may cause the spread of GERD symptoms and lead to the spread of esophageal adenocarcinoma worldwide **(15, 21)**.

In recent years, many scientists around the world have studied the association between extra-gastrointestinal diseases and *H. pylori* infection. In fact, *H. pylori* possibly is associated with a variety of biological procedures both outside and inside the gastrointestinal tract and is likely to determine and affect the incidence of many extragastrointestinal disorders. However, the association of *H. pylori* with sideropenic anemia and idiopathic thrombocytopenic purpura has already been identified. Recent evidence shown that *H. pylori* is related with increased risk of acute coronary syndrome, insulin resistance, neurogenic and respiratory diseases, and other disorders. Various pathogenic mechanisms such as the induce of low-grade chronic inflammation and the incidence of molecular mimicry mechanisms have been proposed in this field **(11, 22)**.

Extragastric Diseases

Cardiovascular Diseases

Wang *et al.* (2018) studied the relationship between the infection by *H. pylori* and the risk of coronary heart disease (CHD). They designed a comprehensive cohort study using Taiwan's National Health Database and compared 3,713 patients with peptic ulcer disorder treated by anti *H. pylori* medicine with available data of untreated patients. The results of this study showed that mortality was reduced in patients affected by *H. pylori* infection who underwent eradication therapy **(23)**. In their cohort study, Lai *et al.* (2015) found a direct relationship between *H. pylori* infection and increased prevalence of acute coronary syndrome, even following the elimination of pathogens, and it increases with aging **(24)**. The results of the study conducted by Hughes (2014) on a military group born in the 1930s showed a decrease in the simultaneous heart attack and duodenal ulcers. Hughes concluded that duodenal ulcer is highly associated with the infection with *H. pylori* and one of the reasons for the reduction in heart attacks is the eradication of *H. pylori* **(25)**. Since inflammation has a major role in atherosclerotic plaque rupture, high levels of serum IL-6 appear to be significantly related to *H. pylori* infection and may actively contribute in ischemic heart disease. Other studies have reported a high level of B-type natriuretic peptide and IL-6 (biomarkers of heart failure) in the body of patients suffering from coronary artery disorder infected with CagA-positive strains **(11)**.

Diabetes and Insulin Resistance

Insulin resistance (IR) is among the main pathogens of type 2 diabetes **(1).** The relationship among *H. pylori* and diabetes was first studied in 1989, and it was found that the rate of infected cases with *H. pylori* was higher in diabetic patients compared the control (62% vs. 21%). A systematic review (2011) reported a very significant score in the hemostatic model for assessing insulin resistance in individuals infected with *H. pylori* in comparison with non-infected individuals in seven cross-sectional analyses **(26)**. Yang *et al.* (2014) study also showed a meaningful correlation among diabetics and *H. pylori* infection by studying 1,285 subjects (age range: 19-85 years), and in line with these researchers, similar results were reported by Indian researchers **(27)**. Diabetic patients infected with *H. pylori* have poorer glycemic control than non-infected cases. In addition, other researchers identified higher diabetes rates of prevalence in *H. pylori* infected patients and there is a positive relationship between IR and *H. pylori* infection **(11, 28).** The potential mechanism proposed is that *H. pylori* lipopolysaccharides activate Toll-like receptors, which are often expressed in macrophages and dendritic cells, causing energy absorbing, fat accumulating and eventually IR. In severe inflammation, cytokines inhibit the insulin to affect its receptor via phosphorylation of residual serine in the receptor, leading to IR **(1)**.

Despite the significant correlation between diabetes and *H. pylori* infection, the issue is still under debate among researchers. The reason for this disagreement is different results in comparing the levels of diabetes pre and after the *H. pylori* eradication in several experiments. Most of the experiments have reported the favorable effects of *H. pylori* eradication in reducing diabetes, but other reports indicate a lack of correlation between IR level and diabetes before and after the eradication **(1, 11, 29)**. Numerous studies have shown that diabetics are more susceptible to infection. Diabetes-induced humoral and cellular immune disorders may increase a person's susceptibility to *H. pylori* infection. On the other side, diabetes reduces the rate of acid secretion and gastrointestinal motility, which may contribute to *H. pylori* colonization and gastrointestinal infection. Alterations in glucose metabolism may also lead to chemical changes in gastric mucus, which in turn promotes *H. pylori* colonization. In addition, people with diabetes are more exposed to pathogens in the hospital environment than other individuals **(30)**.

Metabolic Syndrome (MetS)

MetS refers to a set of metabolic disorders which are considered as a risk factor for various gastrointestinal diseases as well as cardiovascular diseases. MetS, known as syndrome x and IR syndrome, has been steadily increasing worldwide and has placed a significant burden on public health **(31-33)**. MetS is so closely related to IR

that it is known as one of the mechanisms of MetS expression. *H. pylori* is also regarded as a mechanism involved in the development of MetS. There are multitude studies indicating the global spread of MetS and H. pylori infection, and growing evidence exists regarding the possible link of H. pylori infection with both IR and MetS. Evidence suggests that these syndromes are associated with diseases like cardiovascular disease, diabetes mellitus type 2, abdominal obesity, dyslipidemia, hypertension, and non-alcoholic fatty liver disease (NAFLD).

Nabiour *et al.* (2006) was the first study that assessed the correlation between *H. pylori* infection and MetS and reported that *H. pylori* infected cases was 1.5 times more prone to MetS compared to healthy individuals **(34)**. Using histological diagnosis of *H. pylori* and urea breath test, Chen et al. (2015) concluded that MetS prevalence in patients with *H. pylori* infection was higher compared to non-infected cases in both males and females **(35)**. A same association between IR and *H. pylori* has also been noted in a systematic review by Polyzos et al. (2011) **(36)**. The relationship of H. pylori eradication with MetS recurrence was investigated to assess the impact of *H. pylori* infection on MetS pathogenicity among black populations. The results of this study showed improvement in three components including plasma glucose, HDL-cholesterol, and systolic and diastolic blood pressure compared to base values following 3 weeks of *H. pylory* eradication (1).

A review article titled *"The Possible Role of Helicobacter pylori Infection in Non-alcoholic Fatty Liver Disease"* by Cheng *et al.* (2017) is a good illustration of the mechanism by which *H. pylori* infection affect the development of NAFLD disease. IR is considered as an important part of the development of NAFLD disease and many studies have confirmed the important role of *H. pylori* infection on IR development. Infection by *H. pylori* can increase low-grade chronic inflammation and levels of anti-inflammatory factors, including TNF- α and IL-6, and subsequently activate IKK/NF-κB, causing IR. Inhibiting leptin release by white adipose tissue is another possible effect of *H. pylori* infection, which causes an increase in the activity of desaturase CoA stearoyl (SCDI) in the liver, thereby accelerating the deposition of fat and VLDL-C in the liver tissues (Figure 4). Regarding the interaction between intestines and stomach, *H. pylori* infection may cause other gastrointestinal diseases [37]. Chen *et al.* (2019) also stated that people infected with *H. pylori* are more susceptible to NAFLD than those not infected by *H. pylori* **(38).**

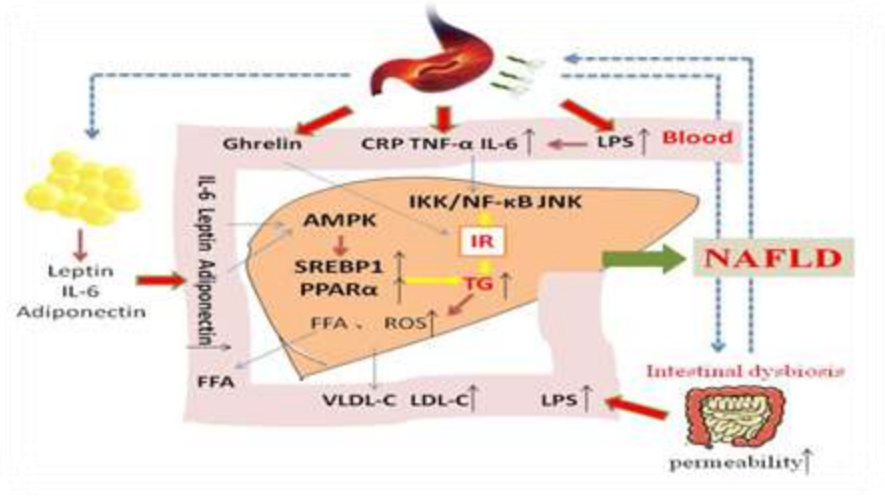

Figure 4. Possible relationship between NAFLD and *H. pylori* infection **(38).**

Neurogenic Diseases

The relationship between neurodegenerative diseases and neuroinflammation can potentially be triggered by environmental conditions and disruption of the blood-brain barrier. Recent studies outlined that various pathogens (including *H. pylori*) may reach the central nervous system (CNS) via blood flow, gastrointestinal tract, and olfactory tract. Thus, *H. pylori* is able to induce cellular and humoral immune responses and also, interact with CNS components through sharing homologous epitopes, thereby causing damage to nerve tissue. Hence, one could associate *H. pylori* with several CNS-related degenerative and autoimmune diseases **(39-42)**.

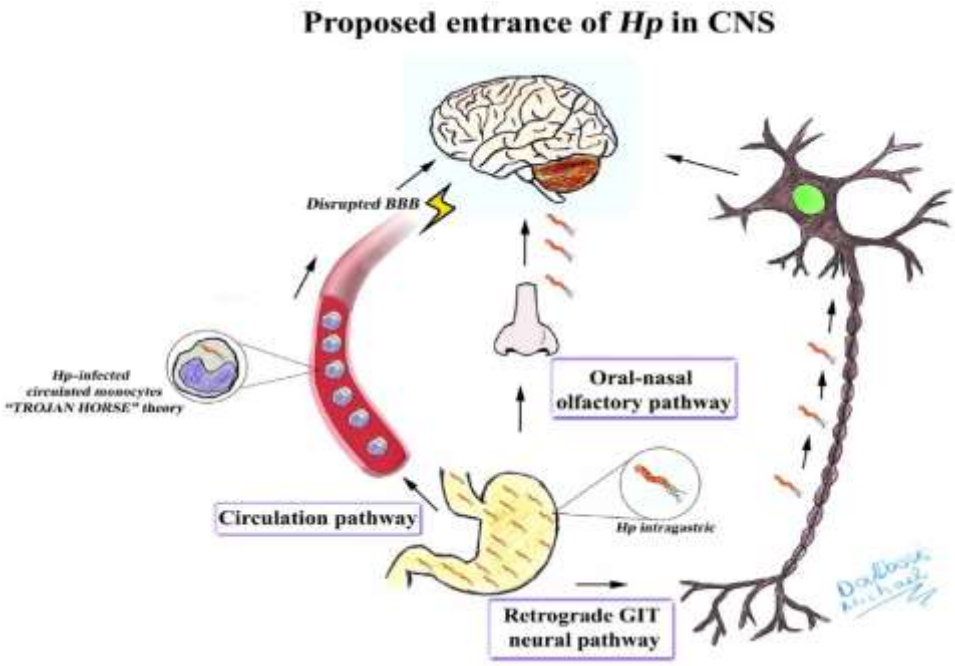

Figure 5. Schematic representation of three theories that mechanically explain the possibility of *H. pylori* entering the CNS **(40)**

Parkinson's Disease

Parkinson's disease (PD) ranked in the 2th place among neurological disorder worldwide. The disease has been specified as accumulating cytoplasmic proteins, including α-synuclein, causing gradual degeneration of dopaminergic neurons **(43)**. Degeneration leads to tremors, stiffness, and difficulty with movement as symptoms of PD. The risk of PD may increase in the presence of *H. pylori* infection. L-3, 4-Dihydroxyphenyl alanine (L-dopa), a dopamine precursor, is prescribed to treat PD. The accessibility of L-DOPA may be affected by *H. pylori* infection via disrupting the duodenal mucosa in which initial L-DOPA uptake occurs. Recent studies have argued that *H. pylori* eradication improves L-DOPA accessibility and reduces motor instabilities in PD patients. Parkinsonism is also a neurological disease with same symptoms as PD. If anti-inflammatory cytokines such as IL-1β, TNF-α, and IL-8 are presented in the bloodstream, the immune response induces a blood-brain barrier disorder and ultimately causes neurotoxicity and neuroinflammation. Researchers have found that infection by *H. pylori* provides the necessary basis for autoimmune disease, which in turn leads to nerve damage and eventually Parkinsonism **(41, 44, 45)**.

Alzheimer's Disease (AD)

Alzheimer's disease (AD) is regarded as the most prevalent form of dementia, especially in industrialized countries, affecting approximately 20 million people worldwide [40]. AD is a progressive neurogenic disorder specified by nerve death and synaptic loss due to intra- and extra-cellular accumulation of neurofibrillary tangles and beta-amyloid deposits in those brain areas that are involved in cognitive and memory processes The inflammatory reaction has an significant role in the pathophysiology of AD. Given the *H. pylori*-induced inflammatory reactions and high levels of *H. pylori*, TNF-α, IL-8, and IgG in the cerebrospinal fluid (CSF) of *H. pylori*-infected patients suffering AD, it could be concluded that *H. pylori* may contribute in AD. This confirms the results of the studies that noticed an improvement in cognitive status, functional parameters, and survival of AD patients after *H. pylori* eradication **(41)**. Chronic atrophic gastritis caused by *H. pylori* reduces the concentration of B vitamins in the serum and thus increases the concentration of homocysteine; concentration of homocysteine in serum corresponds with the intensity of dementia. Oxidative damage may be induced by homocysteine in the brains of patients with mild cognitive disorder is possible. The information suggests that oxidative damage may be considered as one of the first events occurs at the onset and development of AD **(41, 44).**

Multiple Sclerosis

Multiple sclerosis (MS) is a complex multifactorial and autoimmune disease, which causes demyelinating inflamed lesions in the CNS system. The etiology of MS is not yet fully understood. Several environmental factors, including microbial agents, are known to cause the disease. Among microbial agents, *H. pylori* has been considered as a microbial agent of the disease. This hypothesis is confirmed by the high prevalence and occurrence of gastrointestinal symptoms in MS **(44, 46, 47)**. *H. pylori* infections are known as important risk factors in the progression of anti-aquaporin 4 (AQP4) and the results of some studies confirm the improvement of

patients after *H. pylori* eradication. Neuromyelitis optica (NMO) is an inflammatory disorder that electively influences the spinal cord and optic nerve. Optic neuromyelitis development may be affected by chronic infection via molecular mimicry existed between bacterial AQP4 and human AQP4. Moreover, the protein responsible for activating *H. pylori* neutrophil is involved in pathogenesis by inducing activation and migration of neutrophils **(42, 44)**.

Ischemic Stroke

Studies indicate that some infectious agents have a role in the progression of neurological disorders like ischemic stroke. There are a positive relationship between H. pylori infection and the occurrence of stroke. The pathophysiological mechanism of most strokes is cerebrovascular and carotid occlusion [48]. The presence of CagA-positive strains and *H. pylori*-chronic infection are two main risk factors for stroke. Likewise, there are a clear relationship between CagA-positive strains of *H. pylori* and higher risk of atherosclerotic strokes in patients with active infection. The underlying mechanism through which chronic *H. pylori* infection augments the risk of ischemic stroke is not yet wholly known. *H. pylori* is thought to affect coagulation by activating platelets. According to the results of various studies, the levels of plasma and LDL cholesterols, IL-8, and fibrinogen were significantly decreased following six months of *H. pylori* infection eradication compared to the control group and patients infected with *H. pylori* suffering from stroke **(44, 48, 49)**.

Hematological Diseases

Iron Deficiency Anemia (IDA)

There are a large body of studies examining the relation between IDA and *H. pylori* infection. Blaser *et al.* (1991) described the relationship between hemorrhagic gastric and infection by *H. pylori,* and also suggested a possible association between IDA and *H. pylori* infection **(7, 51)**. The same association has been confirmed in children and adults in several studies [50-53]; however, few studies did not confirm this association. A meta-analysis consisting 15 case-control studies was conducted by Qu et al. (2010) in order to examine the association between IDA and H. pylori infection. In 5 studies, the diagnosis of the infection was successfully done using endoscopy and histological tests, which did not include gastric ulcer and gastric cancer cases. In 10 other studies, *H. pylori* infection was identified using serological tests and urea breath test; the data showed with high reliability the association between *H. pylori* infection and higher risk of IDA in these people **(54)**. A recent study also confirmed the relationship between IDA and *H. pylori* infection **(55)**. Improvement of IDA patients following *H. pylori* eradication in the absent of iron supplementation has also been confirmed in other studies **(51).**

H. pylori can result in IDA through certain mechanisms. First, iron loss may increase because of peptic ulcer disorder, hemorrhagic gastritis, and gastric adenocarcinoma. Secondly, the role of H. pylori CagA protein has been confirmed in the absorption of iron from interstitial holotransferrin. The rate of iron uptake by *H. pylori* increases during bacterial development. In summary, the relationship between IDA and *H. pylori* has been established in various research, and currently national and international instructions suggest *H. pylori* infection eradication in IDA patients **(51, 52).**

Immune Thrombocytopenic Purpura (ITP)

ITP, formerly known as autoimmune- and idiopathic-thrombocytopenic purpura, refers to an autoimmune disruption specified by isolated thrombocytopenia when other causes are absent. In 1999, the first relation of ITP with *H. pylori* infection was explained in Spain. In addition to this association, several researchers have also reported a significant increase in the number of platelets due to *H. pylori* eradication from 32% to 100% in Italy and 26% to 100% in other parts of the world **(50, 56)**.

H. pylori affects ITP through several mechanisms. An interesting hypothesis about molecular mimicry outlines that antibodies with cross-reactivity can react with platelet surface antigens as well as *H. pylori*. By washing the platelets of *H. pylori*-infected ITP patients, the researchers identified the CagA protein in the immunoblots, whereas it was not detected in *H. pylori*-infected patients who were free from ITP. Other researchers have outlined that the reaction of *H. pylori* urease with GP IIb/IIIa expressed on platelet surface resulted in monoclonal antibodies. Although these results represent a molecular mimicry between platelet surface antigens and *H. pylori* components, the pathogenic role of these cross-reactive antibodies is still unclear [57 Other possible mechanisms may be due to the destabilizing impact of *H. pylori* infection on the balance of Fcγ receptor of monocytes/macrophages, resulting the formation of autoantibodies. Based on a recent study, the expression of FcγR II B in circulating monocytes was reduced in patients infected by *H. pylori* who had IPT. Thus, *H. pylori* may change the balance of Fcγ receptor of monocytes/macrophages by reductive regulation **(51)**.

Vitamin B12 Deficiency

There are several major enzymatic reactions inside the body, in which vitamin B12 acts as the coenzyme, thereby results in DNA synthesis. Lahner et al. (2012) performed a systematic review of 17 studies including a total of 2,454 patients and found a direct association between *H. pylori* infection and low levels of serum vitamin B12

Homocysteine is an important ingredient of the vitamin B12 metabolism pathway, and many researchers have reported a positive association between *H. pylori* infection and both high serum homocysteine levels and low serum vitamin B12 levels. Reduced homocysteine and increased vitamin B12 serum levels after *H. pylori* eradication have also been reported **(50, 58, 59).**

As described in the previous sections, *H. pylori* infection is strongly related with chronic gastritis and disrupts gastric acid and pepsin secretion. Thus, *H. pylori* is associated with incomplete absorption of vitamin B12 in food, however, the underlying pathophysiological metabolism is still unknown. Pangastritis related with *H. pylori* infection leads to the destruction of gastric parietal cells, which in turn reduces the level of endogenous factors and leads to a decrease in the absorption of vitamin B12 [50, 60]. The possible mechanisms that lead to the association between IDA, ITP, and vitamin B12 shortage with *H. pylori* infection are summarized in Figure 6.

Conclusion

The results of various studies over the years indicate the involvement and impact of *H. pylori* infection on many biological processes associated with gastrointestinal and extra-gastrointestinal diseases. *H. pylori* contribute in several gastrointestinal disorders including peptic and duodenal ulcer, gastritis dyspepsia, gastric adenocarcinoma, and MALT lymphoma. The pathogenic mechanism of these diseases is not fully known yet. The bacterium also causes many extra-gastrointestinal diseases, including cardiovascular disease, diabetes, IR, MetS, PD, AD, MS, ischemic stroke, IDA, ITP, and deficiency of vitamin B12. The likely mechanism of *H. pylori* leading to these diseases has also been investigated in the last few years.

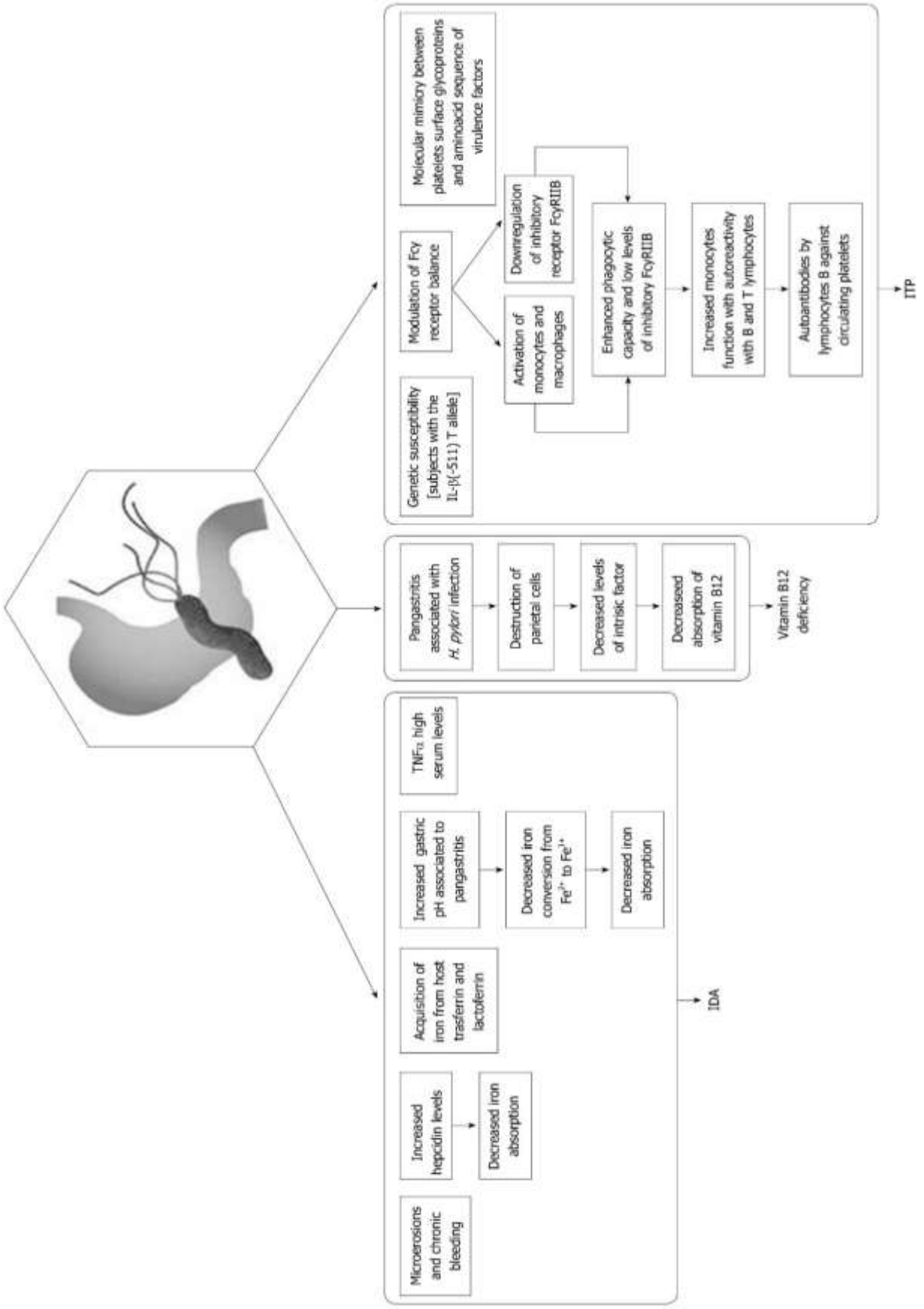

Figure 6. Possible mechanisms leading to the connection between hematologic diseases and the infection by *H. pylori* **(50).**

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Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of Interest

Authors declared no conflict of interests.